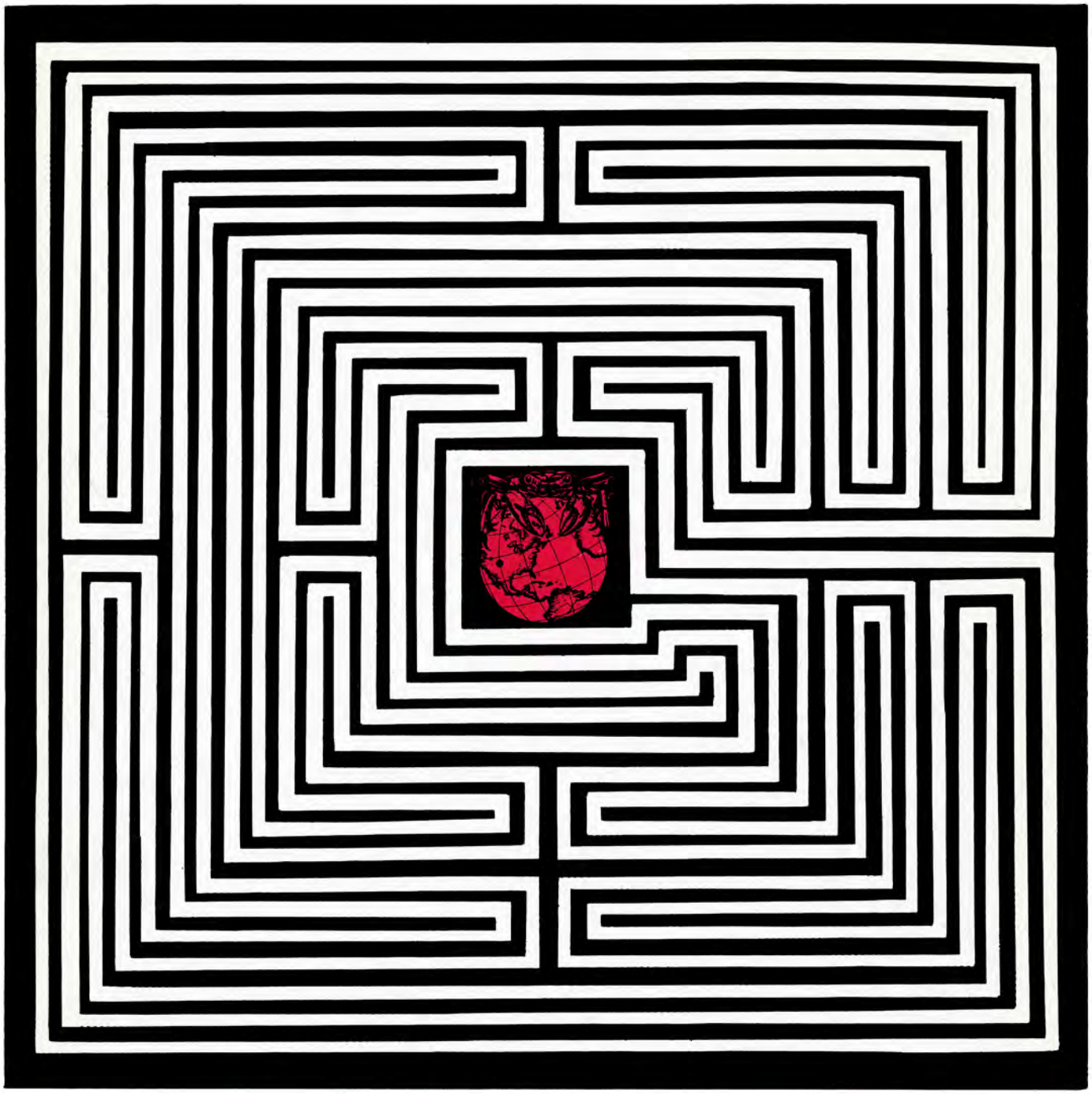

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VOLUME FOUR APRIL, 1973 NUMBER SIX

Juan A. del Regato, M.D., *Editor*

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J. A. del Regato, M.D.

Jessie L. Ternberg, M.D.

Harvey S. Rosenberg, M.D.

J. Scott Dunbar, M.D.

PEDIATRIC TUMORS

With this issue of CANCER SEMINAR we complete the 4th Volume of this publication gathering the discussions of 360 cases in 24 consecutive annual meetings in Colorado Springs. This type of confrontation, originated by us nearly a quarter of a century ago, has been repeatedly acknowledged by thousands of participants for its educational value. The CANCER SEMINAR has shown us the diagnostic possibilities that arise from the intelligent exploitation of radiologic techniques and interpretation; often, also, it has clearly shown that histopathology is not the exact science that we like to assume it is. In a variety of tumors, we have not yet learned to integrate the clinical, radiologic and histologic information, as we do in bone tumors.

The occurrence of malignant tumors in children is always more poignant and imposing; the problems of diagnosis and treatment of these tumors are more complex and the responsibility to be discharged more seriously. The reader of this issue will be delighted by the clear presentations of Dr. Scott Dunbar and the succinct discussions of Dr. Jessie Ternberg; we are all indebted to Dr. Harvey Rosenberg for the care given to his discussion of cases and for the quality of the photomicrographs and their captions.

We regret to announce that we have decided to discontinue this type of CANCER SEMINAR; it has not been an easy decision to make and we know that it will displease many of our friends. These conferences are to be replaced by a new series of CANCER SEMINARS with a different format: the new approach will face problems of everyday practice, including radiodiagnostic and histopathologic considerations, but allowing for greater considerations of treatment modalities of greater interest to a wider audience. It has been our privilege to be able to distribute these printed proceedings to participants and libraries at no cost to them; this issue puts an end to their gratuitous distribution. Costs of publication and mailing have consistently risen and we must face present-day realities.

We know how much the value of these CANCER SEMINARS has been enhanced by the direct and indirect contributions of many. Once more, for this last time, we offer our thanks to all.

J. A. del Regato, M.D.
Colorado Springs, Colorado
April, 1973

Juan A. del Regato Foundation 2008

1. *Ganglioglioma of the Temporal Lobe*

Contributed by **Mario Kornfeld, M.D.,** Albuquerque, New Mexico

THE PATIENT was a 9-year-old boy in December, 1971, when he complained of headaches and left arm tremors of three months duration. On examination there was mild left hemianopsia and blurring of the temporal and nasal margins of his optic discs. CBC was within normal limits; there was a large amount of WBC in the urine; BUN was normal.

Dr. Dunbar: The films show at least suggestive evidence of increase in intracranial pressure of some months duration, as demonstrated by abnormally large head size and slight widening of the coronal suture with elongation of its serrations. The middle fossa of the skull is almost certainly enlarged, and the right parietal and squamous bones may be thinned, bulging laterally slightly. The arteriogram shows stretching of the carotid siphon, marked displacement upward and medially of the middle cerebral artery, and displacement to the left of the anterior cerebral artery and its branches. No early venous shunting is identified. No tumor stain can be seen but the capillary phase of the study is not available to us. The lesion appears to originate in the temporal lobe, or at least in the temporal area. The petromastoid bones bilaterally appear normal which militates against spread of infection from the mastoids. There is no intracranial calcification.

A complete differential diagnosis would include secondary lesions from infection elsewhere (abscess or tuberculoma) and primary tumor elsewhere with cerebral metastasis. Assuming that there is no evidence of a primary inflammatory or neoplastic lesion elsewhere, the list can be abbreviated somewhat. The evidence of prolonged increase in intracranial pressure and enlargement of the middle fossa suggests that the lesion has been present for at least some months. Focal cerebritis and localized encephalitis are thus unlikely. A congenital cyst is possible but rare as an isolated or primary abnormality. Primary brain tumors are second only to leukemia in the incidence of childhood malignancy; a primary brain tumor is a good possibility, presumably of low malignancy and slow growth. An astrocytoma is therefore the best possibility. Cerebellar medullo-blastoma is common in childhood, cerebral medullo-blastoma very rare.

Dr. Dunbar's impression: TEMPORAL LOBE NEOPLASM (probable cystic astrocytoma).

Roentgenologic impressions submitted by mail:

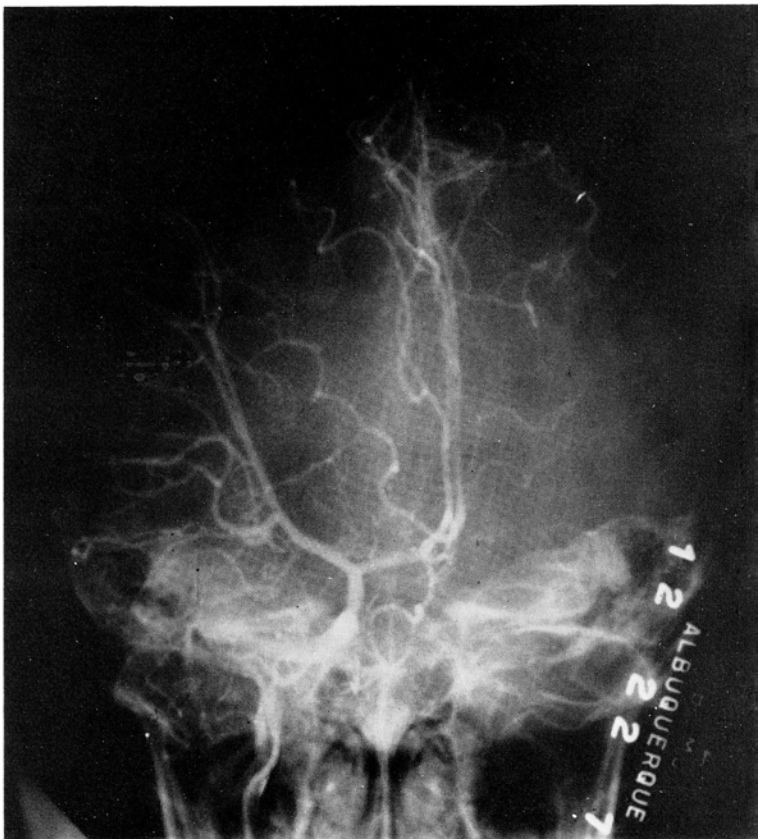
Cystic tumor, parencephalic cyst	25
Astrocytoma	19
Temporal abscess	18
Temporal glioma	15
Avascular mass	13
Subdural collection	5
Others	16

Dr. Dunbar: As you see, a cystic tumor was the favorite diagnosis, combined with an astrocytoma. A temporal abscess seems unlikely for the reasons I have mentioned. I am very much impressed by the evidence of long standing increased intracranial pressure, of at least some months; a huge cerebral abscess of this size, extending over such a long time, without evidence of a febrile response and intense leukocytosis, and without evidence of infection elsewhere would be, I think, unlikely; we have looked at the petromastoid bone just to be sure there is no mastoiditis. A temporal glioma is another way of saying an astrocytoma; if one assumes that it is of low malignancy, it includes the possibility of an oligodendroglioma; astrocytoma of cystic character is more likely. A single arteriographic study does show that the mass in this phase of the study does appear to be avascular; this reinforces our impression that it is of low-grade malignancy and probably cystic in character. A subdural collection of fluid or blood or pus, tends to displace the small vascular structures away from the parietal area producing usually a lentiform mass between the bone of the calvaria and the brain as shown by the vessels of the brain.

Dr. Regato: Dr. Benjamin Felson, of Cincinnati, suggested a large temporo-parietal cystic lesion. Dr. C. A. Poole, of Miami, also suggested an avascular cystic tumor. Dr. E. J. Keeffe, of Pontiac, Michigan, wondered as to the possibility of an aneurysm of the vein of Galen.

Operative findings: On December 27, 1971, a right-sided craniotomy was done. A large cystic lesion was found on the temporal lobe; the cyst was entered and a mural nodule 4 cm in diameter found on its anterior wall; the

Fig. 1—Medial displacement of the middle cerebral artery.



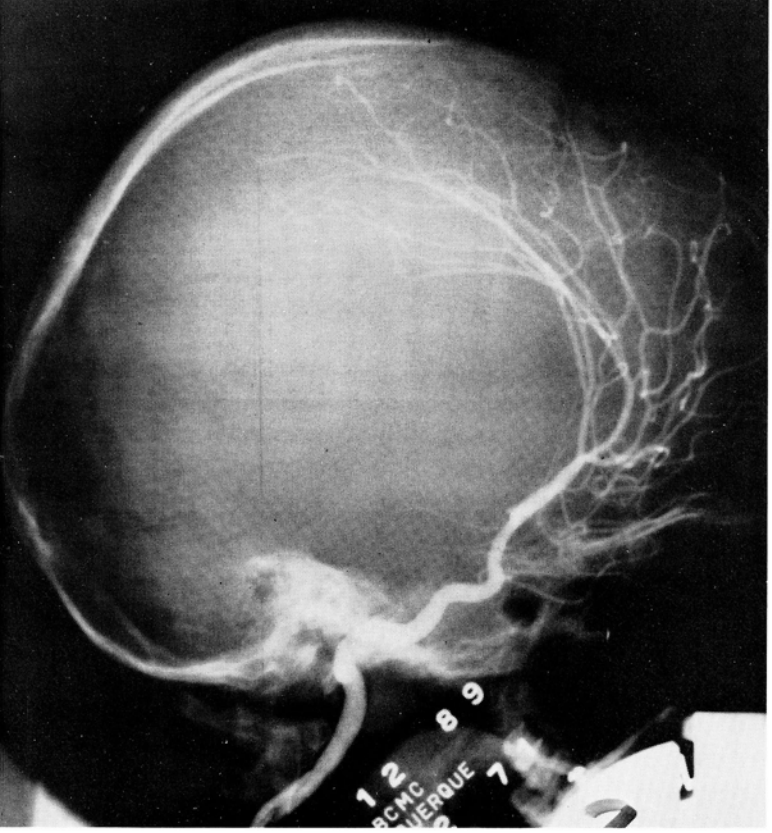


Fig. 2—Marked stretching of carotid siphon by mass in temporal lobe.

nodule was removed and a frozen section diagnosis of astrocytoma was rendered. Other biopsied areas were reported as showing only reactive gliosis. The entire cystic lesion was resected; the specimen measured 10 x 10 x 4 cm.

Dr. Rosenberg: The neurological symptoms and the radiologic findings indicate a temporal lobe mass. From additional data that I received, the lesion was restricted to a mural nodule in the anterior wall of a cyst which reached the leptominges in the temporal lobe area.

The cyst is not apparent in the histologic preparations. An unencapsulated infiltrate diffusely distorts the white matter with the apparent preservation of the gray matter providing the only circumscription. In the infiltrate, the abundant cytoplasm of a number of cells accentuates the moderate pleomorphism. These large cells contain one or more large, vesicular nuclei and cytoplasmic condensations interpreted as Nissl granules. Small, poorly differentiated mononuclears accumulate about dilated blood vessels. Cresyl violet stain accentuates the Nissl granules but the Bielschowsky stain for intracytoplasmic neurofibrils is equivocal.

The indentification of this lesion resides in the interpretation of the large cells and their resemblance to ganglion cells. If these are interpreted as glia one would lean towards a gemistocytic astrocytoma or a reactive gliosis. If these are interpreted as ganglion cells, the lesion assumes the identity of a primary neural tumor such as a ganglioglioma.

As with a number of the lesions in this CANCER SEMINAR, this tumor masquerades under a number of synonyms, usually dependent on the qualitative nature of the lesion: gangliocytoma, central or hamartomatous ganglioneuroma, ganglioma, ganglioblastoma, and glioneuroma. Since ganglioglioma represents a single aspect in a histologic continuum of nerve cell tumors, the differential diagnosis includes the other lesions in the spectrum. Medulloblastoma may be considered the most undifferentiated form of this series, with central nervous system neuroblastoma as slightly more differentiated. Neuroblastoma of the central nervous system, an uncommon but fairly well defined lesion usually involving the cerebrum during childhood, is allegedly slightly more benign than medulloblastoma although the single case in the Texas Children's Hospital series had a relatively brief course.

The well differentiated neuronal tumors include gangliocytoma in which ganglion cells mix with immature nerve cells; ganglioneuroma in which ganglion cells mix with abundant neural fibers; and ganglioglioma in which mature ganglion cells mix with glial elements. In each variety, the mixture of ganglion cells with other elements may be very broad with either few or many ganglion cells mixed with the other components in inverse proportions. Alternate diagnoses must either deny the identity of the ganglion cells or assume that they represent the normal neural components of the brain infiltrated by the cellular tumor.

The abundant cytoplasm of the large cells gives then a resemblance to gemistocytic astrocytes. Gemistocytic astrocytomas are rare tumors, usually restricted to the cerebral hemispheres, and made up of large, closely packed globoid cells. The loose arrangement in our case does not conform to that description. The central nervous system tumors in the files of Texas Children's Hospital contain no example of a gemistocytic astrocytoma. The presence of neural elements in the white matter also precludes a reactive lesion.

A consideration of some consequence is the relationship of this lesion to hamartomas and the tuberous sclerosis complex. The circumstantial relationship to tuberous sclerosis derives from tumors of similar structure occuring both with and without the general tuberous sclerosis syndrome. In tuberous sclerosis, the lesion known as Subependymal giant cell astrocytoma usually occupies the wall of the lateral ventricle over the basal ganglia. It is sharply defined, vascular, and frequently focally calcified. Microscopically, it consists of large fusiform cells resembling gemistocytic astrocytes plus less well differentiated elements interpreted as astroblasts frequently arranged in perivascular pseudorosettes. Both binucleate and multinucleate forms occur and some have large vesicular nuclei resembling neurons similar to the case under discussion. Although the full syndrome of tuberous sclerosis includes adenoma sebaceum, mental retardation, and visceral hamartomas, not all components need exist in a given patient. The identity of the syndrome is therefore indistinct and hazy. The association with tuberous sclerosis depends more on the definition of that syndrome than anything else.

In general, differentiated central nervous system neural tumors have a benign course with some reports of remarkable recovery of neurological faculties after excision of the lesion although isolated reports indicate an ultimate malignancy. The malignant behavior usually involves the glial rather than the ganglion cell component of the tumor. This conforms with a generally held concept that the ganglion cell is a mature cell with little capacity for dedifferentiation. Undifferentiated central nervous system tumors such as neuroblastoma and medulloblastoma have been described with maturation to mature ganglion cells but dedifferentiation of ganglion cells has not been observed. Russel and Rubinstein characterize the distinction between ganglioneuroma and ganglioglioma on the basis of a spindle cell stroma in ganglioneuroma and mature

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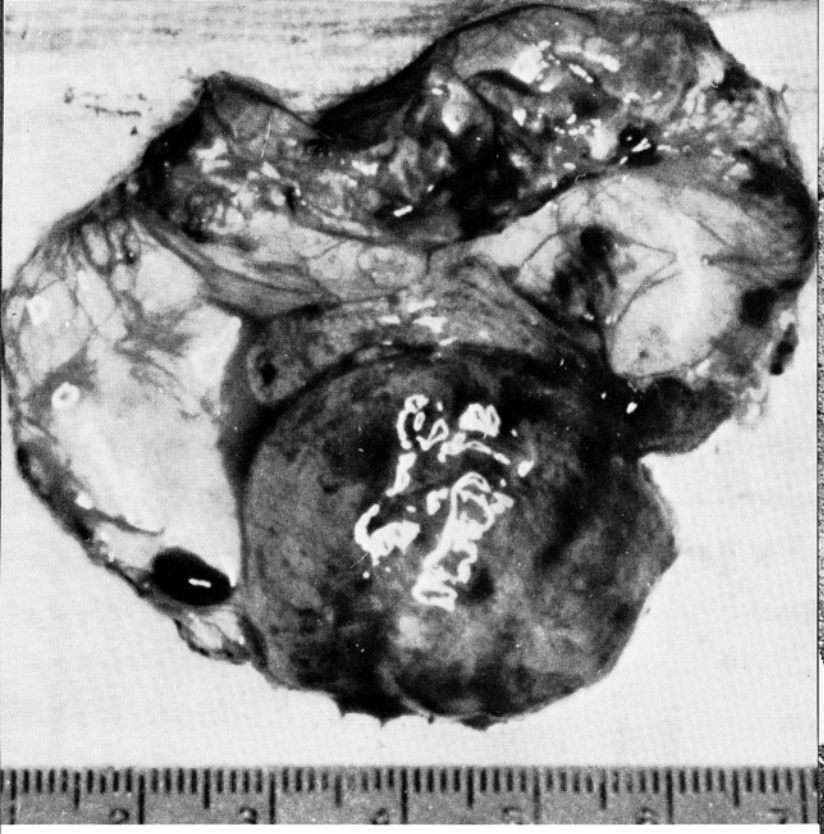

Fig. 3—Cystic lesion containing nodule.

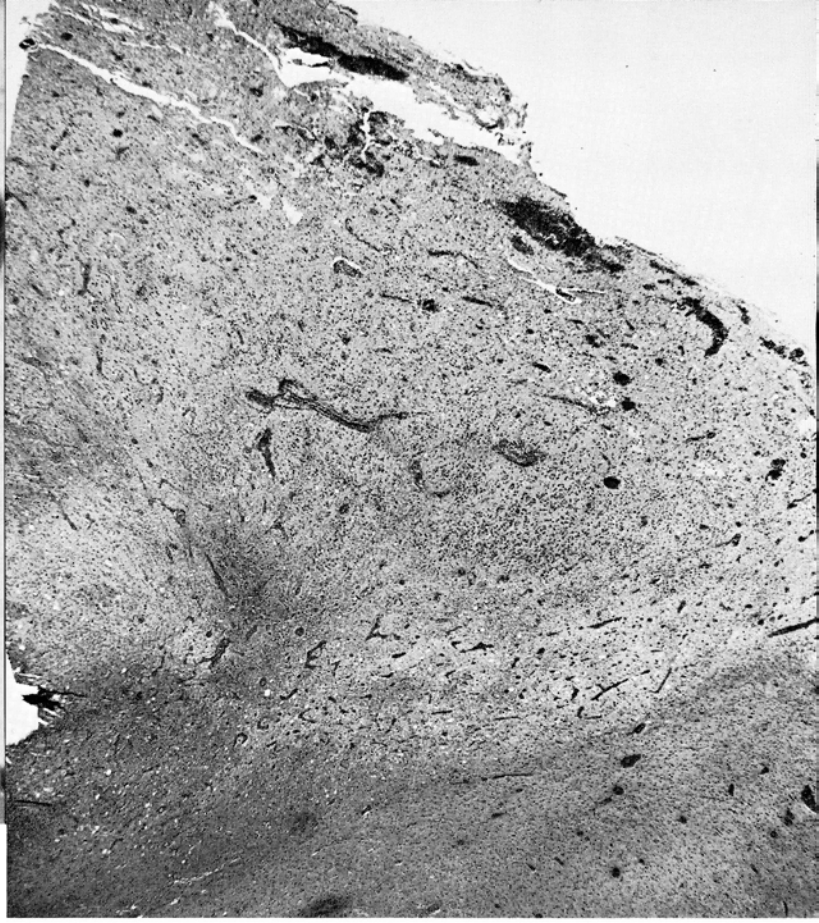

Fig. 4—The cellular, vascular tumor in the white matter has no distinct border, but does not extend into the grey matter. (Hematoxylin-eosin, X14.5)

glial elements in ganglioglioma but they emphasize the difficulty in distinguishing the two. They require three essential criteria in establishing the diagnosis: 1) The tumor cells must be unequivocally ganglion cells with identification of Nissl substance and neurofibrils as distinct from glial cells with large vesicular nuclei and prominent nucleoli. 2) The ganglion cells must be in the tumor and not invaded by the tumor. 3) Ganglion cell precursors may be identified. Of all neoplasms in childhood, central nervous system tumors make up approximately 25% and are the most common group of solid tumors in childhood. Of the central nervous system tumors, 75% are gliomas, usually astrocytoma and medulloblastoma, both usually appearing in the posterior fossa. Primary neural tumors, in contrast to glial tumors, are very uncommon making up less than 2% of the total. No typical ganglioneuromas were found in the central nervous system tumors in the files of the Texas Children's Hospital although there was one neuroblastoma and one hamartoma of the tuber cinerium.

Dr. Rosenberg's diagnosis: GANGLIOGLIOMA.

Histopathologic diagnoses submitted by mail:

Astrocytoma	75
Ungraded	14
Grade I	2
(gemast.) Grade II	39
(multif.) Grade III	15
(gigant.) Grade IV	5
Ganglioglioma	33
Ganglioneuroma	9
Yonoseoma of Ramon y Cajal	1 !
Others	11

Dr. Rosenberg: I assume that most participants would put an astrocytoma into the gemistocytic variety, on the basis of the large fat cytoplasmic cells; certainly, this is a very legitimate consideration. It is my personal thesis that the presence of Nissl granules in those large cells removes this from the glio category and puts it instead into the ganglioglioma and ganglioneuroma.

Dr. Regato: Drs. Samruay Shuangshoti, of Bangkok, and Walter Bauer, of Saint Louis, also made a diagnosis of ganglioneuroma. Dr. E. Bemis, of Milwaukee, diagnosed astrocytoma, grade I. Drs. H. Hamperl, of Bonn, Germany, and F. Cabanne, of Dijon, France, offered gemistocytic astrocytoma (or astrocytoma, grade II). Dr. L. Lowbeer, of Tulsa, preferred cerebral gangliocytoma, probably malignant, resembling protoplasmic to gigantocellular astrocytoma (grade III to IV).

Subsequent history: The patient is presently hospitalized for evaluation of his chronic urinary tract infection associated with bilateral hydronephrosis and hydroureters. He had a meatotomy for meatal stenosis but his condition did not improve. Presently (October, 1972) an anomalous insertion of ureters is being investigated and if confirmed, ureteral implantation will be carried out. The patient has no signs and symptoms referable to the CNS lesion removed last December.

Dr. Ternberg: I feel like a cat in a dog pound, being a surgeon among all these radiologists and pathologists. If I get called to see a patient that has a problem such as this it is usually because somebody is anticipating that it is a metastatic lesion; all that I can add is that if it is not an intracranial lesion, most tumors are either visible or palpable; like most cliches, of course, that has its exceptions.

M. Kornfeld, M.D., Albuquerque, New Mexico: In the slides from various portions of the lesion, the great majority of cells could clearly be identified as abnormal ganglionic cells; also present were cells which in routine stain could be interpreted as being either oligodendroglial or astrocytic in origin. However, special stains for both of these classes of glial cells were negative. As Dr. Rosenberg

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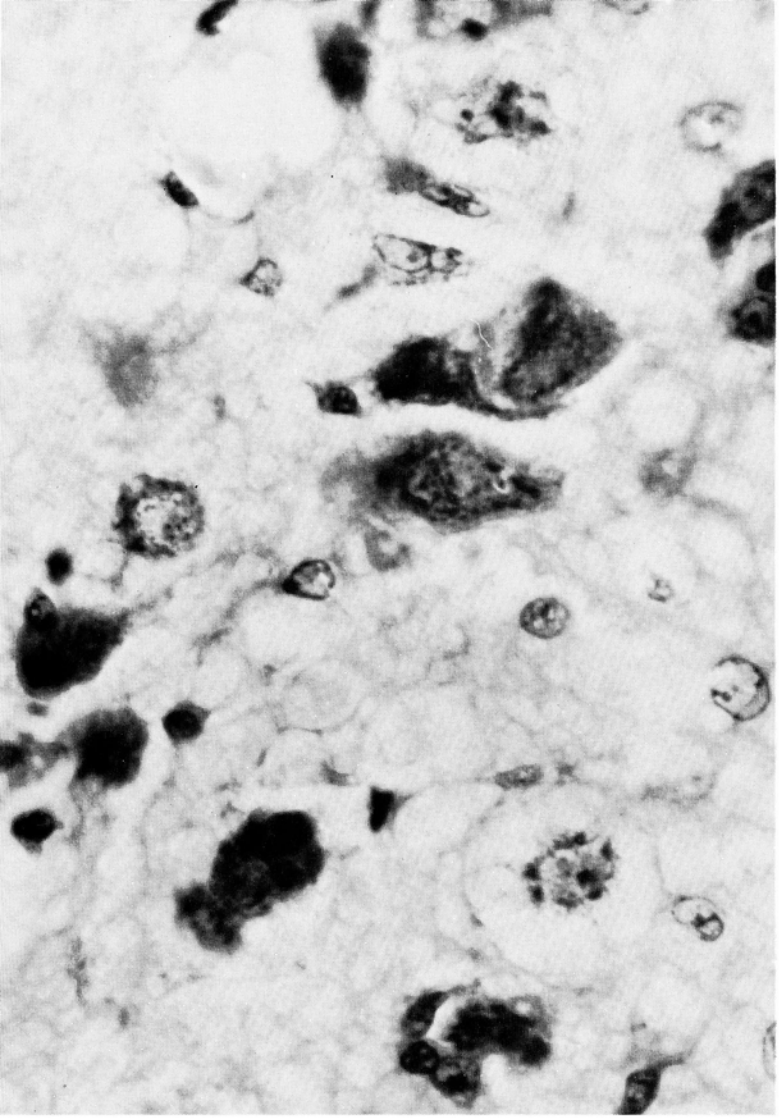

Fig. 5—The neuronal cells in the tumor have large nuclei with prominent nucleoli, cytoplasmic vacuoles, and Nissl granules. (Hematoxylin-eosin, X160).

pointed out, in many of the cells which showed the features of neurons it was difficult, or impossible, to demonstrate neurofibrils. It was also somewhat disappointing to see that in the areas of dense neuronal population there were fewer axons present than one would expect. Electromicroscopy clarified these findings. The neuropil consisted of multiple processes which were axons and often contained dense core granules; however, many showed very few, or no neurofilaments or neurotubules, the structure on which the positive axonal stains are based. In addition, the very enlarged axonal processes showed degenerative changes resembling dystrophic axons. Glial cells and processes were not observed in electronmicrographs. The tumor cells could be positively identified on ultrastructural level as belonging to the neuronal series; this identification was based not only on the presence of multiple stacks of the cisternae of granular endoplastic reticulum, translated into light microscopy as abundant Nissl granules, but also on the presence of synapses. Again, neurofilaments and neurotubules were sparse in cell bodies. Also present in the perikarya of these neoplastic neurons were dense granules, 1,000 to 2,000 angstroms in diameter. Similar granules were reported in peripheral ganglioneuromas or ganglioneuroblastomas and they could be equated with an increase of catecholamines in urine; catecholamines were found to be present in the tumor mass itself. In the central nervous system only two tumors are on record in which ganglionic cells were shown on ultrastructural level to have such granules; one was a ganglioglioma and the other a gangliocytoma. No positive identification of these granules as catecholamines has been carried out; the other strong possibility, in central nervous system gangliomas, is that they represent neurosecretion.

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2. *Teratoma of the Liver*

Contributed by **Bertram L. Pear, M.D.** and **Jon E. Boline, M.D.,** Denver, Colorado

THE PATIENT was a 5-month old baby girl in August, 1966, when she developed dyspnea and expiratory stertors. (The patient's twin sister had been born with a large mass on the side of her face and neck and had died shortly after birth). Examination revealed a very large liver.

Dr. Dunbar: There is a large mass in the right side of the abdomen, elevating the right leaf of the diaphragm, displacing the stomach and gut to the left and inferiorly, and likely containing a small (less than 1 cm diameter) faint calcification to the right of the twelfth thoracic vertebra, and approximately in the area of the right adrenal gland. The right kidney is displaced inferiorly and its superior margin is ill-defined and perhaps slightly deformed. There is widening of the rib spaces inferiorly on the right, but the bones are not eroded, invaded or destroyed, and there are evident vertebral or rib anomalies. The gut, though displaced, is not invaded or obstructed. The lower thorax is partially shown, and there is no evidence of cardiac enlargement, pulmonary edema or pleural effusion.

From the roentgen evidence alone, the most likely diagnosis would be neuroblastoma. In early life, neuroblastoma commonly metastasizes to the liver which becomes greatly enlarged, and indeed sometimes no primary site can be found. If the calcification in the general area of the adrenal

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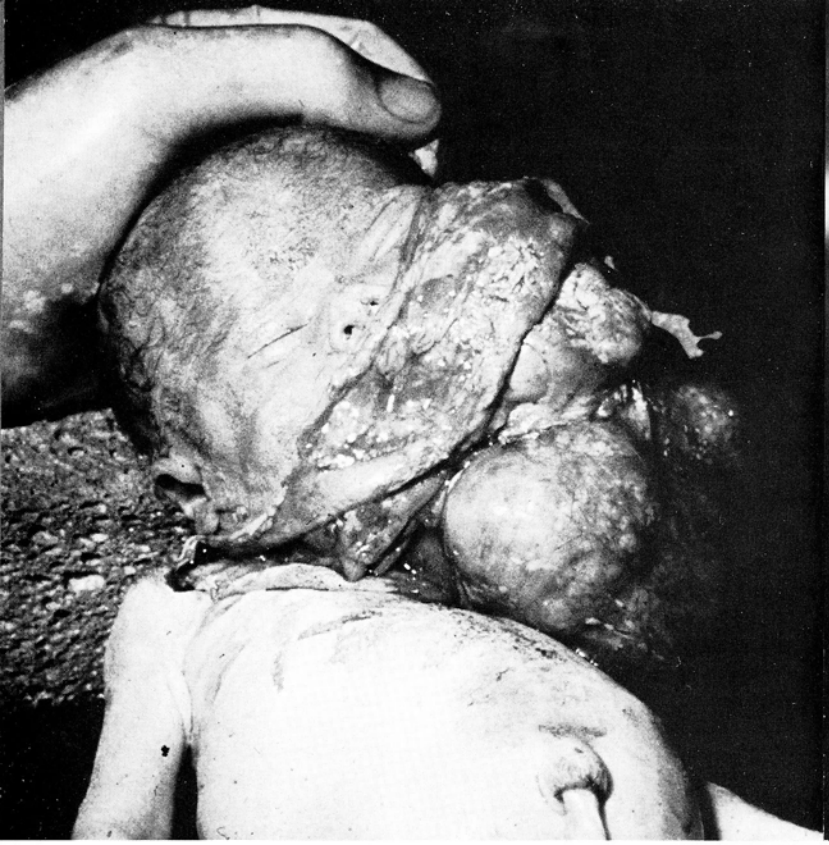

Fig. 1—Post-mortem photograph of the patient's twin sister born with large cervical teratoma.

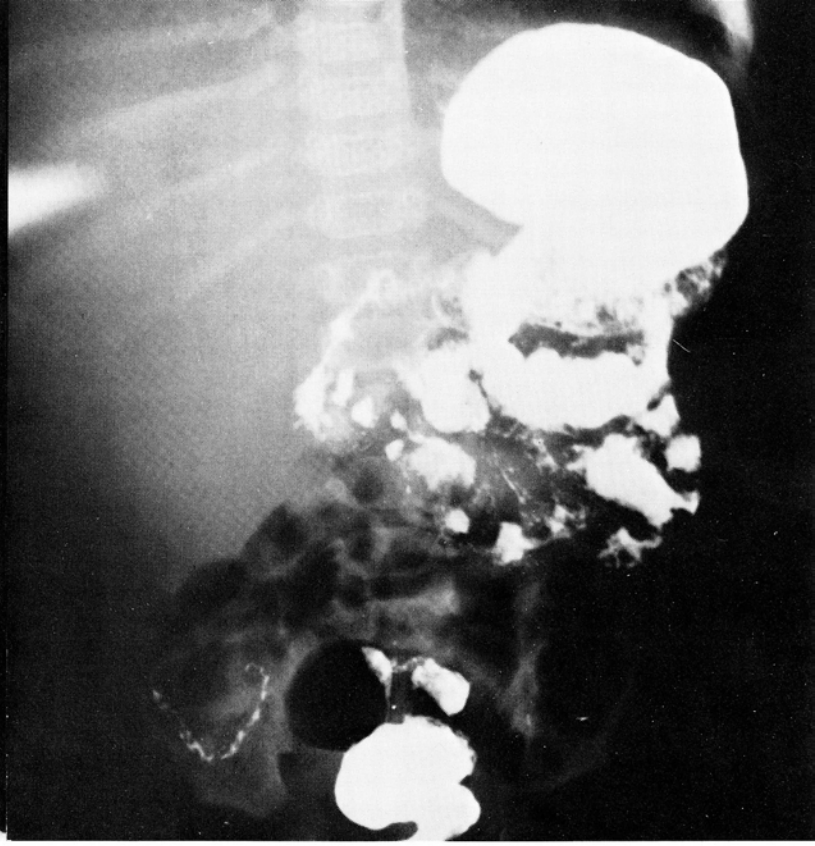

Fig. 2—Large right abdominal mass displacing the stomach and intestines as well as the right kidney.

gland is a true finding, neuroblastoma becomes still more likely. The second most likely possibility at this age is a hamangioma of the liver, but if present, this usually causes heart failure in the neonatal period, and there is no evidence, roentgenologically or clinically, for heart failure. A hepatoma can enlarge the liver in the first few months of life, but is usually not calcified.

The problem is made more challenging by the presenting of signs and symptoms of dyspnea and expiratory stertors, and by the history of the twin sister. The twin's history rather suggests a cystic hygroma, which if it involves or invades the thorax has a bad prognosis. Cystic hygroma, however, almost never involves the liver in early life.

Radiographs of this child's chest would be of obvious importance in coming to a diagnosis, as would detailed information about the twin. On the roentgen evidence alone, however, the provisional diagnosis would have to be neuroblastoma.

Dr. Dunbar's impression: ADRENAL NEUROBLASTOMA.

Roentgenologic impressions submitted by mail:

Hemangioma	22
Malignant hepatoma (hepatoblastoma)	21
Hemangioendothelioma	15
Metastatic neuroblastoma	13
Teratoma	2
Others	25

Dr. Dunbar: Hemangioma, when it does occur in the liver, usually produces heart failure and usually presents in the neonatal first few days or first month of life. We are not told of any concomitant skin hemangiomas present here. Malignant hepatoma or hepatoblastoma is certainly a possible lesion depending on whether or not it is strictly the liver which is enlarged; it is a diagnosis that I do not believe can be made on roentgen evidence alone, with or without an arteriogram. Hemangioendothelioma, is not a common diagnosis in this early stage of life. Neuroblastoma, metastatic to or even arising in the liver, is my favorite diagnosis in this case. A teratoma causing this massive enlargement of the liver would, in my experience, and from published literature, be extremely unlikely.

Dr. Regato: Colonel R. O. Hagen, of Fort Sam Houston, suggested a cystic hygroma. Dr. P. H. Riemenschneider, of Santa Barbara, California, offered lymphangioma. Dr. M. L. Daves, of Denver, preferred hepatoma.

Operative findings: On August 20, 1966, a partial hepatectomy was carried out. The removed part of the right lobe of the liver weighed 260 gm and was replaced by a lobulated soft tan-yellow colored tumor measuring 7.5 cm with multiple areas of hemorrhage and cystic degeneration.

Dr. Rosenberg: In a fairly well localized area of the liver a tumor composed of a number of different tissues compresses the adjacent parenchyma. A thin fibrous capsule separates the major portion of the tumor from the liver and from a smaller similar nodule in the adjacent liver.

In the tumor nodule, well differentiated tissues include islands of hepatic parenchyma, cartilage, pigmented epithelium, pancreatic acini, and broad sheets of central nervous tissue consisting of glia but no well defined ganglion cells. In several areas, an organoid pattern contains columnar elements oriented toward ill defined centrally placed lumens. Mesenchymal elements include striated muscle fibers. Although the structure of many elements forms cysts, tubules, and an organoid pattern, the specific tissue in many instances is not recognizable. In the single nodule outside the capsule in the adjacent parenchyma, there is little evidence of differentiation. Most of the cells are small and dark with an inconspicuous cytoplasm and a single rounded or oval nucleus. Mitotic activity is sparse.

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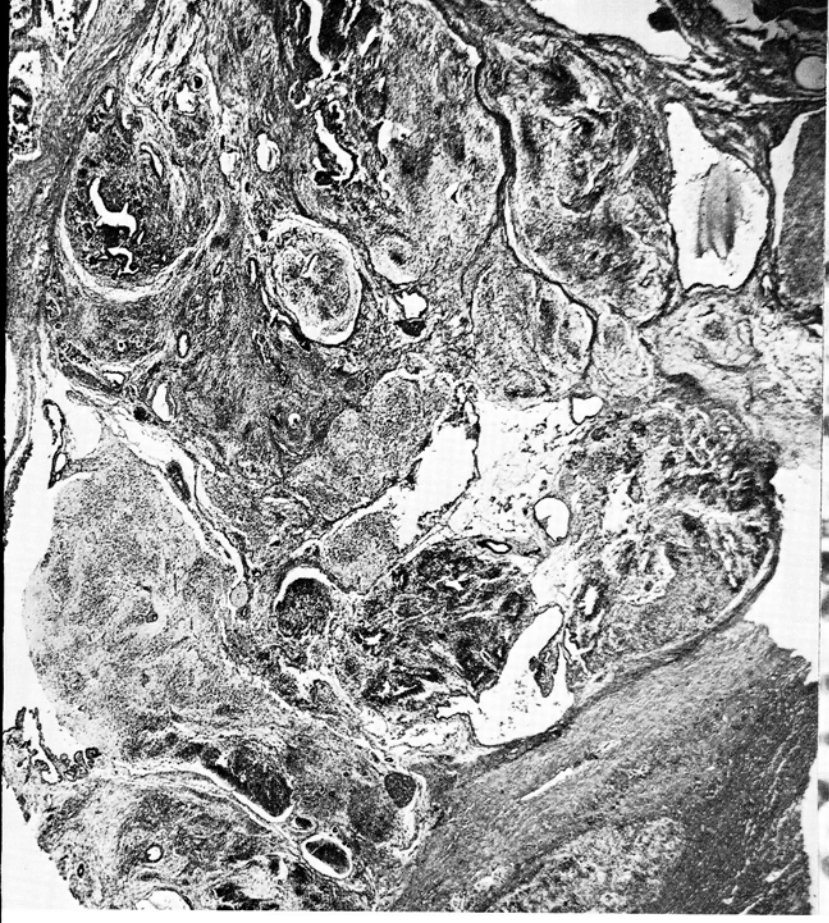

Fig. 3—The teratoma in the liver contains the characteristic structure formed by elements derived from all three germ layers. (Hematoxylin-eosin, X19).

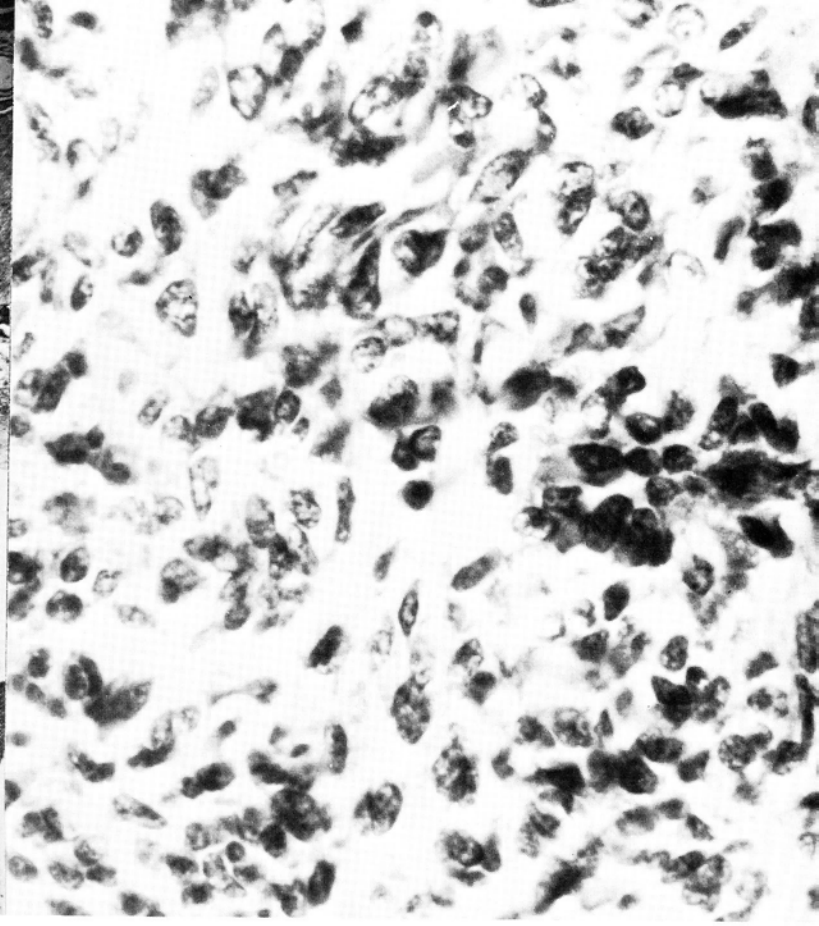

Fig. 4—Islands of undifferentiated, embryonal cells occupy small areas of the teratoma between well-organized neural, glandular, and cartilaginous structures. (Hematoxylin-eosin, X160).

The tissues of multiple germ cell layer origin are diagnostic of a teratoma. The focal poor differentiation does not provoke histologic evidence of malignancy. Although embryonic tissue occurs more frequently in tumors that become malignant, they may also be encountered in those tumors which remain benign. Of somewhat greater concern is the isolated nodule outside the capsule and extending into the adjacent parenchyma. This has the same general pattern as that encountered within the central portion of the liver and could be interpreted as invasive. Of primary tumors of the liver in infancy and childhood, teratoma must make up one of the rarest forms. In a 1965 review, only five primary teratomas of the liver, benign and malignant, were reported in the medical literature, three of these in children. Of all teratomas, involvement of the liver makes up an insignificant incidence. Of 33 teratomas in the material from Texas Children's Hospital and 91 teratomas from the Hospital For Sick Children in Great Ormond Street, in London, none involved the liver.

The histological differential diagnosis must include a hepatoblastoma of the mixed type. Hepatoblastomas are tumors with a malignant potential which occur exclusively in infants and children. They are distinguished from other primary parenchymal hepatic tumors on a morphologic basis and, by some, on an age basis as well, with hepatoblastoma confined to the first five years, and hepatocarcinoma principally involving older children. Of hepatoblastomas, the epithelial type consists entirely of embryonal and fetal hepatic parenchymal elements. In the mixed type, mesenchymal elements of which osteoid is the most prominent component, occurs in conjunction with the epithelial forms.

The major clinical difference is prognostic. We have had no survivors at Texas Children's Hospital in the children with mixed hepatoblastoma, while several patients with the epithelial type had apparent cures after hepatic lobectomy.

Occasional hepatoblastomas have been described, including some in our own material, with squamous cell nests in addition to the mesenchymal elements. The presence of tissues of multiple germ layer origin required alternate interpretation. A most unusual lesion was described in a two-year-old boy by Misugi and Reiner who were good enough to let me review their slide. The lesion in their case contains a teratoma combined with the characteristic hepatic parenchymal and mesenchymal elements of a mixed hepatoblastoma. In their case, there were subsequent metastases which contained embryonic hepatic cells, sarcomatous mesenchymal elements, and osteoid. While Musugi and Reiner interpret this as a true malignant teratoma, Ishak and Glunz suggested an alternate hypothesis of a hepatoblastoma with tridermal elements.

While this concept of hepatoblastoma with tridermal elements may hold for the unique lesion of Misugi and Reiner, I am unable to transpose this interpretation to the present lesion. The few islands of liver in the teratoma are the minority components which contrasts with the usual hepatoblastoma where a few mesenchymal elements occupy a primarily hepatic lesion. The conclusion, therefore, is that of a teratoma originating in the liver with embry-

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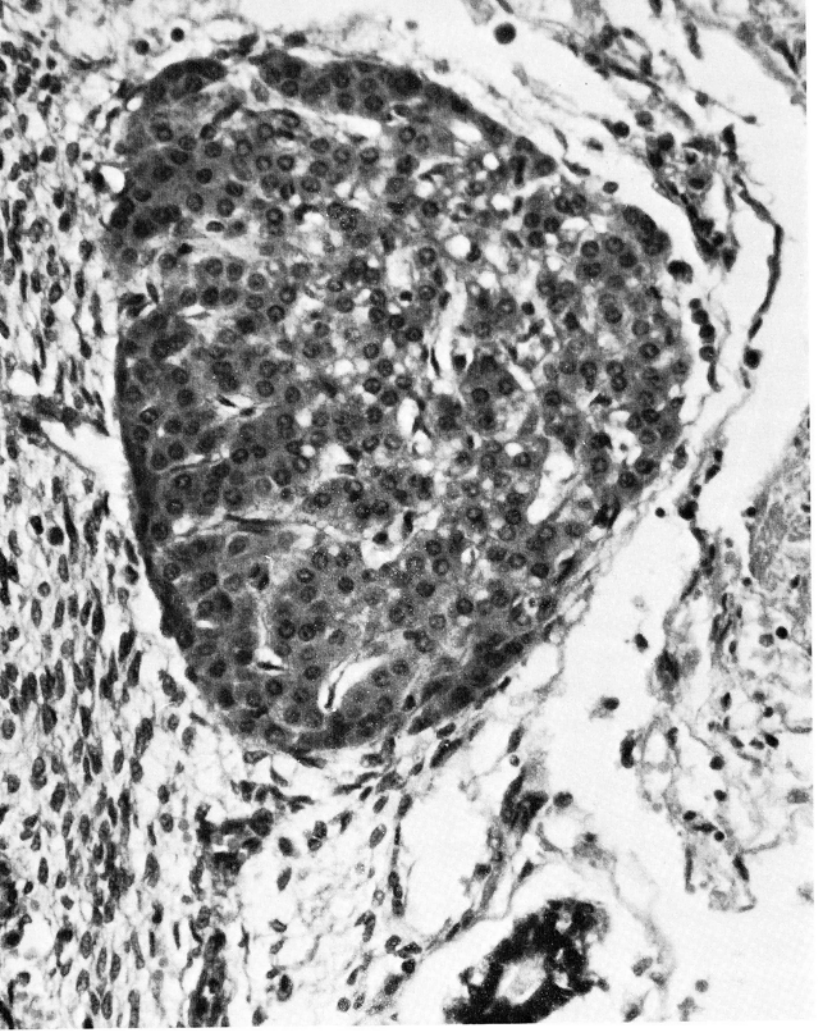

Fig. 5—Small nodules of liver within the tumor have a well-defined sinusoidal pattern but no ducts. (Hematoxylin-eosin, X64).

onal components providing a malignant potential. This interpretation does not represent idle concepts of histogenesis. A teratoma in a five month old child, even with embryonal elements, does not necessarily present a bad prognosis. In contrast, mixed hepatoblastomas generally, and those at Texas Children's Hospital specifically, have a poor prognosis.

Several features are worth consideration complementing the anatomic pathology: the age, the status of twinning, and associated malformations.

The general incidence of twinning in teratomas is about 10% with a range of 7.5-20%. Associated malformations occur in an estimated 5%. The age of the patient at the time of excision of a teratoma is particularly important. Though the number of hepatic teratomas is so small as to preclude generalizations from this specific site, the data with regard to teratomas in general indicate that presentation after one year of age or incomplete excision are associated with a bad prognosis. This is particularly true of sacrococcygeal teratomas where a high risk of malignancy exists if the lesion is not resected in the first two months of life. Gonadal teratomas seem to undergo malignant change somewhat later in life indicating some difference in prognosis depending on the site.

Dr. Rosenberg's diagnosis: TERATOMA of the LIVER

Histopathologic diagnoses submitted by mail:

Teratoma	45
Malignant teratoma (teratocarcinoma)	53
Hepatoblastoma	10
Wilms' tumor (metastatic)	9
Others	8

Dr. Rosenberg: I don't think we need add the pathologists are obviously of sterling quality and we all agree so well. The only area of concern is whether this is benign or malignant and I have taken my stand. Hepatoblastoma is a diagnosis which could very readily be supported; I do not believe that this is a metastatic Wilms' tumor.

Dr. Regato: Drs. M. J. Demeo, of San Rafael, California made a diagnosis of benign teratoma. Dr. J. M. Kissane, of Saint Louis, also designated the lesion as benign noting that the neural element is immature as the baby herself. Drs. Prapont Piyaratn, of Bangkok, and J. Clifford, of Denver, preferred malignant teratoma. Dr. P. H. Larson, of Robbinsdale, Minnesota, called it a hepatoblastoma. Dr. Leo Lowbeer, of Tulsa, offered teratocarcinoma and suggested that this lesion may better be called embryonal carcinoma with ecto-, endo-, and mesodermal embryoids.

Subsequent history: In April, 1972 the patient was living and well. She is under the care of Dr. Robert E. Eastman.

Dr. Ternberg: As Dr. Dunbar, I think an early assumption would be that it was a metastatic neuroblastoma to the liver. We would get a urogram, start collections for VMA right away and do a bone marrow aspiration. We would still be left with a mass in the liver. I would assume that on photoscanning of the liver, this would show up as a tumor within the liver, which would leave you with the possible diagnosis of hepatoblastoma as being the next most likely. As has been pointed out, teratoma is extremely rare; the interesting thing in this case is the twin sister with presumably a cervical teratoma. Twinning is common in sacrococcygeal teratomas but, as far as I am aware, that is the only teratoma that has this association, except for possibly this case. I once saw a teratoma of the liver in which you could see teeth in the roentgenogram of the liver, unfortunately, the child had a teratoma of the ovary as well and I assume that the liver lesion was metastatic.

B. L. Pear, M.D., Denver, Colorado: There are a number of interesting features about this case; one being that the twins each had a teratoma, one of the neck and the other of the liver. The first twin had a large mass in the neck; this mass contained calcium and it deviated and compressed the trachea. Teratoma of the neck in the newborn has been discussed by several authors: Goodwin and Gay collected 90 cases in the world literature and virtually all of them were in newborn infants: 16% of the children were stillborn and all of the children not operated upon, died; of the ones who had surgery, 90% survived. The common feature to all of the cases were the tracheal compression and the presence of calcification. The differential diagnosis included cystic hygroma which is generally fluctuant, congenital goiter, thyroglossal duct cyst and carcinoma of the thyroid. However, the calcifications were only found in the teratomas. We did have pelvic roentgenograms of the mother before delivery and showed the two infants in utero. The child with teratoma of the neck had an extended neck. Deflection of the neck has been discussed by Barnett and Nairn: they indicated that deflection of the neck or extension of the neck, particularly in the breech, can occasionally occur due to the apparent laxity of the maternal abdominal musculature.

A. Weinberg, M.D., Dallas, Texas: I wonder if we know whether these twins were dizygotic or monozygotic; one may consider the possibility of the hepatic tumor being metastatic from the cervical lesion in the twin that died through transplacental anastomoses.

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Dr. Rosenberg: Very few twins are born with teratomas, but among children born with teratomas the proportion of twins is about 10%.

Dr. Dunbar: We knew from the radiographs and the clinical findings that this child's liver was enormously enlarged by a tumor; that is all that a scan would have shown us.

R. F. Carter, M.D., Adelaide, South Australia: I want to ask Dr. Dunbar whether one would consider doing hepatic angiography if one were able to exclude such things as secondary neuroblastoma. I think in the more recent liver tumors we have had in the Children's at Adelaide, our radiologist has been rather keen to have this done, thinking that firstly, the actual vascular pattern of the tumor might be helpful in diagnosis, and secondly, of course, that this might help to delineate the tumor and make the surgeon's attempts at removal more effective and perhaps easier.

Dr. Dunbar: Dr. Carter's question is a very important one which we shall discuss in one of the cases to come.

B. Favara, M.D., Denver, Colorado: The evidence for liver tumors implies that we must consider alpha beta protein as a biochemical study too; this has been reported to be positive in not only primary liver tumors but other conditions including teratoma and may have only confused us in this case. Dr. Rosenberg, when does the presence of embryonal neuroblastic elements imply malignancy? What age do you use as your cut-off point?

Dr. Rosenberg: Dr. Favara, as you well know, that is a superb question and I am dying to hear the answer. I have really no particular idea about when one would ever interpret that as malignant. I personally doubt if I ever would. Generally when teratomas become malignant, they do not have this embryonal behavior. They are usually papillary or glandular, occasionally, we see large cell anaplastic forms, but I think it would be an extremely unusual form that would ever present just as an embryonal tumor of this sort.

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3. *Non-functional Intrathoracic Paraganglioma*

Contributed by **R. G. Vernon, M.D.** and **B. J. Holleran, M.D.,** Dubuque, Iowa

THE PATIENT was a 14-year old girl in May, 1971, when she complained of pain in the left shoulder. On physical examination the pain was attributed to playing volley ball; however, a grade II systolic murmur was heard in the left apical segment radiating to the base of the heart, suggesting pulmonic stenosis.

Dr. Dunbar: On a single left anterior oblique projection of the thorax, there is a sharply defined approximately spherical, slightly lobulated non-calcified mass projecting into the thorax from the left upper posterolateral chest wall. The angle made by the mass with the thoracic wall is obtuse. The lung vasculature is not altered, and there is no inflammatory reaction contiguous to the mass nor elsewhere in the lungs. There is no evidence of hilar or other mediastinal lymph node enlargement. The third rib postero-laterally shows slight thinning contiguous to the mass, with likely slight subperiosteal new bone formation. The second rib laterally, and approximately at the center of the presumed site of origin of the mass, shows subperiosteal new bone formation, slight widening, and irregular sclerosis. There is likely a soft tissue mass externally overlying this abnormal left second rib, and elevating the scapula slightly. This external soft tissue mass is not calcified. The remainder of the bones in the thorax and those of the shoulder are intact. The spleen and liver are not visualized, and there is no evidence of pleural reaction elsewhere in the thorax.

It must first be decided whether the mass is originating in the lung or in the chest wall. The configuration, location, associated pleural reaction, and the angle made with the thoracic wall, in addition to the lesion in the second rib, all strongly suggest that the mass originates in the second rib. The differential diagnosis must include inflammatory and neoplastic lesions, primary or secondary. Inflammatory (osteomyelitis) seems unlikely because of the predominantly sclerotic nature of the lesion without sinuses or sequestrae and because of the disparity between the mass size and the rib involvement. Secondary (metastatic) neoplasm is not likely because of the large size of this solitary thoracic wall mass without evidence of other lesions

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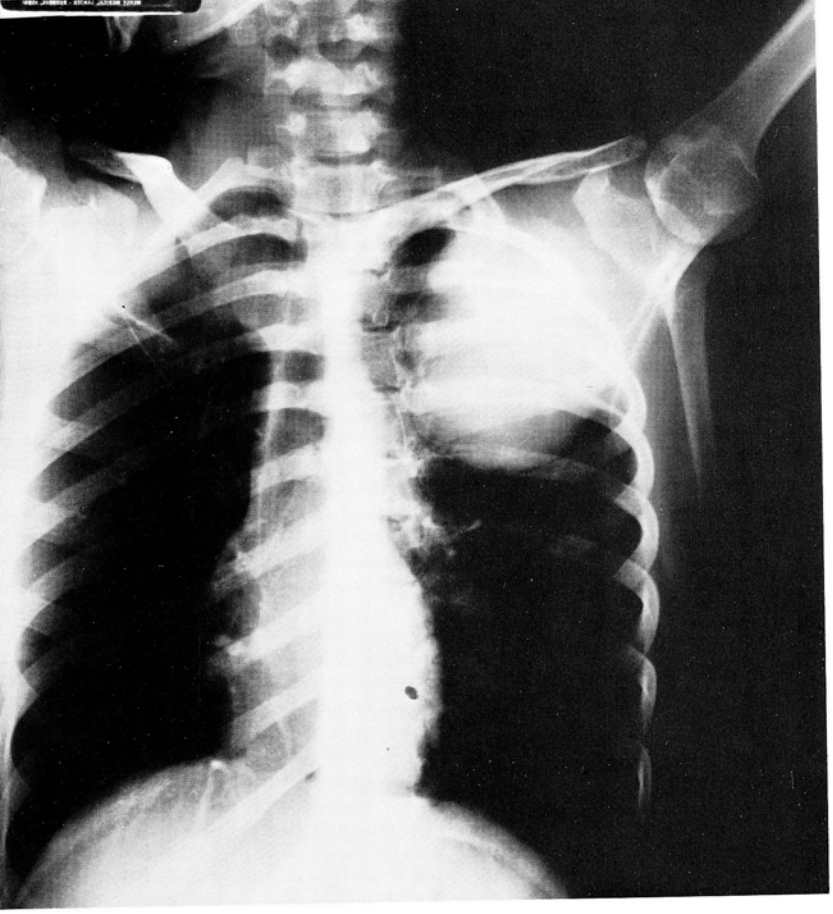

Fig. 1—Sharply defined apical mass.

in the lungs or visible bones. A primary tumor of the rib thus seems most likely. The child's age, the diaphyseal involvement of the rib, the sub-periosteal new bone formation, are all consistent with a Ewing's tumor, but the sclerosis and the likely associated soft tissue mass are more in favor of osteogenic sarcoma. A benign lesion such as an eosinophilic granuloma, osteoid osteoma or osteoblastoma would likely have a lytic component which seems to be missing.

Dr. Dunbar's impression: EWING'S TUMOR LEFT SECOND RIB.

Roentgenologic impressions submitted by mail:

Ewing's tumor	23
A-V malformation	14
Hemangiopericytoma	12
Rhabdomyosarcoma	11
Chondrosarcoma	9
Neurofibroma	8
Others	23

Dr. Dunbar: Ewing's tumor was the most favored. An A-V malformation frankly didn't occur to me; an A-V aneurysm affecting the left second rib seems to me to be unlikely on the clinical and the roentgen evidence. A hemangiopericytoma is possible; it is a vascular lesion and one might expect that there would be vascular changes in the related lung or hilus. A rhabdomyosarcoma is, of course, possible, but I am assuming from the evidence that this is a lesion which is arising in the rib and not in the related soft tissues. The rib is enlarged slightly, irregularly sclerotic, a rhabdomyosarcoma usually originates in soft tissues and would tend to destroy or erode the rib, not produce this apparently inherent or intrinsic change in the rib. Chondrosarcoma usually produces a lytic change in the rib and characteristically with some intraosseous calcifications within that lysis; the age is wrong for that lesion. A neurofibroma tends to be multiple; there tends to be some evidence of neurofibromatous lesions elsewhere in the thoracic bones and a huge mass like this is quite unlikely in neurofibromatosis.

Dr. Regato: Dr. E. C. Hwa, of Newton, Kansas, suggested a chondromyxoid fibroma of the rib. Dr. Benjamin Felson, of Cincinnati, offered an impression of Gorham's disease (vanishing tumor or "angioma") of the rib. Dr. D. H. Kersey, of Colorado Springs, suggested Ewing's sarcoma. Dr. R. E. Wesenberg, of Denver, preferred neurofibrosarcoma.

Operative findings: On May 12, 1971, a thoracotomy was done and a tumor was found on the chest wall over the apex of the left lung in the area of the first to the third rib. The tumor was attached to the lung; resection of the mass and of the invaded portion of the lung caused considerable blood loss. The specimen measured 7.5 cm in diameter and weighed 210 gm. The growth was reddish-brown in color; both the parietal and visceral pleura were involved.

Dr. Rosenberg: The tumor extends into the pleura but not into the underlying edematous, compressed lung. An indistinct, vascular trabecular pattern divides the tumor into incomplete lobules. The larger lobules are separated by delicate vascular trabeculae into indistinct clusters some of which are solid while others have a pseudoacinar pattern due to central degeneration. Some solid areas contain uniform cells with an abundant eosinophilic coarsely granular cytoplasm and lightly stained, granular nuclear chromatin. A few cells contain a single large nucleolus.

Pleomorphism makes up most of the tumor with large cells, some multinucleated, hyperchromatic nuclei, and giant clear nucleoli. Some cells have eosinophilic nucleoli or large lacunae due to inclusions of cytoplasm in an apparently indented nucleus. Mitoses are not identified. The cytoplasm of some cells contains yellow-brown pigment which varies in concentration from fine granules to dense aggregates obscuring the nucleus. Small clusters of lymphocytes and plasma cells occupy the trabeculae and the fibrous capsule. Tongues of neoplasm extend into the capsule and into capsular blood vessels.

A small amount of fat lies adjacent to some muscle on the external aspect of the tumor. This is mature fat, not brown fat.

In the Fontana-Masson preparations the pigment stains quite densely with moderate variation from light yellow-brown to dark brown. In a single area, fine crystalline fragments of yellow-brown material within a single cell and in an extracellular location is more refractile than the granular elements and is confined to a portion of the cytoplasm. The crystals in the single cell did not take the PAS stain. The entire cell population stained very weakly with PAS, but the pigment granules were red-brown and accentuated. In an isolated focus, a hyaline extracellular droplet was PAS positive.

Histologically the pigment and pleomorphism require consideration of a malignant melanoma. Up to 1970, fewer than 50 cases had been reported, none from Texas Children's Hospital. Metastases may occur without a conspicuous primary lesion but the usual metastatic melanoma contains mitoses, a lymphocytic infiltrate, and a greater tendency toward spindle cell arrangement. The nonspecific Fontana-Masson stain indicates a melanin-like pigment but cannot establish an unequivocal diagnosis of melanoma.

The morphology, histology, cytology, and pigmentation bring us to the consideration of a lesion of the chromaffin

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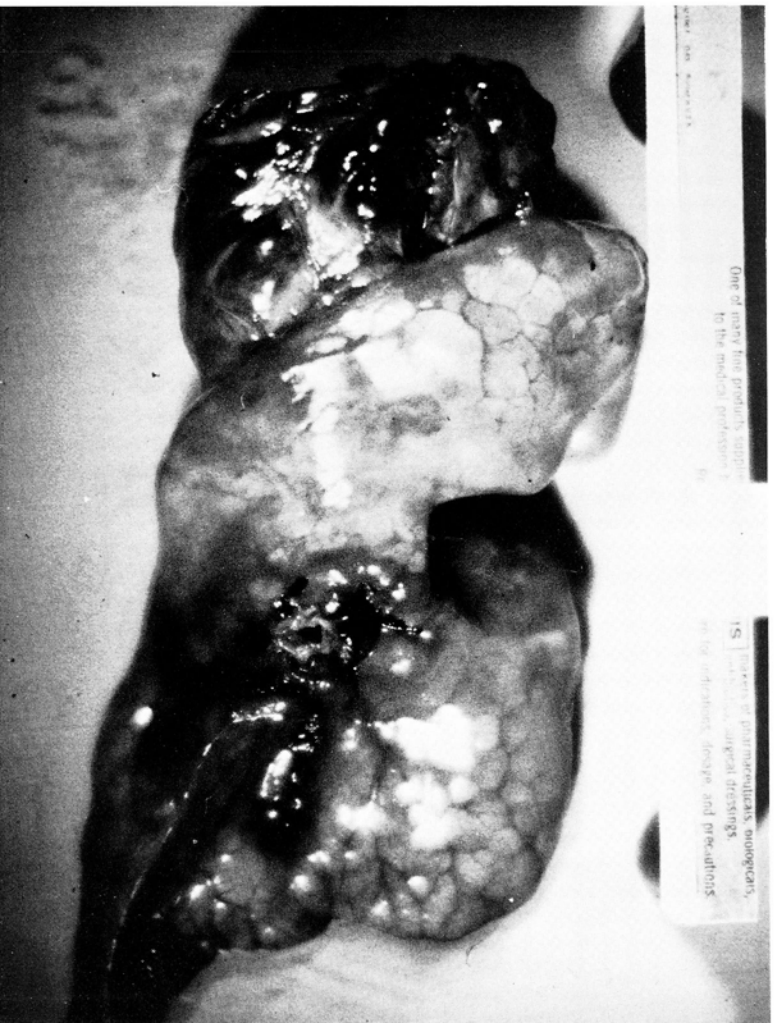
and chemoreceptor systems. Neither chromaffin nor nonchromaffin tissue would normally be expected in the upper lateral thorax. Chromaffin tissue would be more likely in the posterior mediastinum along the sympathetic trunk. Nonchromaffin paraganglia such as the aortic bodies occur about the ductus arteriosus, the pulmonary artery, the root of the bracheocephalic artery, and at the aortic arch. Although nonchromaffin paraganglia are not typically associated with the extra pleural space, they have been identified in various soft tissues and their presence has been inferred by the occurrence of soft tissue paragangliomas. Without considering the odd anatomic site, the morphology strongly suggests either a pheochromocytoma or a chemodectoma.

Is there a distinction between pheochromocytoma and chemodectoma and can we make it? Classically, the chromaffin positive tissues and the tumors derived from them produce catecholamines, associate with efferent sympathetic nerves, and have no chemoreceptor function. Chromaffin negative tissues and their tumors have no endocrine function, have efferent cranial nerve, and do have a chemoreceptor function. The distinction, based so arbitrarily on the chromaffin reaction, should be considered as to its specificity. The chromaffin reaction results from the oxidation of catechols and catecholamines by potassium dichromate or potassium iodate producing a dark brown color in the presence of epinephrine or a light tan or yellow color with norepinephrine. The test must be performed promptly on fresh unfixed tissues since the pigment is water soluble and removed by formalin. The usual fixation, as performed in the present case, obviates the chromaffin reaction.

Fig. 2—Surgical specimen; tumor was attached to the lung and the parietal and visceral pleura.



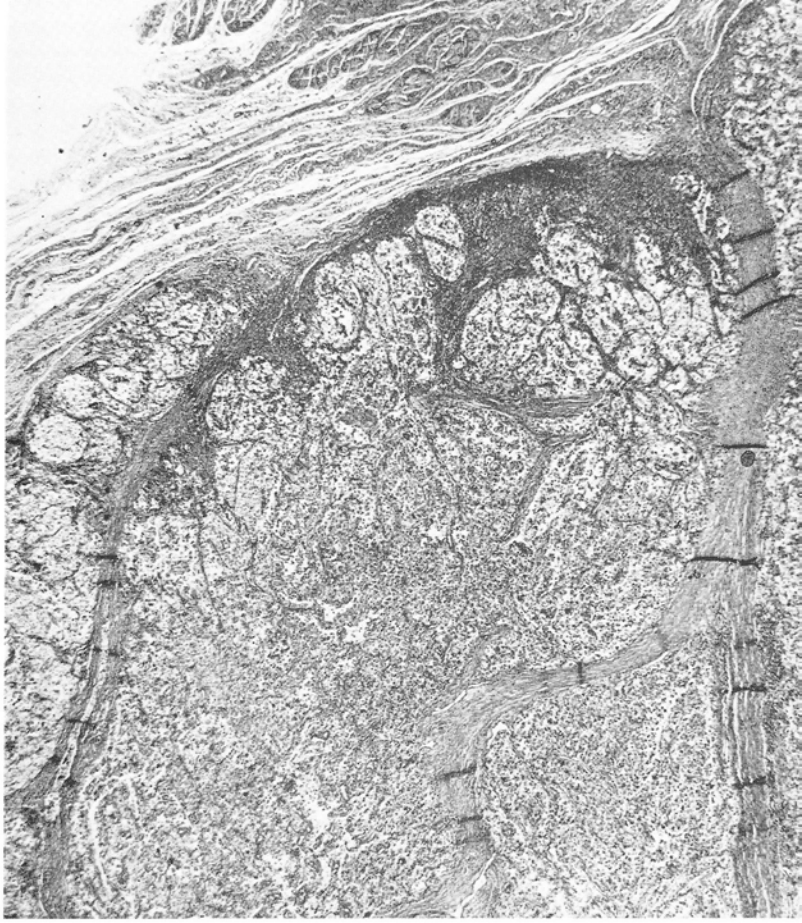


Fig. 3—Fibrous trabeculae extend inward from the capsule dividing the tumor into lobules. A small amount of mature fat lies in the striated muscle outside the capsule. (Hematoxylin-eosin, X21).

The classic distinction between chromaffin positive and negative tissues has been obscured by the demonstration of intermediate forms. Catecholamines have been detected in nonchromaffin tissues by more sensitive techniques such as formalin induced flourescence. The neurodectodermal origin of both the chemoreceptor and the chromaffin tissue give them both the biochemical potential of catechol formation. A clinico-pathologic classification proposed by Abell, Hart and Olson uses the chromaffin reaction as an arbitrary dividing line for functional and nonfunctional, chromaffin and nonchromaffin tumors. Chromaffin positive tumors are functional or nonfunctional pheochromocytoma; chromaffin negative tumors are functional or nonfunctional chemodectomas. The histology does not distinguish between those that do and those that do not function.

The definition of malignancy in chemodectoma and pheochromocytoma is difficult, if possible. Malignant tumors contain mitoses, necrosis, and giant cells but so do benign tumors. Anaplasia, capsular and blood vessel invasion are inapplicable since they occur in both benign and malignant forms. The critical criterion for malignancy is lymph node or distant metastasis. Even identification of metastases may be difficult since pheochromocytoma tends to be multicentric.

Metastatic adrenal cortical carcinoma presents a differential consideration although one would have expected true acini rather than pseudoacini. The cell droplets favors pheochromocytomas as does the scarcity of mitosis although the intense pigmentation may occur in adrenal cortical carcinoma.

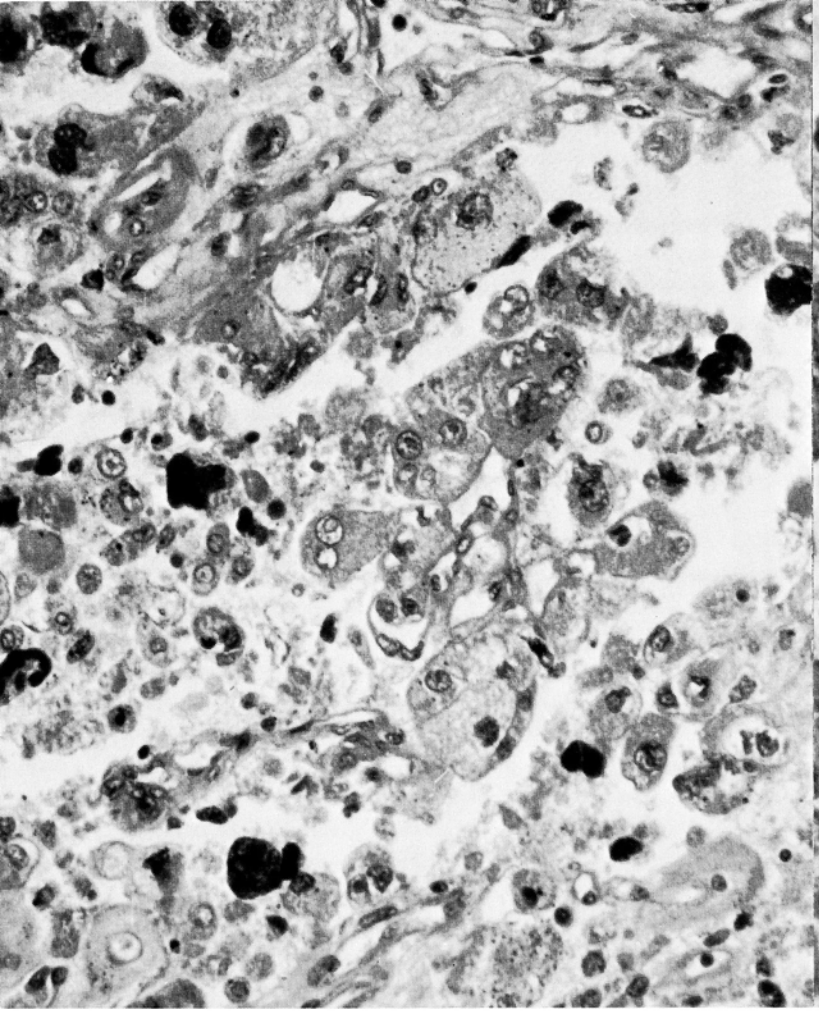


Fig. 4—Central degeneration in the lobules produces a pseudoacinar pattern with loose tumor cells occupying the center and cohesive tumor cells about the periphery suggesting epithelium. (Hematoxylin-eosin, X64).

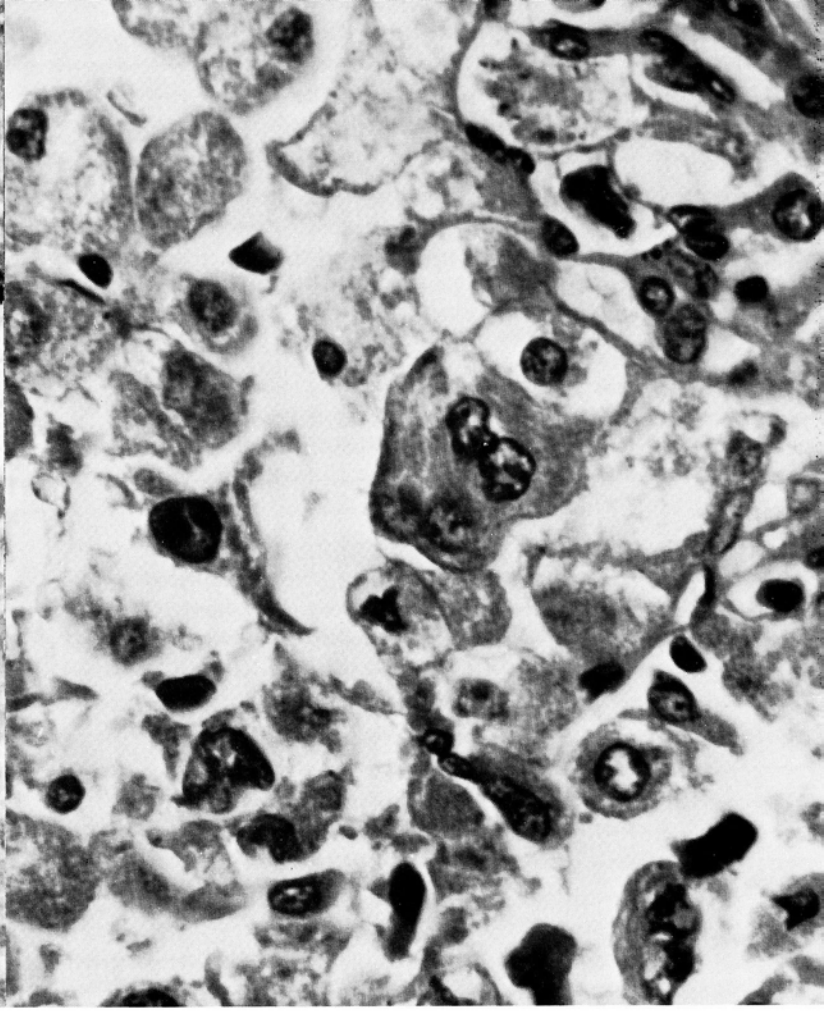


Fig. 5—The pleomorphic tumor cells have clear, granular, and occasionally pigmented cytoplasm. Many cells contain more than one nucleus. (Hematoxylin-eosin, X160).

The mature fat adjacent to the tumor casts further doubt on the functional nature of the lesion, already apparent from the clinical presentation. Functional pheochromocytoma usually associates with fetal fat.

In conclusion I am unable to identify this as chromaffin or non-chromaffin, but based on the position and lack of function, it seems more likely a chemodectoma. Despite the apparent invasion, anaplasia, and pleomorphism, this may well have a benign course.

Dr. Rosenberg's diagnosis: NON-FUNCTIONAL PARAGANGLIOMA.

Histopathologic diagnoses submitted by mail:

Alveolar soft parts sarcoma	35
Rhabdomyosarcoma	14
Metastatic melanoma	21
Metastatic carcinoma (embryonal, anaplastic, chorio, clear-cell, alveolar)	32
Malignant granular-cell myoblastoma	9
Paraganglioma	1
Others	10

Dr. Rosenberg: Alveolar soft parts sarcoma is certainly a lesion which can be substantiated. The basis for my rejecting this is what Fred Shipkey has taught me about this tumor, that there should be PAS positive, crystalline rods in the cytoplasm. If those are not essential to the diagnosis, then you can perhaps substantiate this; although the obvious close relationship of paraganglioma and alveolar soft parts sarcoma is probably generally accepted. An alveolar rhabdomyosarcoma is certainly a valid suggestion; yet, I didn't see in these alveoli any of the more characteristic strap cells going around the lobules. Metastatic melanoma is certainly a lesion which would cause a considerable amount of second thoughts. Melanomas do occur in children. There have been approximately 50 reported, but I have never seen one. The possibility of a metastatic tumor obviously exists, but I would have expected a more widespread dissemination. My Fontana stains revealed a red-brown pigment and not the black that we usually see; for that reason I have not accepted this diagnosis.

Dr. Regato: Dr. R. E. Stanford, of Denver, and J. Ray, Jr., of Lubbock, Texas, made a diagnosis of alveolar soft parts or rhabdomyosarcoma. Dr. F. Cabanne, of Dijon, offered malignant melanoma. Dr. Morgan Berthrong, of Colorado Springs, and Dr. Paul Gikas, of Ann Arbor, Michigan, also diagnosed metastatic melanoma. Dr. R. M. Sherwin, of Colorado Springs, preferred granular-cell myoblastoma. Dr. J. M. Kissane, of Saint Louis, offered metastatic carcinoma, possibly choriocarcinoma; he noted that the degree of anaplasia would be unusual for a kidney primary. Subsequently Dr. Kissane sacrificed his slide in order to identify the pigment; he observed that there is a lot of homosiderin but that the intracellular pigment granules do not stain for iron and are proven by the method of Fontana and Masson and therefore concluded to metastatic melano carcinoma.

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The contributors of this case had sought the opinion of Dr. D. C. Dahlin, of Rochester, Minnesota; he concluded to a diagnosis of malignant tumor, unclassified. Dr. Fred Stewart, of New York, wrote: "I don't really know what this lesion is. Some areas would fit my understanding of alveolar soft parts sarcoma but others not. It is malignant. Four people from our laboratory would not make a diagnosis." The opinion of the AFIP was also sought (Accession number 1380841): Colonel R. W. Morrissey rendered a report of poorly differentiated malignant neoplasm.

Subsequent history: In June, 1972, the patient showed no recurrence; she was active in her state high school golf tournament. On September 13, 1972, it was decided to reoperate in view of suspected residual tumor since the first operation and some evidence of recurrence.

Dr. Ternberg: One wonders whether radiotherapy and/or chemotherapy should have been instituted and, of course, that would depend upon your pathologist's diagnosis. If it is a metastatic lesion from a malignant melanoma, it probably won't make any difference, but if it is a soft parts or alveolar rhabdomyosarcoma, or such a tumor as this, then I think that this becomes an important consideration.

Dr. Dunbar: It seemed to me that the tumor at least involved and possibly originated from that left second rib. I wonder if it wouldn't have been wiser to remove that portion of the rib that seemed at least to be intimately involved in it, if not giving rise to the lesion.

B. J. Holleran, M.D., Dubuque, Iowa: After you have pumped nine units of blood over a 30-minute period into a 14-year-old girl, you are just happy to be able to close her up. I had a terrific problem at the time of surgery with bleeding and I elected to proceed no further. The resection was done in an extrapleural fashion, it peeled off the entire chest wall with the exception of the second rib and this was not removed with difficulty; I felt it did probably involve the second rib, but I elected at that time to wait and see. After operation the girl's "cardiac murmur" disappeared. The patient returned for a routine examination and on the roentgenogram of the chest there was an area of recurrence overlaying the second rib. I felt that further surgery must be undertaken and proceeded with a radical chest wall resection, removing the fourth, the third and the second rib, full thickness chest wall including the pectoralis minor muscle. There was no evidence of extension through the chest wall at the time of the first or of the second operation.

J. P. Moore, M.D., Lubbock, Texas: I would like to ask Dr. Rosenberg about the location; this was peripheral to the site that you usually see a paraganglioma. I would also like to ask if he has seen a paraganglioma arise in a peripheral nerve or a spinal nerve root?

Dr. Rosenberg: We have no paragangliomas in the files at Children's Hospital; there have been a small number of retroperitoneal paragangliomas described. In fact, recently some twenty have been described with a fairly high incidence of malignancy. You are absolutely correct that they should not be found this far distally; perhaps the furthest out one would expect would be in the region of the ductus and this one seems lateral to the lung. My conclusion, however, was based on the identification of paragangliomas in soft tissue, but not necessarily in relationship to nerves.

Dr. Holleran: Dr. del Regato, would you consider radiotherapy on this child at this point?

R. G. Vernon, M.D., Dubuque, Iowa: We are desperately looking for advice as to how to proceed at this point; this case is active presently and any words of advice would be very welcome.

Dr. Regato: I will have to be explicit about my answer to you: If I had been in Houston and the diagnosis of paraganglioma had been made in this case, I wouldn't have even been consulted as to any additional treatment for none would appear necessary. If I had been in 21 other institutions where the diagnosis of malignant melanoma was made, I wouldn't have been consulted because radiotherapy would have been thought to be useless. That is not necessarily a good generalization because malignant melanomas sometimes are radiosensitive although not necessarily radiocurable. And then, if I had been in 50 other institutions where a diagnosis of alveolar soft parts or alveolar rhabdomyosarcoma was done, then there was proper indication to do post-operative radiotherapy. In a child this age, one always proceeds with caution about doing radiotherapy over an extensive field, but with the latter diagnosis, one would have been justified to do post-operative radiotherapy for this has been done fruitfully in such cases. But as you see we are here behind the histopathology. These Seminars show the diversity of opinions that might be obtained on the same specimen; in our own individual hospitals, we are seldom aware, ourselves, our own pathologist, our own surgeons, are unaware of the fact that there might be such difference of opinion.

R. E. Stanford, M.D., Denver, Colorado: I would like to ask either Dr. Holleran or Dr. Vernon what the pathologic findings were of the second specimen. Whether the rib was involved and whether a chromaffin reaction was done?

Dr. Vernon: Yes, the rib appeared to be involved but in a secondary manner rather than a primary. It appeared that the tumor was invading into the rib rather than originating from the rib and extending.

M. Berthrong, M. D., Colorado Springs, Colorado: We certainly have disagreed widely or have different opinions and I think justifiably. But if I were sending this report, you would have received on this case a page and a half of evasive description and we would have warned you to take care of all of the possibilities that were listed.

Dr. Regato: Whether we have one diagnosis, one that is favored over several others or an equal choice of various possibilities, the fact remains that the decision as to post-operative radiotherapy in this case depends on the decision as to one of them.

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4. *Osteosarcoma of the Humerus*

Contributed by **A. O. Severance, M.D.** and **H. Elmendorf, M.D.,** San Antonio, Texas

THE PATIENT was a 15-year old boy in September, 1971, when he complained of pain in the left shoulder and arm. A diagnosis of tumor had been made and surgery advised, but refused. There was marked swelling of the arm and purulent discharge from the site of biopsy; there was also considerable edema of the forearm which had become functionless. The hemoglobin was 10 gm%; there were 17,000 WBC per cubic mm with 88% segmented forms.

Dr. Dunbar: The left mid and distal humeral diaphysis is partially destroyed by a lobe lesion exhibiting sclerosis, partial destruction of cortex, subperiosteal new bone formation, right angled bone spicule ("Sunburst") formation, and a huge mass with irregular plaques of calcification in the arm. The proximal forearm is partially visualized and is edematous. The distal humerus is not sufficiently visualized to identify or exclude metaphysial, epiphysial, or joint involvement. The proximal humeral diaphysis, metaphysis and epiphysis are intact, as is the shoulder joint.

There can be little doubt that this is a primary malignant tumor of the left humeral diaphysis. The patient is in the right age group for Ewing's tumor and osteogenic sarcoma, but the huge partially calcified soft tissue mass concentric to severe diaphysial involvement is typical of both these diseases. An angiosarcoma of bone is rare but does occur in this age, may produce a huge mass and profound circulatory impairment as well as extensive calcification. Neuroblastoma may occur at this age but is unlikely to produce such massive soft tissue calcification.

Dr. Dunbar's impression: ANGIOSARCOMA OF BONE

Roentgenologic impressions submitted by mail:

Osteosarcoma	65
Ewing's tumor	14
Chondrosarcoma	9
Others	5

Dr. Dunbar: Osteosarcoma was diagnosed by the great majority of the radiologists submitting diagnoses. The points against osteosarcoma are the huge nature of the ill defined soft tissue mass and the multiple calcifications, or ossifications, within the soft tissues surrounding the mass. Ewing's tumor is a perfectly good diagnosis particularly because of the age and the diaphysial involvement with the clinical story. Chondrosarcoma is unlikely for it tends to be very uncommon in this age group and usually produces initially a lytic lesion of bone having within it calcifications. This is a malignant lesion primary in that humeral diaphysis; while I have suggested angiosarcoma, I should say that the Ewing's tumor of bone in spite of its being atypical in this case, would be my second choice.

Dr. Regato: Most of our experts agreed in the diagnosis of osteosarcoma.

Operative findings: The patient had received palliative radiotherapy and chemotherapy without favorable results. On September 11, 1971 he had a palliative interscapulo-thoracic amputation. The mass measured 45 cm in diameter extending from the head of the humerus to below the elbow, destroying one-third of the ulna and radius. Thirty-one axillary nodes were found free of tumor.

Dr. Rosenberg: Most of the material, in the slides submitted to me, consisted of bright eosinophilic strands of collagen adjacent to a lacey organization resembling osteoid, and very little cellular detail. A few islands suggestive of cartilage and focal areas of intense calcification were scattered irregularly in the material resembling osteoid as well as in the loose, less well organized areas. The loosely arranged cellular elements were not well stained, presumably the result of degeneration. In a rare cellular island, poorly differentiated cells had relatively large, deeply staining nuclei and an abundant vacuolated cytoplasm. The poor preservation of cells in the cartilaginous and osteoid areas made determination of cytologic detail difficult.

Additional material obtained from Doctor Severance provided a much better opportunity for histologic examination. Nodules of tumor extended through the collagen into the adjacent muscle. Except for a few islands of cartilage within the cellular area, the elements were loosely arranged with broad areas of intercellular clearing suggesting edema. Most of the cells were mononuclear although an occasional cell was multinucleated. The nuclei were pleomorphic and densely stained. In several areas the anaplastic forms were in direct proximity to islands of brightly eosinophilic collagen interpreted as osteoid. In the intertrabecular space of the bone extensive deposition of osteoid surrounded the anaplastic cells.

In considering the differential diagnosis of this lesion, prudence dictates the correlation of all available clinical, radiologic, and pathologic features. We have all been admonished and pointed to with alarm against the tendency to interpret bone lesions from the histology without precise and close radiologic and clinical correlation. Benign lesions to be considered should include osteomyelitis, myositis ossificans, and other reactive bone lesions such as fracture callus. Misinterpretation of a fracture callus has gained sufficiently wide publicity as to unnerve many pathologists with a minimal exposure to bone tumors. Because of the general rarity of primary bone lesions, this minimal exposure probably includes most of us.

In consideration of a fracture callus, any clinical evidence of trauma would be of value. Unfortunately, the lack of history is not always consequential since the trauma could be relatively minor, particularly if the fracture callus were superimposed on a pathologic fracture through an existing lesion. Identification of a callus depends on a regular arrangement of osteoid trabeculae, a lining rim of osteoblasts, and a partially cellular intervening stroma. Unfortunately, atypism, mitotic figures, and a haphazard arrangement of osteoid may also occur. Confusion may also arise if there is an underlying lesion such as a cortical defect or an aneurysmal bone cyst.

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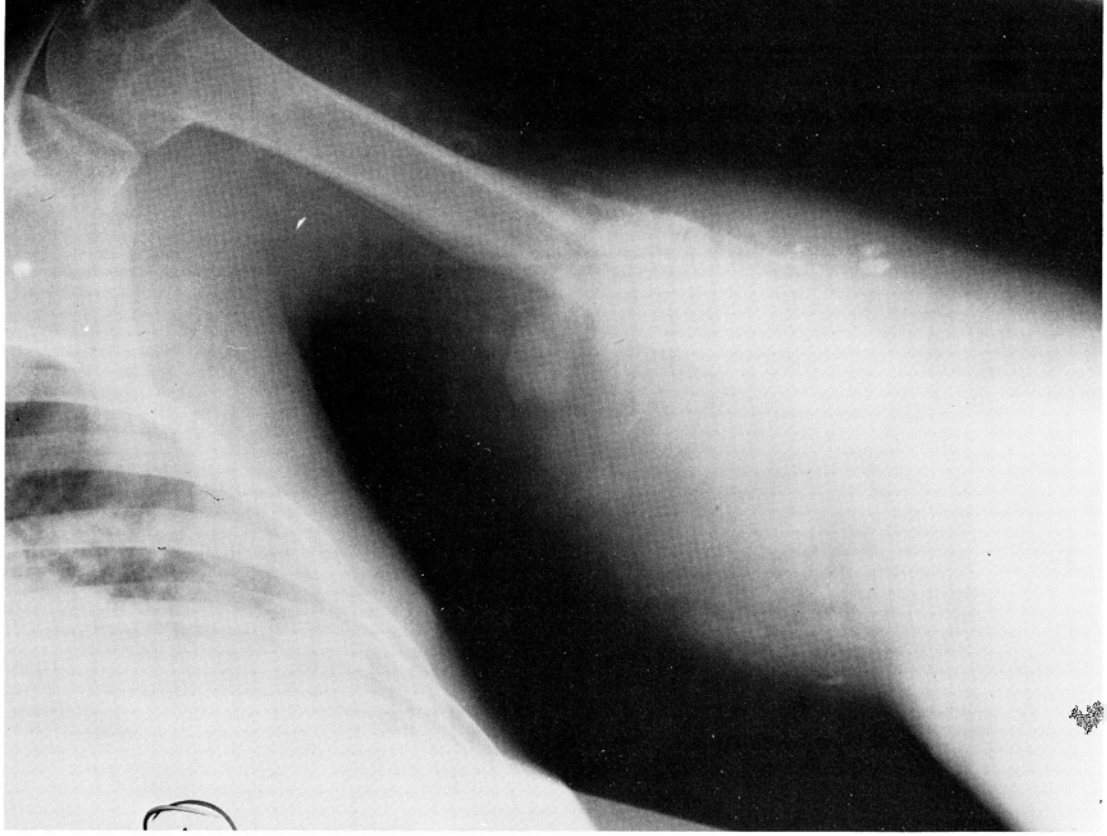

Fig. 1—Humeral diaphysis partially destroyed by mass showing subperiosteal bone formation.

In the present case of extensive necrosis, the anaplasia, the abundant peripheral cellularity with isolated strands of osteoid deposition suggest a malignant tumor. For the same reason, myositis ossificans does not appear a likely possibility. A history of trauma would also be of value in myositis ossificans but this may be relatively minor and a negative history is not always of value. A practical clue in myositis ossificans is the tendency toward peripheral organization of the trabeculae in contrast to the peripheral cellular proliferations in neoplasia. The absence of well defined acute or chronic inflammatory response would not support the presence of an inflammatory lesion. In the differential diagnosis, as described by Jaffe, a radio-opaque tumor, which had broken out of the cortex of the shaft end of a long bone in a patient 10-25 years old is almost certainly an osteosarcoma.

Clinically, this young man falls in the proper age group for osteosarcoma since the peak incidence is between 10 and 25 years with 75% of osteosarcoma occurring in this age period. The sex ratio also favors osteosarcoma since approximately twice as many males as females are affected by osteosarcoma. The location is atypical since an estimated 50 to 70% of osteosarcoma occur about the knee and most of the remainder occur at the proximal humerus. Although nonspecific, pain is a characteristic early symptom.

The lesion is interpreted as an osteosarcoma characterized by direct formation of osteoid by malignant osteoblasts without an intermediate matrix. Some brief mention of terminology may be necessary for purposes of communication. The term osteosarcoma refers to the specific tumor forming osteoid and contrasts with the term osteogenic sarcoma which could include other lesions in which bone is formed, such as fibrosarcoma and chondrosarcoma. Dahlin and Price describe osteoblastic, chondroblastic, and fibroblastic sub-groups depending on the outstanding feature of the tumor as to bone production, cartilage production, or fibrous proliferation. The prognosis, generally bad, seems slightly better in those which are primarily fibrous and worse in those which are primarily osteoid producing. The five year survival is variously described as 5 to 20%. Duration of symptoms varies inversely with survival. The shorter the symptom period, the higher the mortality, suggesting an increased aggressive nature.

Mention was made of the negative lymph nodes in the axilla of this present case. Osteosarcoma metastasized to lymph nodes in 3% of cases; metastases are usually hematogenous to the lung. Tumor emboli leave the primary mass to metastasize with apparent ease. Biopsy of the lesion, manipulation, and even palpation increases the number of tumor cells in the blood draining the tumor. Although tumor cells appear in the venous blood draining the tumor, they do not appear in the peripheral blood and are assumed to be filtered out in the lung. Several therapeutic regimes reflect attempts to overcome this ease with which tumor emboli spread: double tourniquets, preoperative radiation, and inhibition of manipulation. Despite the acknowledged dissemination of tumor cells, biopsy does not seem to adversely affect prognosis.

Dr. Rosenberg's diagnosis: OSTEOSARCOMA

Histopathologic diagnoses submitted by mail:

Osteosarcoma	75
Chondrosarcoma	30
Osteochondrosarcoma	6
Chrondromyxo, myxofibro, etc.	5
Others	8

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Fig. 2—Cross section of the forearm showing gross involvement of bones.

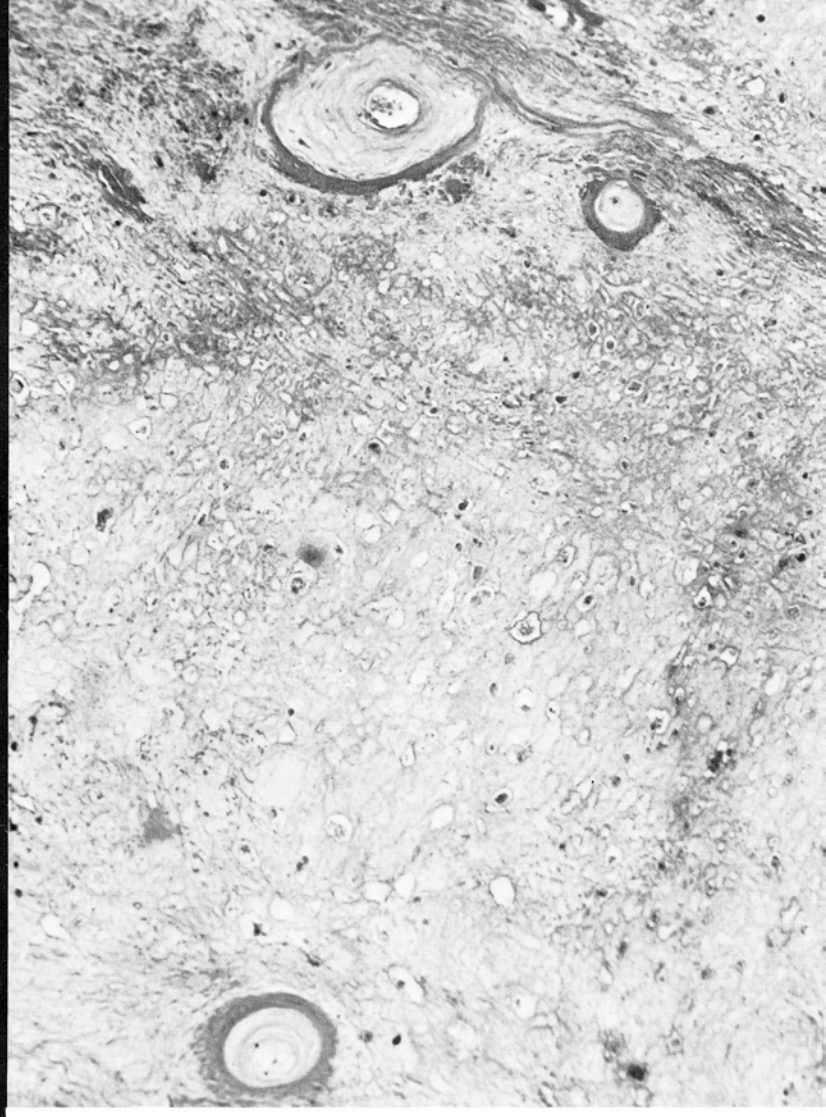

Fig. 3—Much of the tumor has sheets of poorly cellular osteoid, and thin calcified strands sometimes arranged concentrically about blood vessels. (Hematoxlyn-eosin, X25).

Dr. Rosenberg: The designation chondrosarcoma undoubtedly is based on the considerable amount of cartilage; the identification of osteoid among the malignant cells would suggest that this is really an osteosarcoma with a chondroplastic component, and not a chondrosarcoma. There are components, particularly in the invasive areas, that do look like a chondromyxofibroma, but I am unaware of this degree of invasiveness and malignancy in a chondromyxofibroma.

Dr. Regato: Drs. D. Assor, of Columbus, Ohio, and E. Bemis, of Milwaukee, also made a diagnosis of osteosarcoma. Dr. R. A. Brooks, of Phoenix, Arizona, submitted a "composite" diagnosis of pathologists at his hospital, who called it a chondroblastic type of osteosarcoma. Drs. L. J. Clowry, of Milwaukee, and J. M. Hori, of Columbia, Missouri, and D. M. Lang, of Sioux Falls, preferred chondrosarcoma.

Subsequent history: On October 25, 1971, the patient expired. No autopsy was done.

Dr. Dunbar: The chest shows multiple tumors in the lungs with bilateral pleural reaction. There is enlargement of hilar lymph nodes bilaterally, and of upper mediastinal lymph nodes, with displacement and narrowing of the trachea. The bones of the thorax are imperfectly visualized but likely intact. The spleen is not enlarged, and the liver incompletely shown.

Dr. Ternberg: Biopsy in this type of a lesion is a delicate operation because one needs to get an accurate specimen; it is going to make some difference as to how the child is going to be treated. In an osteosarcoma, amputation should be recommended early, yet the parents should be informed that the result may only be palliative. This is an important aspect of tumor surgery in children.

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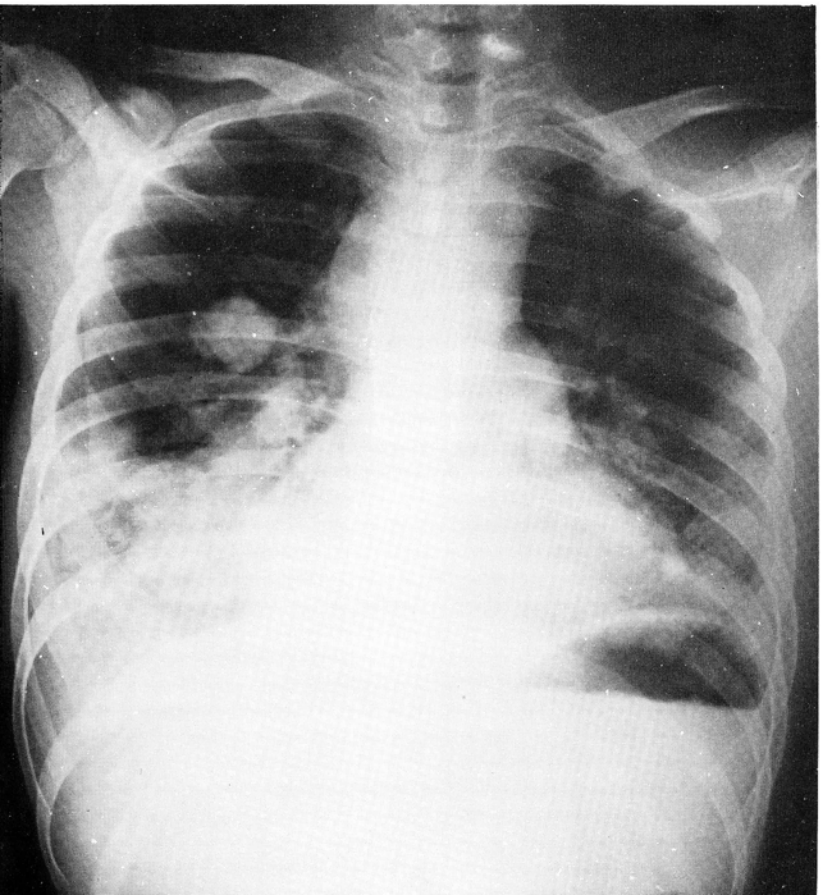
Fig. 4—Within the filigree pattern of osteoid, the cells have varying sizes and shapes, most with large hyperchromatic nuclei and foamy cytoplasm. (Hematoxylin-eosin, X64).

Fig. 5—In the few cellular areas of the tumor there is little evidence of differentiation. The cells are uniform with round or angular nuclei and elongated cytoplasmic strands arranged about unstained clear spaces. (Hematoxylin-eosin, X64).

Fig. 6—Pulmonary metastases from osteosarcoma.



Dr. Regato: The sad part of this is that sometimes the amputation is not accepted on the basis of the rather low curative possibility whereas it may have to be accepted as a palliative procedure later on, as in this instance.

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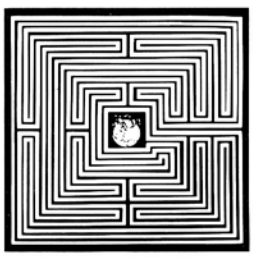


5. *Aneurysmal Cyst of the Ulna*

Contributed by **A. O. Severance, M.D.** and **H. Elmendorf, M.D.,** San Antonio, Texas

THE PATIENT was a 17-year old boy in October, 1971, when he complained of pain and swelling of the left elbow following a football injury; a similar episode of pain and swelling had occurred one year previously. On examination there was a large tumefaction on the medial aspect of the left elbow with limitation of movement. The alkaline phosphatase was 151 mg % and phosphorus 5.5 mg %.

Dr. Dunbar: There is a lytic and markedly expansile lesion of the proximal ulnar shaft, with at least one pathologic fracture. The transitional zone is sharply defined, as is the ballooned, thinned and lobulated cortical margin. There is deformity of the contiguous soft tissues, caused by the protruding bone lesion, but no evidence of calcification, mass or hypervascularity of the contiguous soft tissues. Sub-periosteal new bone formation is present in the ulnar shaft distal to the lesion, and some sclerosis in the shaft proximal and distal to the lesion. There is no tumor bone formation, and no calcification within the lesion. The sharp margination characteristic of most of the lesion changes to ill-defined sclerotic margination inferolaterally. There may be a joint effusion in the elbow. The humerus and radius are intact. The proximal ulnar epiphyses have fused with the shaft and are not involved.

In spite of the sclerosis and sub-periosteal new bone formation which have been excited in the adjacent bone, it is almost certain that this is a benign lesion. It is highly likely that hemorrhage has occurred or recurred to produce the ballooned sharply marginated lobulated configuration of the bone lesion, as well as the adjacent sclerosis and sub-periosteal new bone formation. The history of a similar episode one year previously reinforces the impression that it is a benign lesion and that hemorrhage has contributed to its gross characteristics.

There are two hemorrhagic bone lesions which could produce this result; aneurysmal bone cyst or haemophilia. The possible involvement of the elbow joint and the history of a similar episode previously are somewhat in favor of haemophilia, and haemophilia is known to be an imitator of bone neoplasm. The ballooned, lobulated thin walled expansile lesion, on the other hand, is more likely due to an aneurysmal bone cyst. A simple cyst of bone does not usually produce such massive expansion with thin wall, and is usually in younger patients and immediately on the diaphysial side of an unclosed epiphysial plate.

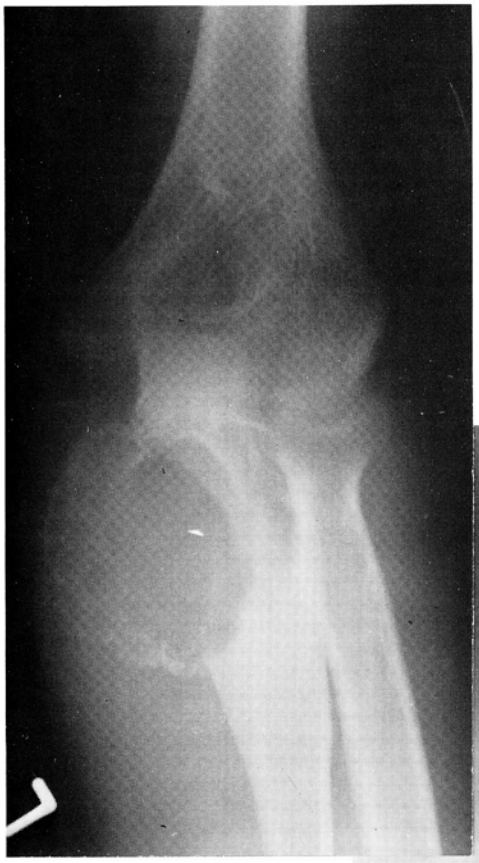
Dr. Dunbar's impression: ANEURYSMAL BONE CYST

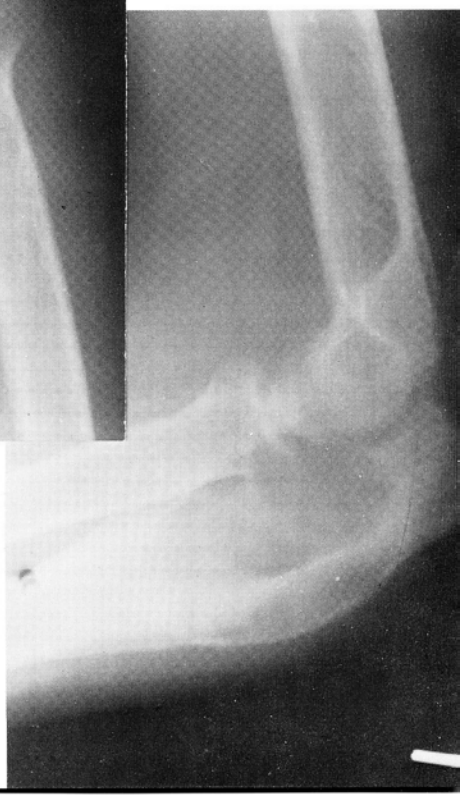
Roentgenologic impressions submitted by mail:

Aneurysmal bone cyst	45
Chondrosarcoma	8
Parosteal sarcoma	7
Giant-cell tumor	5
Brown tumor	5
Others	24

Dr. Dunbar: We are agreed in this initial impression. The absence of tumor bone formation, the absence of a soft tissue mass or invasion of the soft tissues, are against a malignant lesion in spite of some of the modifying characteristics, that is the contiguous sclerosis and the loss of definition in some areas. Parosteal sarcoma is uncommon but not rare in childhood; it usually produces ossification and/or calcification around the bone and is usually separated from the shaft of the bone by a thin radiolucent margin. A giant-cell tumor at this child's age would be exceedingly rare and almost invariably crosses the metaphysis to involve the epiphysis. A 17-year old boy does indeed come within the possible age of

Fig. 1 and 2—Expansile sharply defined lytic lesion in the proximal ulnar shaft.





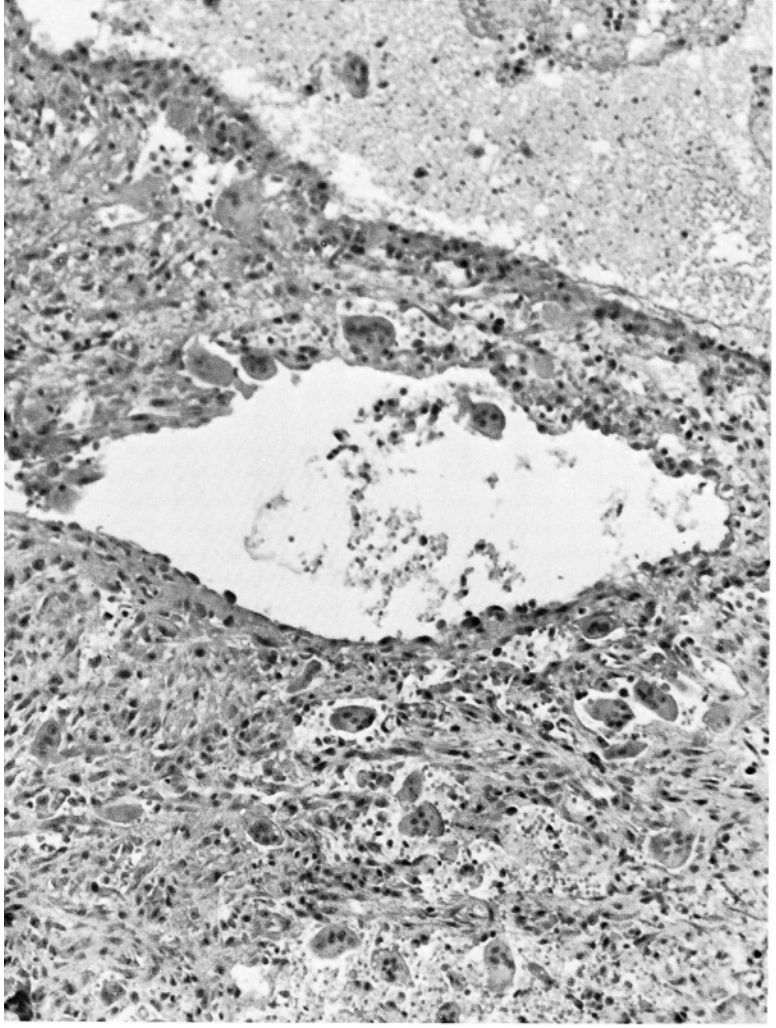


Fig. 3—Of the large and small vascular spaces, some are vacant, some contain blood, and some contain granular material resembling lymph. Multinucleated giant cells are prominent in the stroma and in the lining of the vascular spaces. (Hematoxylin-eosin, X25).

distribution, but the location of the lesion which doesn't involve the epiphysis is very much, in my opinion, against that diagnosis. A brown tumor would not be likely to occur in a child; it would have to be associated with hyperparathyroidism. There is nothing on these films that suggest the subparosteal resorption that is characteristic of hyperparathyroidism; we do not have the calcium level which should be high.

Dr. Regato: Most of our experts agreed with Dr. Dunbar in their diagnostic impression of aneurysmal bone cyst.

Operative findings: On November 3, 1971, a bone cyst was found and curetted; a bone graft was placed. The surgical specimen consisted of numerous fragments of grayish-tan soft tissue and bone showing cystic areas with an aggregate measuring 5 x 4.5 cm and another 3.5 x 1.5 cm.

Dr. Rosenberg: Several large and small channels appear at sporadic intervals in a sheet of connective tissue containing a few islands of bone in irregular sizes and shapes. The bone fragments vary considerably in cellularity with some sparsely populated with osteocytes while others are densely populated. Most of the bone fragments have a distinct osteoblastic layer about the periphery but a few trabeculae lack this distinct layer. Most of the bone fragments have a lamellar pattern, but some of the smaller, irregular fragments have a woven pattern suggesting new bone formation.

The densely cellular stroma has localized areas of fibrosis, some areas with collagen deposition, and many areas with clusters of large multinucleated giant cells. In several areas the multinucleated giant cells line the channels. The interstitium contains focal fresh hemorrhage. The vascular channels have outlines which are variously made up of fibrous tissue, trabeculae, osteoid, and granulation tissue. Many of the channels are vacant while others contain an eosinophilic granular material resembling lymph. A few mononuclear inflammatory cells extend irregularly through the stroma. Rare large mononuclear cells in mitosis are identified.

The interpretation must reflect the age, sex, roentgenologic appearance and clinical information. A fibrous cortical defect or a nonossifying fibroma would not likely cause this degree of peripheral expansion; nor would they be accompanied by the large vascular spaces or the new bone formation. Fibrous dysplasia contains bone trabeculae with a woven pattern without a peripheral layer of osteoblasts. While the tumor does contain giant cells, this is not a giant cell tumor of bone, a lesion which only rarely occurs prior to the age of 20.

The vascular channels in the fibrous stroma characterize the lesion as an aneurysmal bone cyst. This lesion characteristically occupies the metaphyses of long bones, vertebrae, and flat bones sparing the epiphysis. The clinical evidence of swelling, pain and tenderness are typical. Aneurysmal bone cysts expand the cortex while preserving a thin peripheral layer unless a pathological fracture distorts the cortex. The age range is typical in that 80% of patients are less than 20 years of age.

Having proposed the diagnosis of aneurysmal bone cyst, is this enough? Can aneurysmal bone cyst accompany another lesion? This association currently represents a controversal consideration in that some series suggested an incidence of 32% associated lesions with aneurysmal bone cysts while others report no associated lesions. Assuming that other lesions may accompany aneurysmal bone cyst, all the lesions initially considered in the differential diagnosis must be reconsidered. The possibility of each is again eliminated on the same basis but with less certainty when considering the alteration produced by a superimposed lesion. The large numbers of multinucleated giant cells do not present an anaplastic pattern. The possibility of an osteosarcoma cannot be supported by this histology. In summary, this lesion is interpreted as an isolated aneurysmal bone cyst without definite evidence of a pre-existing lesion.

Dr. Rosenberg's diagnosis: ANEURYSMAL BONE CYST

Histopathologic diagnoses submitted by mail:

Aneurysmal bone cyst	68
Giant-cell tumor	21
Osteosarcoma	18
Various, benign	12

Dr. Rosenberg: Giant-cell tumor is a well taken diagnosis; but the presence of such tumor prior to age 20 would be extremely uncommon; there is a much higher content of fibrous stroma here. I did not see the one criterion I would want in osteosarcoma, namely the direct formation of osteoid by malignant cells.

Dr. Regato: Dr. D. L. Dawson, of Colorado Springs, also made a diagnosis of aneurysmal bone cyst, with callus. Dr. L. Lowbeer, of Tulsa, made a diagnosis of benign osteoblastoma. Dr. R. W. Wahl, of Fort Sam

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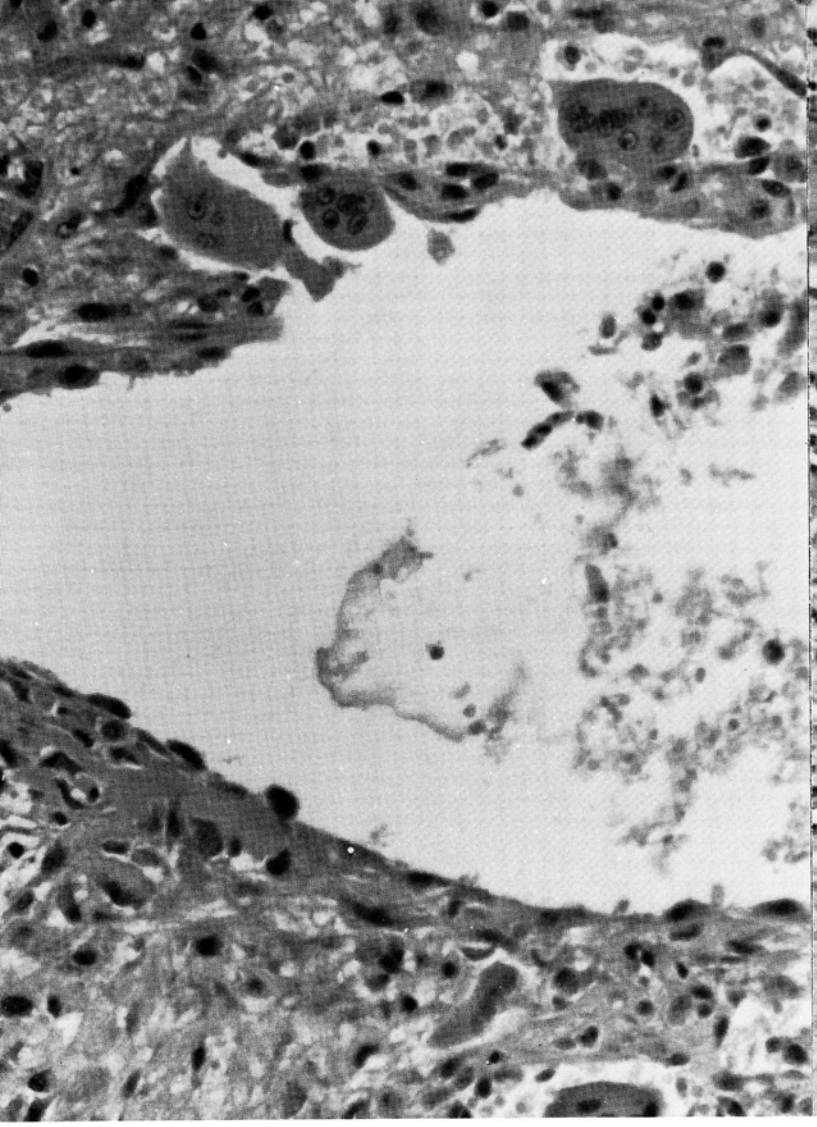

Fig. 4—Many of the vascular spaces are lined by fibroblasts and have giant cells protruding into the lumen. (Hematoxylin-eosin, X160)

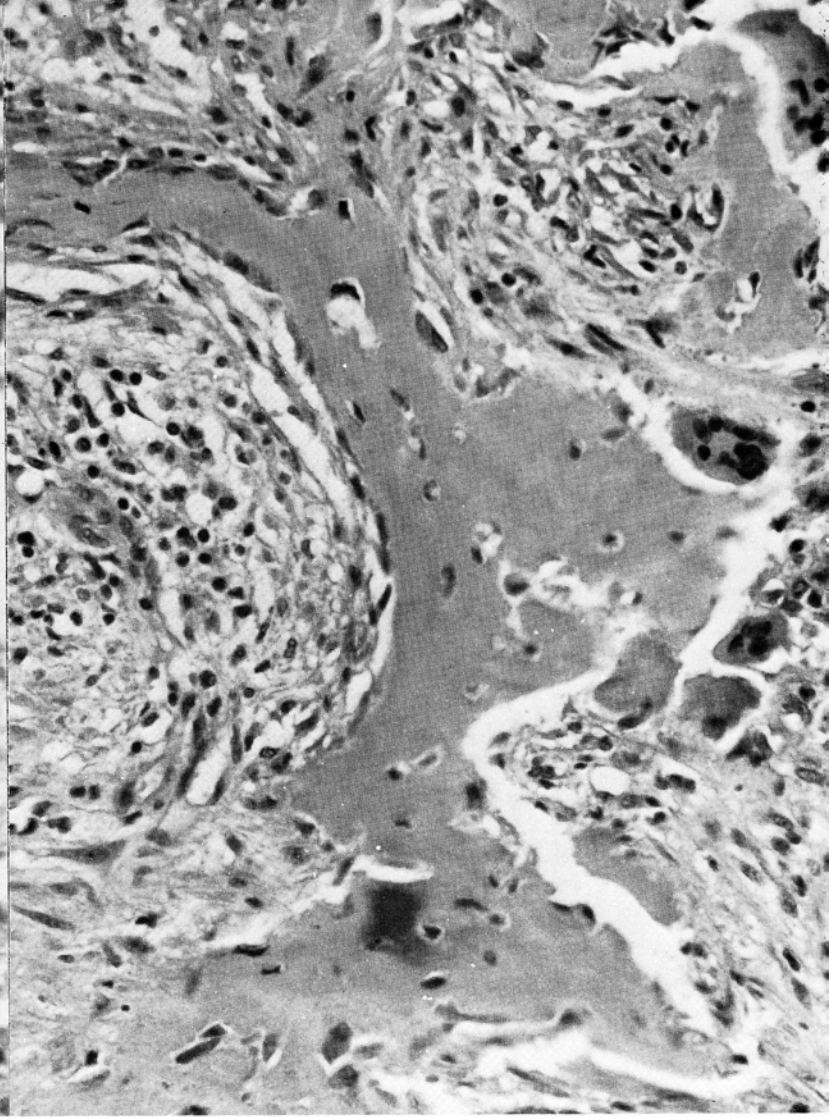

Fig. 5—Most of the bone fragments are surrounded by an orderly rim of osteoblasts. (Hematoxylin-eosin, X64).

Houston, Texas, offered ossifying fibroma; Dr. R. M. Sherwin, of Colorado Springs, brown tumor of hyperparathyroidism; Dr. F. P. Bornstein, of El Paso, giant-cell tumor; Dr. H. Hamperl, of Bonn, Germany, offered malignant giant-cell tumor and Dr. J. McQuaid, of San Diego, osteosarcoma.

Subsequent history: On October 24, 1972 Dr. Pedro Quiroga reported that the patient has normal function of the elbow, no pain and no other difficulty. The roentgenogram of the elbow shows that the cystic lesion has now been filled with bone.

Dr. Ternberg: Dr. Dunbar, I could assure you that the child does not have hemophilia, can I simply go ahead on the basis of your diagnosis and curette this lesion or need I worry about it being something else? Dr. Rosenberg, are these giant-cells similar to those we see in chronic inflammatory lesions, as in biliary atresia?

Dr. Dunbar: I think the evidence is all in favor of a benign lesion and then it would be of obvious importance to do chest roentgenograms and a skeletal survey, as well, of course, as a careful physical examination to be sure that there is no evidence of any other lesion anywhere else. Having done those things, it is my opinion that one could curette this lesion with a fair degree of confidence.

Dr. Rosenberg: That is an interesting point, the similarity of these giant cells to those that are encountered in the liver. They are certainly not the same cell, but perhaps the process could be interpreted as the same. They do seem to be syncytial; in this case they are syncytial of the fibroblasts making up the stroma of the aneurysmal bone cyst. In giant-cell transformation of the liver they are apparently syncytial of the parenchymal hepatic cells, but I think at that point the similarity ends.

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6. *Undifferentiated-cell, Potentially Malignant Tumor of the Pancreas in a 4-year old child*

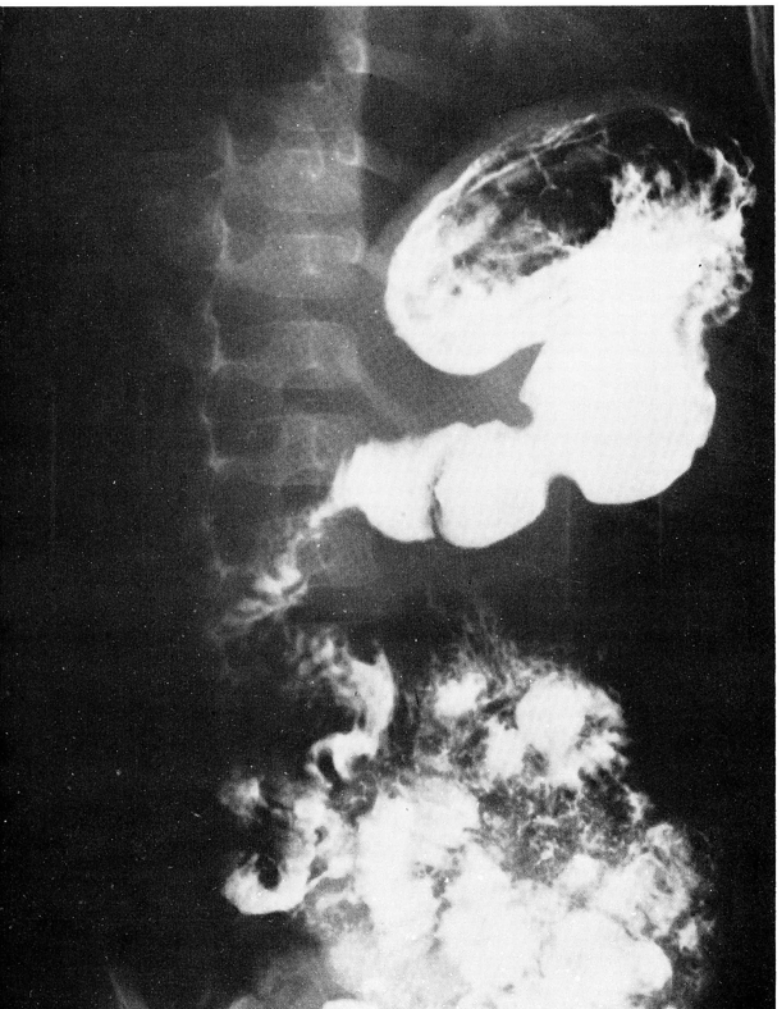
Contributed by **W. C. Bucher, Jr., M.D.** and **E. Blizard, M.D.,** Denver, Colorado

THE PATIENT was a 4-year old girl in May, 1971, when her mother felt a lump in her abdomen. On examination a 5 x7 cm non-tender mass could be felt in the left upper abdominal quadrant. SMA-12 and SMA-6, CBC and urine were all within normal limits.

Dr. Dunbar: There are some defects which resemble polyps in the gastric fundus, but they are likely caused by normal mucosa and gas bubbles.

The distal body and antrum of the stomach and the duodenal cap are elevated and the duodeno-jejunal junction is depressed by a soft tissue and non-calcified, ill-defined mass, which also slightly depresses the transverse colon. The gut is not invaded, ulcerated or obstructed. The stomach and duodenum are not displaced anteriorly. The regional bones are intact. Complete evaluation would require excretory urography, barium enema, chest and esophageal examinations.

Fig. 1—Elevation of the duodeno-jejunal junction by ill-defined mass.



Duplication of the gut, retroperitoneal lymphoma, other retroperitoneal tumors, a mesenteric cyst, and a pancreatic tumor or cyst should be considered. Duplication often, though not invariably, produces some localized deformity of the gut, and a history of pain, obstruction, or melena. A retroperitoneal lymphoma could produce such a change, but in the absence of invasion of the gut and splenomegaly, would be unlikely. Other retroperitoneal tumors such as teratoma could be responsible but unlikely. A mesenteric cyst would not correspond so closely to the position and contour of the pancreas, and is usually more anteriorly situated. It generally causes a soft mass which is difficult to assess on physical examination.

A pancreatic lesion could explain all the changes. Pancreatic tumors are very rare in childhood. Pancreatic cysts are usually pseudocysts, most commonly secondary to trauma, of which there is no available history in this case.

Dr. Dunbar's impression: PSEUDO-CYST OF THE PANCREAS.

Roentgenologic impressions submitted by mail:

Pancreatic cyst (or pseudo cyst)	25
Retroperitoneal malignant lymphoma	23
Neuroblastoma	16
Wilms' tumor	14
Others	15

Dr. Dunbar: A slight majority of the radiologists submitting diagnoses agreed with my impression of a cyst or a pseudo-cyst. Of course, a retroperitoneal malignant lymphoma could do this, but the lesion seems to correspond closely with the position and the configuration of the pancreas. Also, a lymphoma big enough to cause a palpable mass, usually does something by way of invading or distorting the gut which doesn't seem to be the case here. A neuroblastoma usually shows a mass related to the adrenal area, or in the thorax; we just don't see that that is the anatomic location of the lesion. A Wilms' tumor of course usually conforms to the position and the general outline of an enlarged kidney.

Dr. Regato: Dr. E. J. Keeffe, of Pontiac, Michigan, offered pancreatic cyst. Dr. C. A. Poole, of Miami, Florida, preferred pseudo-cyst. Dr. R. E. Wesenberg, of Denver, offered an impression of pancreatic cystadenoma.

Operative findings: On June 9, 1971, a laparotomy was carried out; a mass was found occupying the middle third of the pancreas. An almost total pancreatectomy plus splenectomy were done. The pancreas with the tumor weighed 180 gm and the spleen 60 gm.

Dr. Rosenberg: A fibrous capsule separates a thin rim of normal pancreas from a large tumor containing a broad central necrotic area. The growth pattern includes a mixture of glandular structures and sheets of spindle cells. In the glandular areas, small cells are arranged in cords and acini focally forming a papillary pattern on fibrovascular stalks. The papillary epithelium is arranged

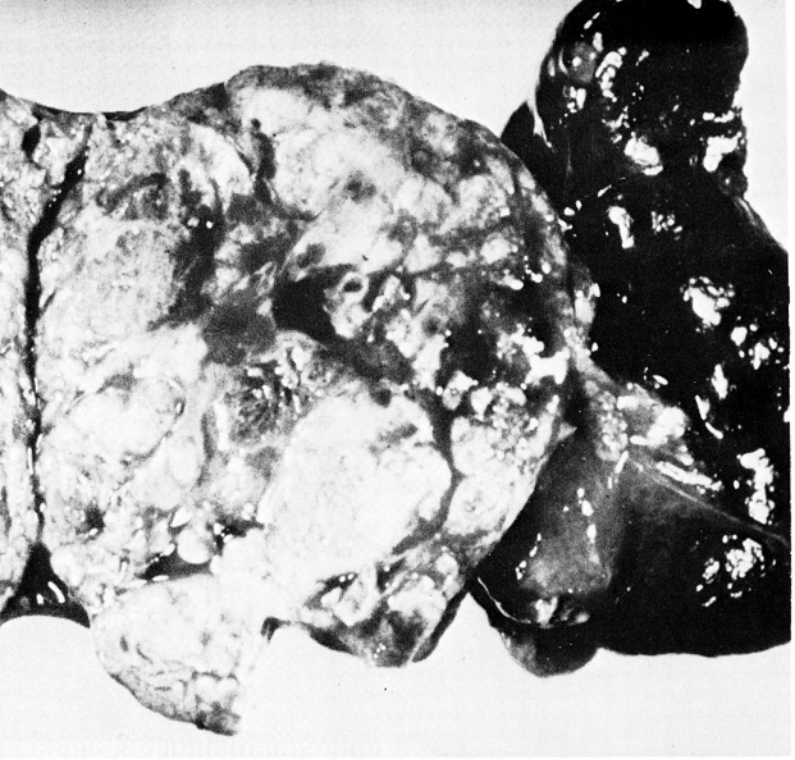


Fig. 2—Gross specimen of transected pancreatic mass and spleen.

in one or two layers on the inconspicuous vascular stroma. A small amount of secretion, accentuated in the PAS preparations, occupies the poorly formed acinar lumens. The individual cells vary from cuboidal to columnar and have a small amount of non-granular cytoplasm and a single oval nucleus with a vesicular chromatin pattern. The cells take a faint pink color with Gomori's chromium alum preparation. The second type of cell growth has solid sheets of spindle cells. The nuclear pattern of the spindle cells varies little from those in the glandular area.

The tumor focally extends into the capsule but without discrete vascular invasion. Mitoses are rare. The fibrous capsule contains a few hemosiderin laden histiocytes.

The clinical data slants the differential diagnosis toward a nonfunctional tumor. Functional tumors of the pancreas in childhood are islet cell adenomas including alpha-1 cell tumor or gastrinoma, alpha-2 cell tumor or glucagonoma, beta cell tumor or insulinoma, and mixed-multihormonal tumor. Any of these lesions would have been expected to produce some clinical or laboratory abnormality other than the stated innocuous clinical history. Assuming that this was a nonfunctional tumor, the differential diagnosis becomes more, or less, obscure depending on one's individual compulsion. Tumors of infantile pancreas with this morphology are variously interpreted as nonfunctioning islet cell tumors, duct cell tumors, or undifferentiated cell tumors. Although nonfunctional exocrine tumors may occur in children, they must be extremely uncommon. The histologic pattern of this tumor conforms well to the lesions variously described as nonfunctioning islet cell adenoma, or epithelial or papillary carcinoma of the pancreas of infancy and childhood. Most difficult to interpret is the ultimate benign or malignant behavior. The usual characteristics of invasion, anaplasia, and hyperchromasia are of no more consequence in this tumor than in any other endocrine tumor. The definitive designation of malignancy resides in identification of metastasis. Even after metastasis, some pancreatic tumors still retain a remarkable benignity. This unpredictable nature of pancreatic tumors has led to a lack of commitment in their identification with qualifying terms such as papillary tumor, questionable malignancy. Identification of the specific cell type by differential staining has not proved reliable due to the capricious nature of the staining methods. Ultrastructual studies suggest that some, at least, of these tumors are related to an undifferentiated duct cell epithelium that has a histogenetic potential toward either acinar or islet cells. The multipotential character of these cells may account for the inconstant cell staining and the difficulty in classification by conventional methods.

Pancreatic tumors in childhood are extremely uncommon. At the Texas Children's Hospital there has been only one pancreatic tumor, a beta cell adenoma. From the medical literature, only about 20 possibly malignant tumors of the pancreas have been described in infants, most of which have been referred to as nonfunctional islet cell tumors. The outcome is varied. In one series the mortality was 14 or 16 while others describe a high survival rate after major surgery.

The lesion in this infant's pancreas is interpreted as an undifferentiated pancreatic cell tumor with a potentially malignant clinical behavior.

Dr. Rosenberg's diagnosis: UNDIFFERENTIATED-CELL TUMOR OF THE PANCREAS

Histopathologic diagnoses submitted by mail:

Pancreatic adenocarcinoma	51
Acinar-cell carcinoma	12
Islet-cell tumor	36
Neuroblastoma	9
Others	10

Dr. Rosenberg: I would include all of these three first diagnoses under the same umbrella that I used. I don't believe this has the morphologic features of a neuroblastoma.

Dr. Regato: Dr. L. B. Henley, of Fort Sam Houston, Texas, diagnosed ductal adenoma of the pancreas. Dr. M. C. Wheelock, of Miami, designated it as nonfunctioning adenoma. Sister Ignatius, of Cincinnati, offered islet cell tumor. Dr. M. E. Williamson, of Palm Desert, California, preferred neuroendocrine carcinoma (carcinoid) of islet cell origin. Dr. G. Vogt-Hoerner, of Tunis, preferred Nesidioblastoma. Dr. H. Hamperl, of Bonn, Germany, diagnosed acinar carcinoma of the pancreas. Dr. J. M. Kissane, of Saint Louis, Missouri, called it an infantile adenocarcinoma of the pancreas, of the type described by Kay and suggested the name Kay-oma. Dr. L. P. Dehner, also of Saint Louis, made the same diagnosis but attributed the type to Frable and associates (Frabloma?).

The contributors of this case had sought the opinion of the AFIP (Accession number 1383222). They wrote: "The staff agrees that the tumor is of pancreatic origin. Our canalicular stains suggest liver-cell carcinoma but this appears to be a false positive. Diagnosis: adenocarcinoma of the pancreas." Dr. B. Landing, of Los Angeles, had been consulted also; he concluded to pancreatoblastoma. Dr. B. E. Favara, of Denver, rendered a diagnosis of mixed tumor of the pancreas.

Subsequent history: On June 7, 1972, the patient was reported in excellent physical condition: she is normal in weight and height and does not require pancreatic enzymes or insulin. In October, 1972 she continued to do very well.

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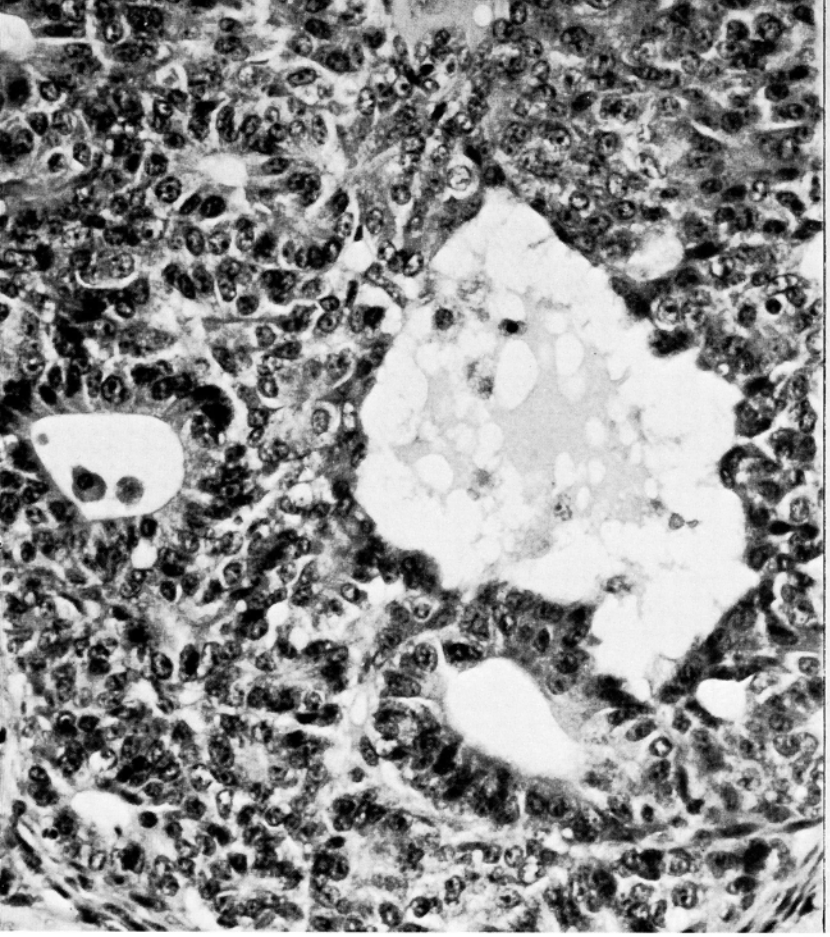

Fig. 3—A dense fibrous capsule separates the focally necrotic tumor from a compressed strip of the normal remaining pancreas. (Hematoxylin-eosin, X28).

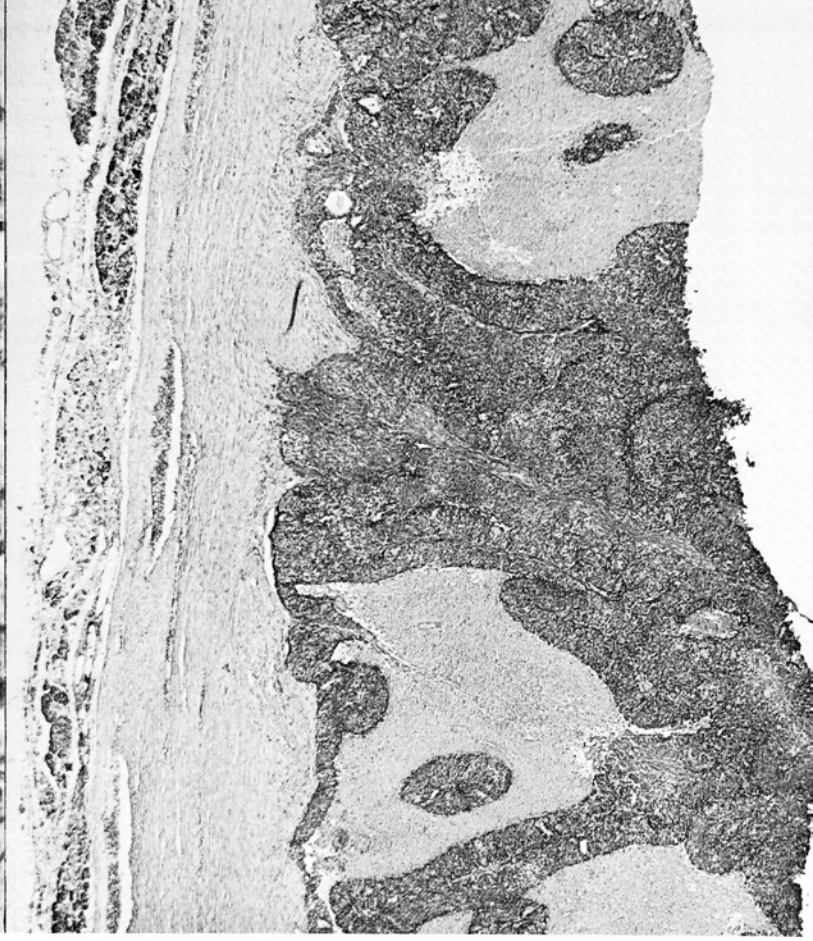

Fig. 4—In the prevailing architectural pattern, the tumor cells form ribbons and acini. (Hematoxylin-eosin, X64).

Dr. Ternberg: We had a patient sent to us with a lesion predominantly in the tail of the pancreas. The Surgical Pathology diagnosis was neuroblastoma. She was treated as a neuroblastoma for three years; when she began to have diarrhea, she was re-operated with the idea that perhaps removing most of this tumor which was still evident would be of benefit and imagine the red faces when at this time it was quite apparent that it was a pancreatic tumor. We see many more pseudo-cysts in this area than we see tumors, so that this could be probably the pre-operative diagnosis. This was a lucky surgeon; I would like to have that kind of luck, having the tumor be in the mid-body where the resection is relatively easier and being able to look at it and see that it is a tumor indeed. The other pitfall is that of pancreatic cystadenomas, which one might marsupialize: I think there is some evidence in the literature that this probably is not a good idea.

W. C. Bucher, Jr., M.D., Tucson, Arizona: An SMA 18 is an SMA 12 plus an SMA 6. This patient appears to be doing very well, is growing normally, needs no exogenous pancreatic enzymes or insulin, despite the fact that perhaps 85 to 90% of the pancreas was removed at surgery.

Dr. Ternberg: In operating for hyperglycemia, in our series, there hasn't been any problem to resect anywhere from 90% to 95% of the pancreas. We haven't had trouble yet with either having to supply the pancreatic enzymes or insulin, so you should expect not to have to supplement the patient.

B. E. Favara, M.D., Denver, Colorado: We had the privilege to look at this tumor at the Children's Hospital. Very rarely does electromicroscopy help, but in this particular situation I think it was a useful study; the zymogenic granules which were present in over half the cells of this tumor depict the acinar configuration of the lesion; there are ductile elements as well, and thus the designation of mixed tumor, acinar, ductular. We agree with Dr. Rosenberg that we can't predict its behavior, although it appears to be behaving in a benign fashion.

R. J. Kahn, M.D., Greeley, Colorado: I would like to just take exception to the 48 hour statement. I think there are certain diagnostic procedures that should be done on a child before the child is taken to surgery for a number of reasons: 1) It makes the surgery possibly simpler for the surgeon, 2) it probably makes the surgery safer for the child. To try to do barium enema examination, GI series, IVP's, and possibly even angiography in a 48 hour period becomes difficult when one considers that when the child goes to surgery he should be in the best possible clinical condition. If you add these diagnostic procedures to possible deterioration of their condition, the 48 hour period is one that may lead to more dangers than it is worth.

Dr. Dunbar: I really agree with both points of view. If you have a patient who needs to be investigated, it is extremely important that, for very obvious reasons already stated, that his condition be optimum before operation. Anything we do, like excretory urography or

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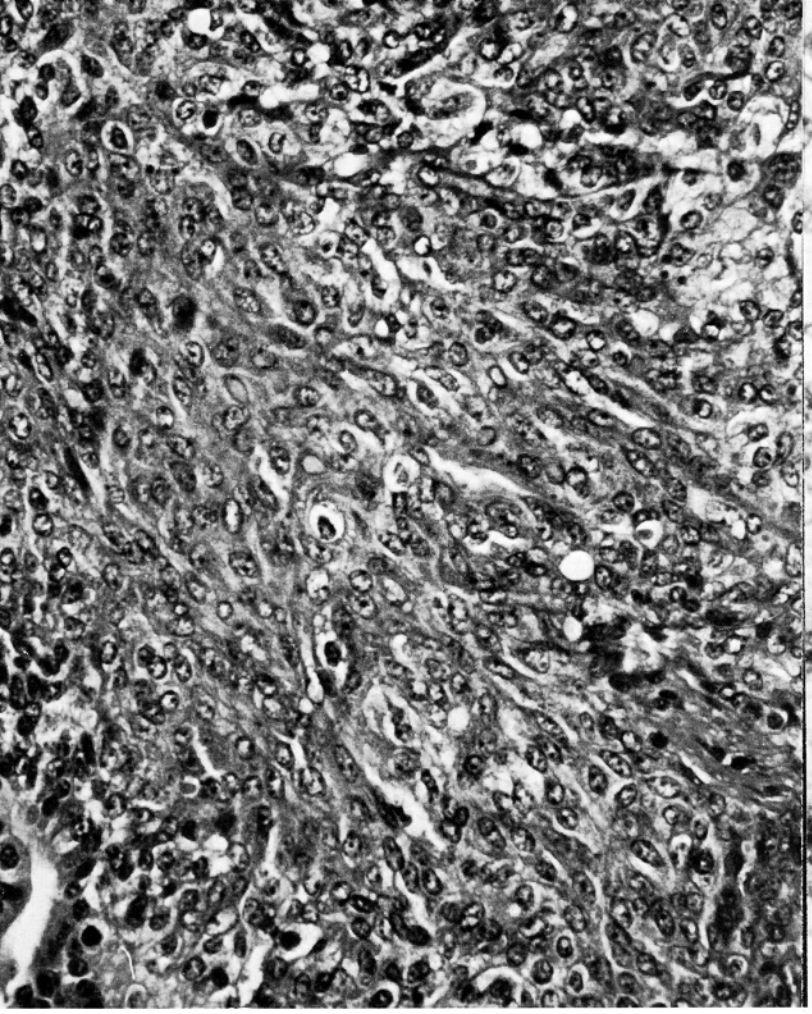

Fig. 5—Focally, the tumor cells are arranged in broad cellular sheets. (Hematoxylin-eosin, X64).

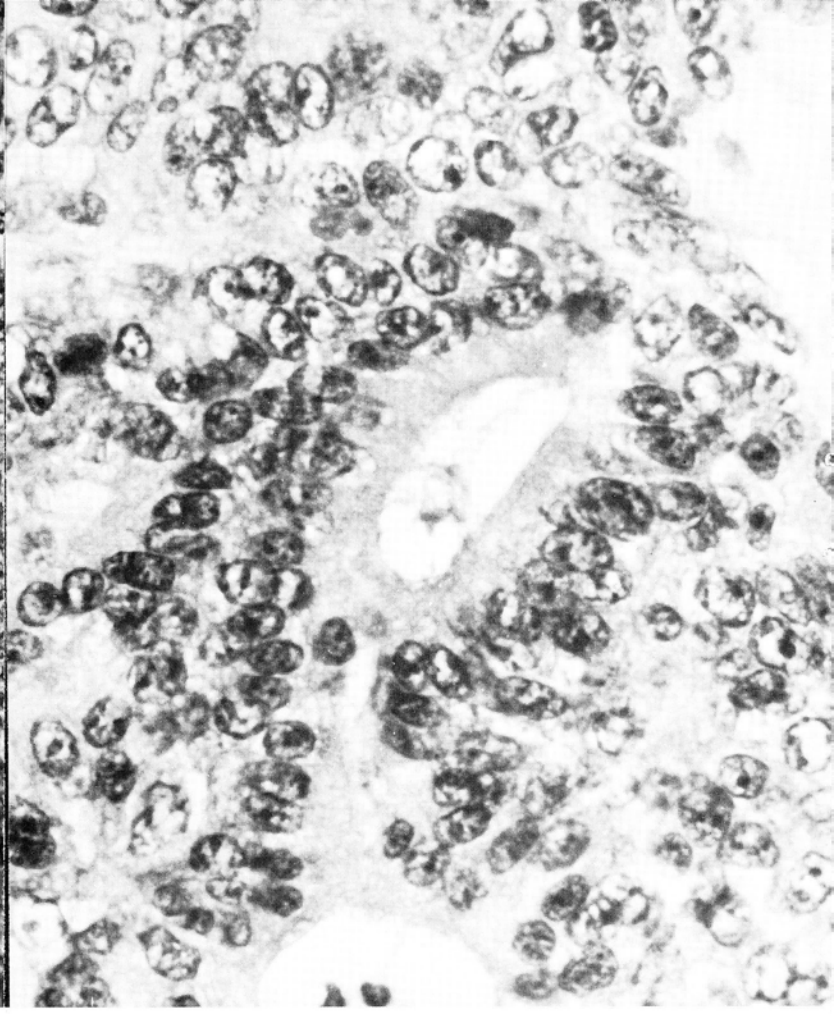

Fig. 6—The cells lining the acini are columnar with dark-staining nuclei, and finely granular cytoplasm. (Hematoxylin-eosin, X160).

angiography may impair his condition and it may make him dehydrated or even, if his condition isn't good enough when the procedure is done, send him into shock. In a well organized Children's Hospital it has been my experience that in most cases that do not require really extensive investigation, such as angiography, the whole gamut of necessary diagnostic procedu es can be done and completed and evaluated within 24 hours of admission. This still leaves room for considering such a thing as angiography. While agreeing that the condition of the child, shock, dehydration, undernutrition, are of paramount importance in the whole evaluation, it does seem to me that a well organized thoughtful investigation can be for the most part completed within 24 hours of admission, if the people in the hospital are seriously addressing themselves to the question of care of the child.

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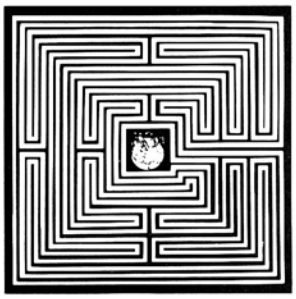

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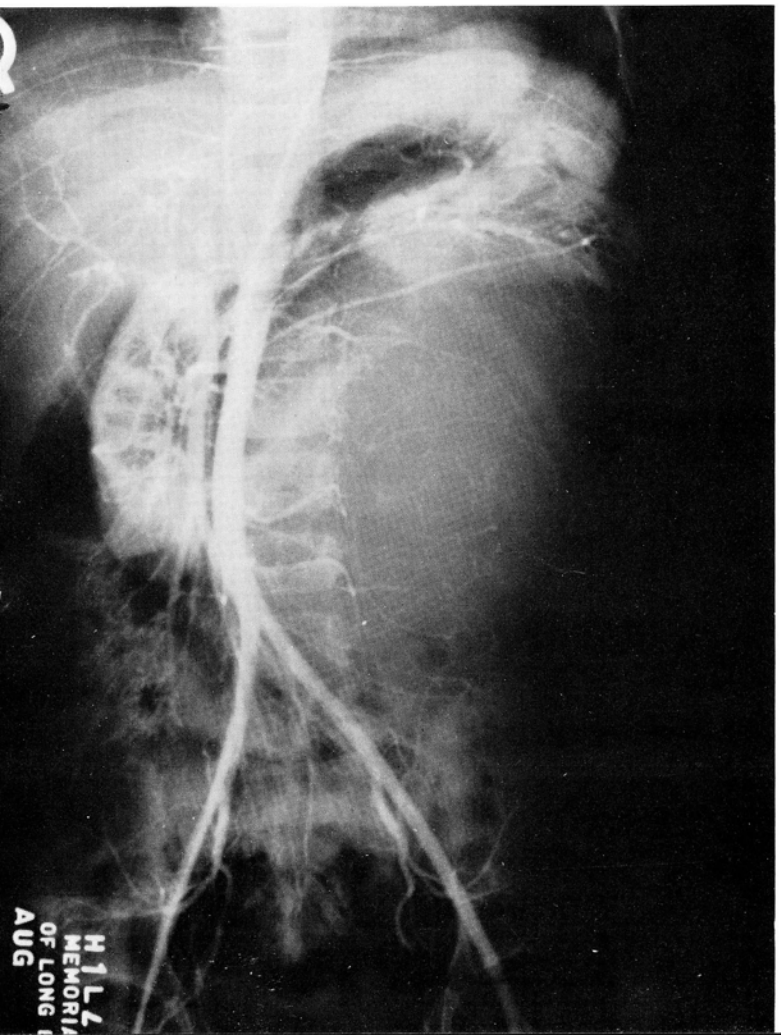
7. Ganglioneuroblastoma

Contributed by **W. M. Talbert, M.D.** and **E. Jennings, M.D.,** Long Beach, California

THE PATIENT was a 4-year old girl in August, 1971, when she was presented with an abdominal mass which had been noted for one year. On examination there was a very large (20 x 10 cm) fixed, smooth, left upper abdominal quadrant mass which did not move with respiration. Routine laboratory work was within normal limits; bone marrow was normal; VMA was 350 mcg/Kg/T.V.

Dr. Dunbar: There is a huge, well-defined non-calcified mass occupying most of the left side of the abdomen, and displacing midline structures to the right. The aortogram shows that the aorta is displaced to the right, but not obstructed. The left kidney is markedly displaced upward and rotated through 90°, to lie horizontally above the mass, but still distinct from it. The spleen is small and likely intact. The right kidney and the liver appear normal. The mass appears to be supplied mostly by lumbar vessels. The fine vessels of the mass show tortuosity and irregularity of the lumen and are thus tumor vessels. No tumor stain or arteriovenous shunt is shown, but such changes might have been demonstrated by later films.

Fig. 1—Huge mass of the left side of the abdomen displacing mid-line structures to the right.



There are criteria indicating malignancy, but countervailing evidence of benignancy; there are tumor vessels present in the huge mass, but it has been present for one year, is well-defined, and does not invade, destroy or obstruct contiguous structures. There is no clinical or roentgen evidence of metastatic disease. A retroperitoneal sarcoma is thus unlikely, as is a frankly malignant neuroblastoma. A benign teratoma or ganglioneuroma is more likely, in spite of the absence of calcification, which is frequent but not invariable in both these tumors.

Dr. Dunbar's impression: GANGLIONEUROBLASTOMA.

Roentgenologic impressions submitted by mail:

Neuroblastoma	26
Wilms' tumor	17
Multicystic kidney	16
Congenital hydronephrosis	11
Retroperitoneal tumor	9
Ganglioneuroma	5
Others	14

Dr. Dunbar: A tumor this size, in a child, which has been present for more than a few weeks or a few months must either be a neuroblastoma which is changed from a more benign tumor, or a neuroblastoma undergoing change to a ganglioneuroma. It is of course the most famous tumor for having a totally unpredictable prognosis and course even when there is good histologic evidence of malignancy. It is important that we look at the bones in a case like this. A neuroblastoma of frank malignancy which has been present in a child for a year and doesn't produce any metastatic lesions in bones is of very low grade malignancy and I prefer to think of it as a ganglioneuroblastoma. A Wilms' tumor is clearly excluded because the kidney is displaced upward. A multicystic kidney and congenital hydronephrosis are similarly excluded. I am describing this as a retroperitoneal tumor. A ganglioneuroma has one characteristic which is occasionally present and helpful in the diagnosis and that is erosion of the bones with which it is in contact. I looked carefully for this and found no evidence of erosion.

Dr. Regato: Dr. E. C. Hwa, of Newton, Kansas, suggested a retroperitoneal tumor. Drs. D. H. Kersey, of Colorado Springs, and B. Felson, of Cincinnati, offered an impression of neuroblastoma.

Operative findings: On August 23, 1971, the abdomen was entered through a left flank incision; a mass 16 x 20 cm in diameter was found with increased superficial vascularity; it was freed from the kidney, ureter and aorta; a few enlarged adjacent lymph nodes were removed.

Dr. Rosenberg: Large and small cellular nests are distributed irregularly in a fibrous stroma consisting of bundles and cords which irregularly interlace, focally separated by a loose edematous material. The entire fibrous area appears quiescent with elongated spindle shaped nuclei in cells with poorly delimited cytoplasmic orders.

The cellular nests have a considerable variation. Many of these nests contain mature ganglion cells with an abundant bright eosinophilic cytoplasm and a single vesicular nucleus with a prominent nucleolus. Some of the ganglion cells are very large with ballooning degeneration consisting of peripheral accumulation of the Nissl granules with central clearing of the cytoplasm. Other cells are less well differentiated ganglion cells with considerably less cytoplasm, more compact nuclei, and inconspicuous nucleoli. Binucleate and multinucleated forms are abundant. In addition to these relatively well differentiated ganglion cells, the cellular nests contain smaller cells with a similar cytoplasm but relatively large nuclei. These are embedded within a feathery, finely fibrillar stroma, occasionally mixed with the more mature ganglion cells. Mitoses are not identified.

The stroma contains focal deposits of amorphous calcification and islands of lymphocytes and few plasma cells. An estimated 50% of the tissue consists of well differentiated ganglion cells or fibrous tissue while the remainder consists of the smaller, poorly differentiated elements embedded within the feathery fibrillar stroma.

In the differential diagnosis of this lesion, a neurofibroma involving a sympathetic ganglion would not accompany an increased urinary excretion of vanilmandelic acid. The ganglion cells of a normal ganglion would not have either the immaturity, the degeneration, or the multinuclear configuration identified here.

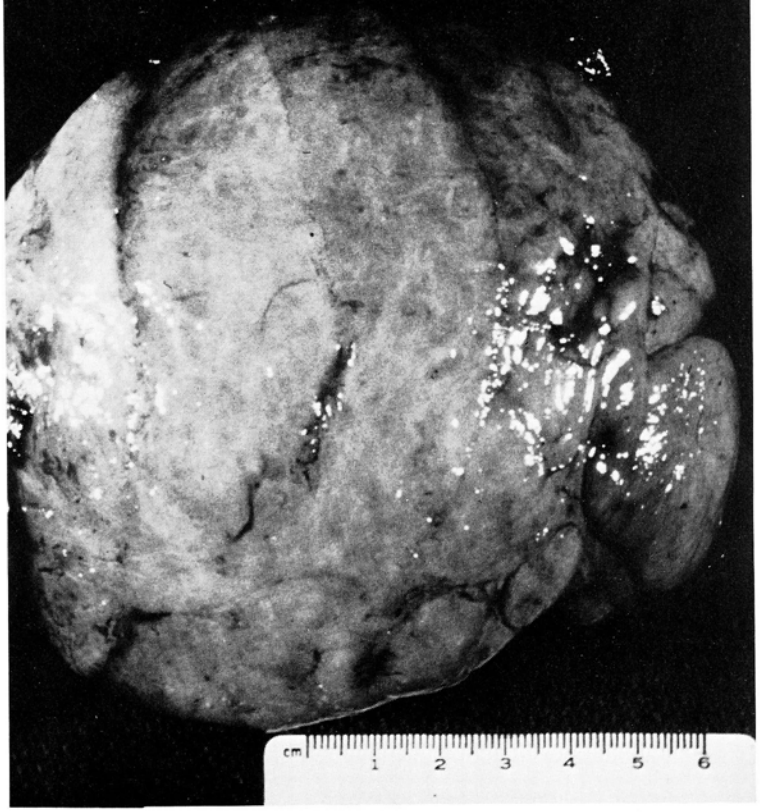
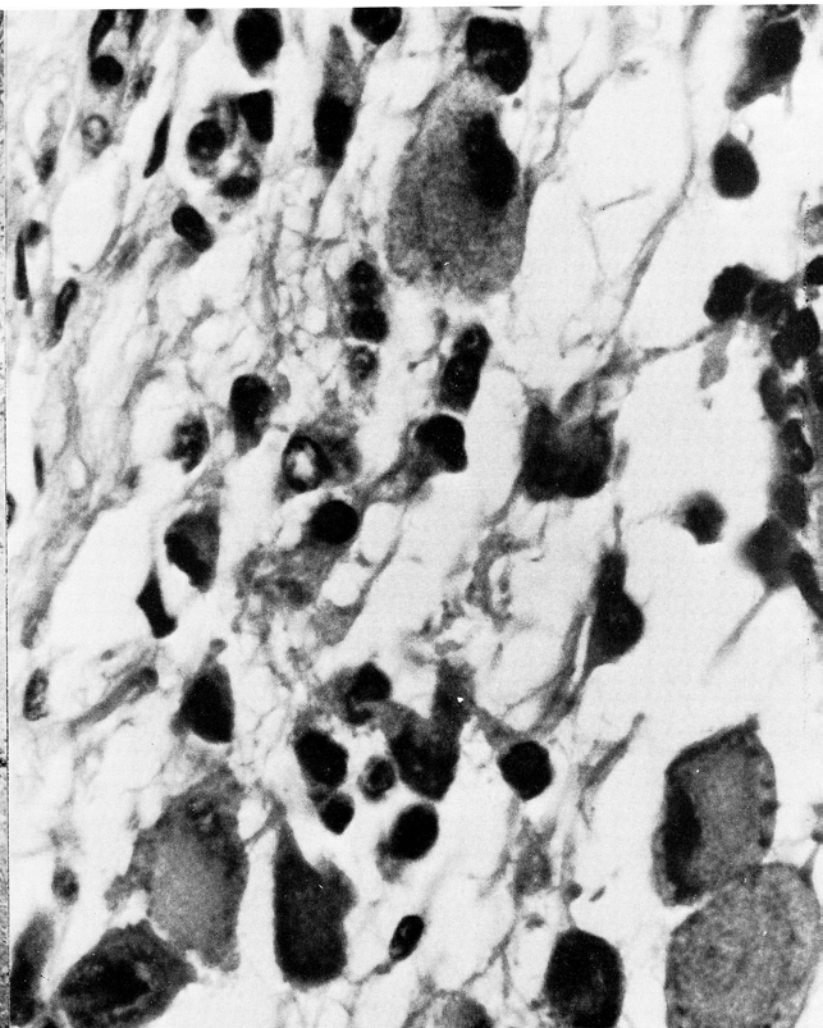


Fig. 2—Fragment of gross specimen of retroperitoneal mass.

Fig. 3—The basically fibrous tumor contains cellular nests, clusters of lymphocytes, and focal calcification. (Hematoxylin-eosin, X13).

Fig. 4—The cellular elements range from small compact immature cells to large well-differentiated ganglion cells. (Hematoxylin-eosin, X160).



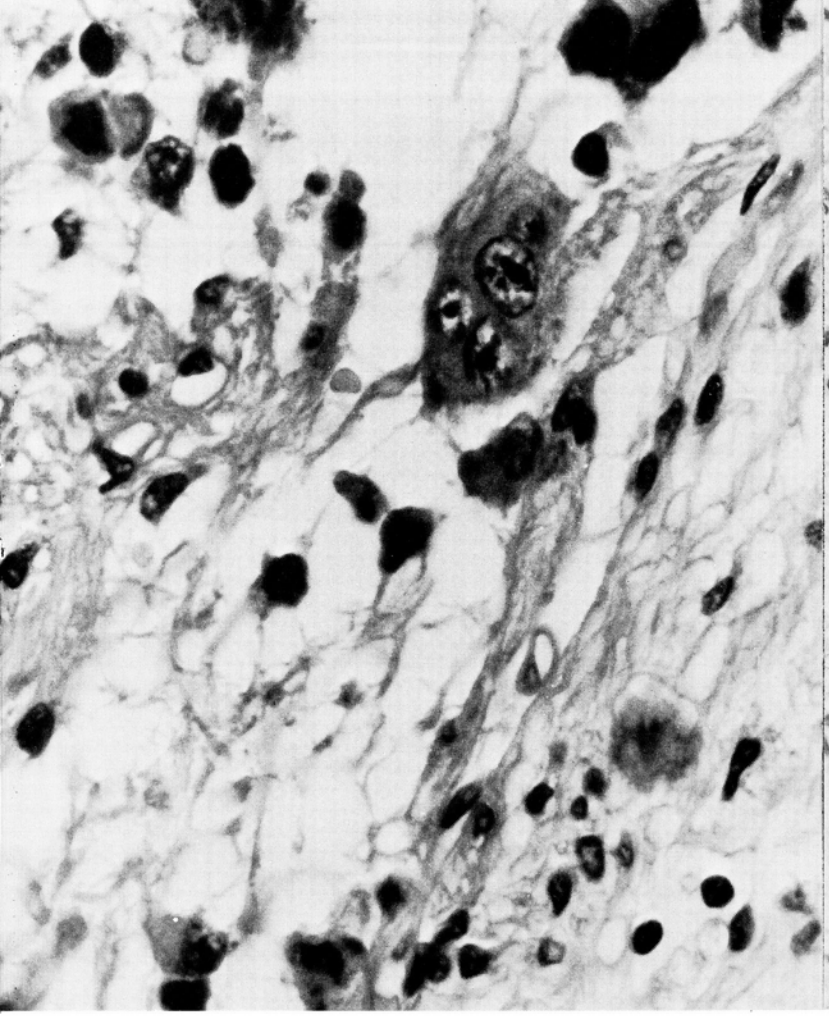


Fig. 5—Multinucleated ganglion cells join the other cells in the feathery fibrillar stroma of the cellular nests. (Hematoxylin-eosin, X160).

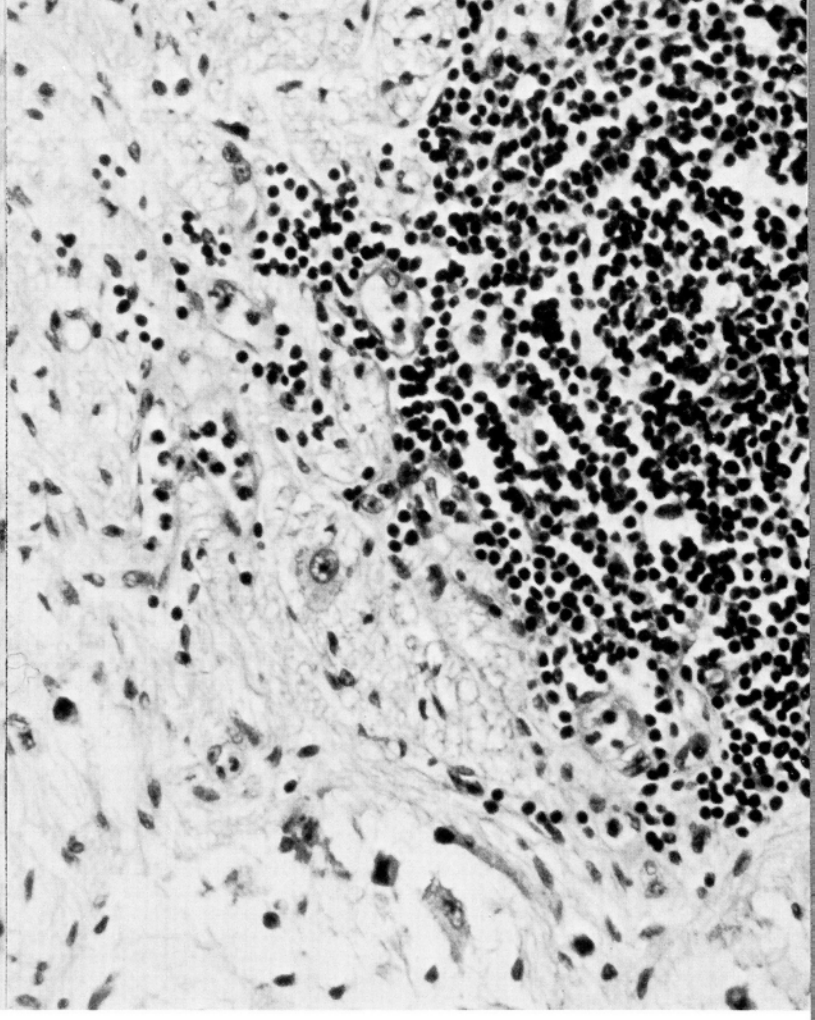


Fig. 6—Nests of lymphocytes in the stroma characterize the differentiating ganglioneuroma. (Hematoxylin-eosin, X64).

The histologic features characterize the lesion as a tumor of sympathetic ganglion cells and the factor for decision is the degree of differentiation. Considering the scale of differentiation from the neuroblastoma as totally undifferentiated to ganglioneuroma as completely differentiated, this lesion would lie somewhere between. The division of tumors of the sympathetic nervous system into neuroblastomas, ganglioneuroblastomas, and ganglioneuroma has as its basis the continuum of maturation from the neuroblast to the ganglion cells. The major consideration is the natural history. Neuroblastoma has a particularly bad prognosis even though this is to some degree age dependent. In contrast, those tumors with some degree of differentiation have a somewhat better prognosis.

In well differentiated ganglioneuroma, a few undifferentiated or multinucleated ganglion cells does not seem to affect the good prognosis. The fine fibrillar material consist of neurofibrils and is interpreted as a component of the undifferentiated elements. The lesion in this case is interpreted as a ganglioneuroblastoma with a good, but not excellent prognosis. The presence of the lymphocytes in the stroma also contribute to the concept of a better differentiation. Lymphocytes are uniformly present in the well differentiated lesions.

The prognosis depends not only on histology but also on the patient's age and the anatomic site and extent of the tumor. As with many solid tumors of childhood, the prognosis is far better during infancy than later in life. The prognosis of mediastinal neural tumors is far superior to those within the abdomen. The best prognoses are in mature tumors in the mediastinum in infants under the age of two. The worst prognoses are in the poorly differentiated tumors of the adrenal or retroperitoneal area in older children.

Dr. Rosenberg's diagnosis: GANGLIONEUROBLASTOMA.

Histopathologic diagnoses submitted by mail:

Ganglioneuroma	92
Ganglioneuroblastoma	23
Rhabdomyosarcoma	2
Others	2

Dr. Rosenberg: It is my interpretation that this represents a ganglioneuroblastoma, a tumor which should have a good prognosis, but a hedge is necessary because of the fairly high concentration of undifferentiated cells. I am not certain of the basis for the designation of rhabdomyosarcoma.

Dr. Regato: Drs. J. Clifford, of Denver, and J. M. Hori, of Columbia, Missouri, also made a diagnosis of ganglioneuroblastoma. Most others offered a diagnosis of ganglioneuroma: Dr. J. M. Kissane, of St. Louis, Missouri, indicated that he preferred ganglioneuroma to ganglioneuroblastoma because the latter term has a tendency to alarm people. Dr. P. H. Larson, of Robbinsdale, Minnesota, called it immature ganglioneuroma. Dr. A. Mazabraud, of Paris, made a diagnosis of sympathicoblas-

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toma with ganglioneuromatous evolution. Dr. F. Cabanne, of Dijon, France, raised the question as to whether the lesion is the result of maturation of a previously existing neuroblastoma.

Subsequent history: Following the operation the patient received supervoltage roentgentherapy with a dose of 3,000 rads administered to the area of the tumor in 28 days. in October 12, 1971, the VMA was 75 mcg/kgT.V. In January, 1972, the patient complained of abdominal pain and vomiting; an abdominal exploration revealed small bowel adhesions that were resected. In April, July and October, 1972, the urine VMA was normal. In October 13, 1972, the child was well and developing normally.

Dr. Ternberg: It makes a difference to me whether you call it a ganglioneuroma or a ganglioneuroblastoma, in considering what else should be done to this patient: if it is a ganglioneuroma, then I don't believe the patient requires post-operative radiotherapy or chemotherapy. I am not sure what degree of blastoma in this tumor will demand future therapy and at this point I go to the surgical pathologist for help. When presented with a diagnosis of ganglioneuroblastoma in which most of the tumor appears to be differentiated, our tendency has been to use chemotherapy for a period of time, rather than radiotherapy. I don't know whether that makes sense or not, but at least chemotherapy doesn't have any of the side effects that you occasionally see in radiotherapy.

Dr. Dunbar: A moderate elevation of VMA like this would help us to come to a conclusion that this wasn't simple ganglioneuroma, but of course, even in a ganglioneuroma the VMA and indeed the catecholamines can be elevated.

Dr. Ternberg: In reference to VMA you really need to know the laboratory and, in children, it may be helpful to know surface area also.

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8. *Mesoblastic Nephroma*

Contributed by **H. S. Rosenberg, M.D.** and **C. E. Carlton, Jr., M.D.,** Houston, Texas

THE PATIENT was a 5-month old baby girl in January, 1972, when a mass was found in the abdomen. On examination the baby's general condition was excellent; there was a large mass occupying the right upper abdominal quadrant. Hemoglobin was 7 gm%.

Dr. Dunbar: There is a large right-sided retroperitoneal abdominal mass which enlarges, distorts, obstructs and largely replaces the right kidney. The liver is ill-defined but may be enlarged. The urinary bladder is asymmetric, with an impression on its superior surface, and superimposed rectal gas partially obscuring its contour, but likely no intraluminal disease. The right ureter is not visible. The spleen and the left kidney collecting system and ureter are well shown and appear normal. The regional bones are intact, with the unlikely exception of some lucencies in the right proximal femur which are probably artifacts rather than true abnormalities. The gut immediately related to the abdominal mass is displaced but not obstructed. The mass is not calcified.

Such a lesion must be considered to be due to Wilms' tumor until proven otherwise. The reason is not that Wilms' tumor, with or without benefit of arteriography, has a pathognomonic or even unique radiologic appearance, but that is by far the commonest malignant renal tumor of early childhood. Experience teaches that there are other lesions which occasionally closely simulate Wilms' tumor. In this case, their probability or possibility could be evaluated by further studies including chest radiographs, a complete skeletal survey, and a liver scan with Technetium 99m sulphur colloid. The place which arteriography should play in such a lesion is controversial. Arteriography would show the size and shape of the liver more clearly, its blood supply, and possible evidence of metastatic disease within it. It would also show the blood supply of the enlarged and deformed kidney. The surgeon who is to operate should have the major responsibility in deciding upon the need for arteriography pre-operatively. Pre-operative or intra-operative radiation therapy is also controversial; when there is even a remote possibility that the diagnosis might be hydronephrosis, radiotherapy is contra-indicated. In this case, hydronephrosis is impossible. Lesions which can produce the same changes, though much less commonly than Wilms' tumor include neuroblastoma, which is usually supra-renal or para-renal in location, malignant neoplasm of the liver (hepatoma or hepatoblastoma) and, very rarely at this age, renal cell carcinoma. Angiomyolipoma, a benign tumor most commonly associated with tuberous sclerosis, is highly unlikely, and simple renal dysplasia is not worth considering. Finally, in any renal mass in childhood, the possibility of duplication with ureterocele should always be considered, but the features described above, and the absence of a characteristic bladder deformity, exclude this diagnosis. In the newborn period, a lesion closely simulating Wilms' tumor is renal hamartoma. Radiologically, it is indistinguishable from Wilms' tumor, but pathologically and in terms of prognosis it is benign. Indeed,

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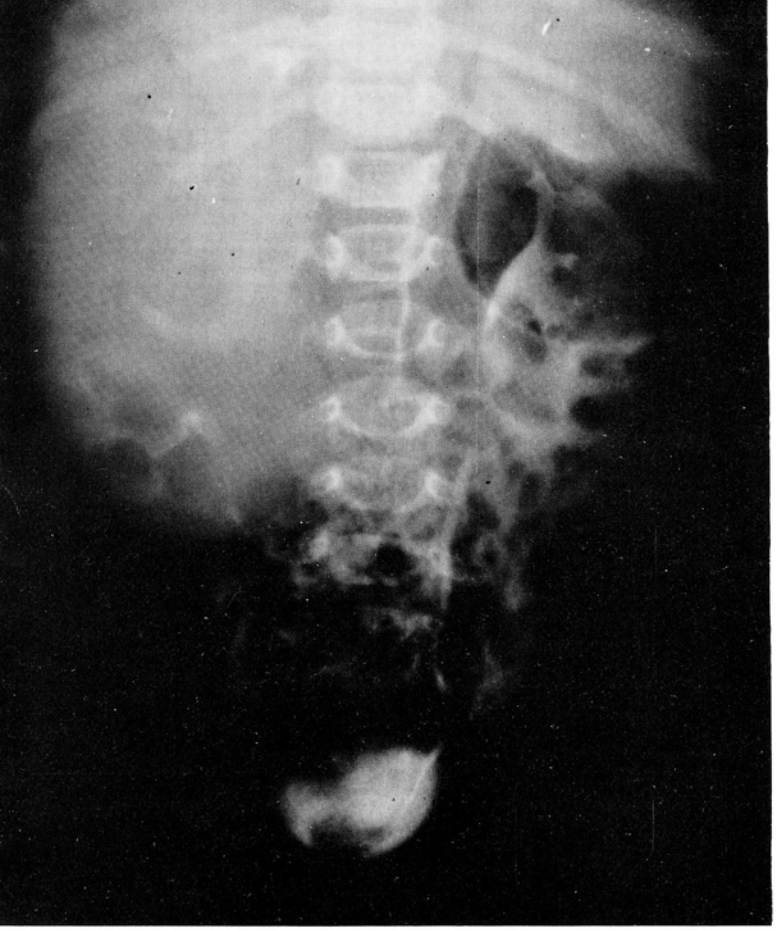

Fig. 1—Large right-sided retroperitoneal mass enlarging, distorting and largely replacing the right kidney.

this recently described distinctive lesion in the newborn period may account for the apparently good prognosis of what was previously considered to be neonatal Wilms' tumor. At the age of five months, however, it is unlikely.

Dr. Dunbar's impression: WILMS' TUMOR.

Roentgenologic impressions submitted by mail:

Wilms' tumor	62
Duplicate kidney	12
Neuroblastoma	9
Hamartoma	5
Others	10

Dr. Dunbar: Neuroblastoma can involve the kidney and we cannot exclude it in this case. Hamartoma is usually a neonatal phenomenon; it is possible that it is the explanation in this case.

Dr. Regato: Drs. R. Hagen, of Fort Sam Houston, Texas, and Dr. E. J. Keeffe, of Pontiac, Michigan, also offered an impression of Wilms' tumor. Dr. P. Riemenschneider, of Santa Barbara, considered a renal hamartoma.

Operative findings: On January 31, 1972, a right nephrectomy was carried out; the left kidney was explored and found normal. The surgical specimen contained a large irregular mass 11 x 8 x 7.5 cm extending into the perinephric tissues.

Dr. Rosenberg: In an area only poorly segregated from the intact kidney, a large collagen rich tumor extends from the renal parenchyma through the capsule into the adjacent perinephric fat. No sharp boundary separates the normal renal structures from the tumor or the tumor from the invaded fat. Focally, a few inflammatory elements surround areas of hemorrhage.

Large and small vascular channels occupy the broad sheets of fibrous tissue making up the tumor. The tumor contains two relatively distinct patterns. In the most prominent pattern, broad areas contain compactly arranged interlacing bundles of collagen rich fibrous tissue. The second pattern merges imperceptively with the collagen rich areas and consists of interlacing densely cellular bundles. The cells in the collagenous area resemble those in the cellular areas, but with considerable more variation and more mitoses in the cellular areas. The cells are elongated spindle forms with cigar-shaped nuclei and finely granular cytoplasm. In the collagen rich areas, there is less pleomorphism and far fewer mitoses. In the trichrome preparations, the cytoplasm has a faint red granularity. In the extension through the renal capsule the cellular pattern predominates.

At the junction with the renal parenchyma, the tumor cells extend between, separate and distort the normal tubular structures. Focally the tumor surrounds dilated and distorted tubules lined by immature epithelium and glomeruli with cuboidal glomerular epithelium. These renal elements are not distinctly identified as either remnants of invaded normal kidney or as dysplastic structures accompanying the neoplasm.

An inflammatory response of many lymphocytes, an occasional plasma cell, and a few multinucleated giant cells occurs where the tumor meets the kidney.

Electron microscopic examination revealed many fibroblasts but no smooth muscle.

The differential considerations of a renal tumor in the first year of life makes a very short list. Polycystic kidneys may present clinically as a tumor but are readily identified morphologically. Renal cell carcinomas in children are extremely uncommon. The remainder of the differential list includes Wilms' tumor and a peculiar connective tissue tumor with a variety of names including mesoblastic nephroma and fetal mesenchymal hamartoma. Because of the difference in natural behavior and management, a distinction between Wilms' tumor and mesoblastic nephroma is critical and, in most circumstances, not difficult. Most mesoblastic nephromas appear in the immediate neonatal period, rarely beyond the first month or two of life. Mesoblastic nephroma makes up 50% of all renal tumors in the first year of life and an even higher proportion of those appearing in the first days of life.

Mesoblastic nephroma is a localized tumor within the kidney which has the capacity for local invasion but does not metastasize and does not kill the patient. The remarkable success with the management of Wilms' tumor in the first year of life has, in part, been attributed to a dilution of the incidence of Wilms' tumor with this relatively benign tumor.

Several characteristic features establish the identity of mesoblastic nephroma. Mesoblastic nephroma lies within the renal capsule but does not have a capsule of its own which contrasts with the usually circumscribed Wilms' tumor. Mesoblastic nephroma is usually firm and rubbery rarely with hemorrhage or necrosis, again contrasting with Wilms' tumor. The microscopic features include the invasion of adjacent connective tissue and the presence of relatively immature forms and large numbers of mitoses. Dysplastic renal structures are frequently included within the dense areas of connective tissue. The epithelial component of Wilms' tumor is totally lacking.

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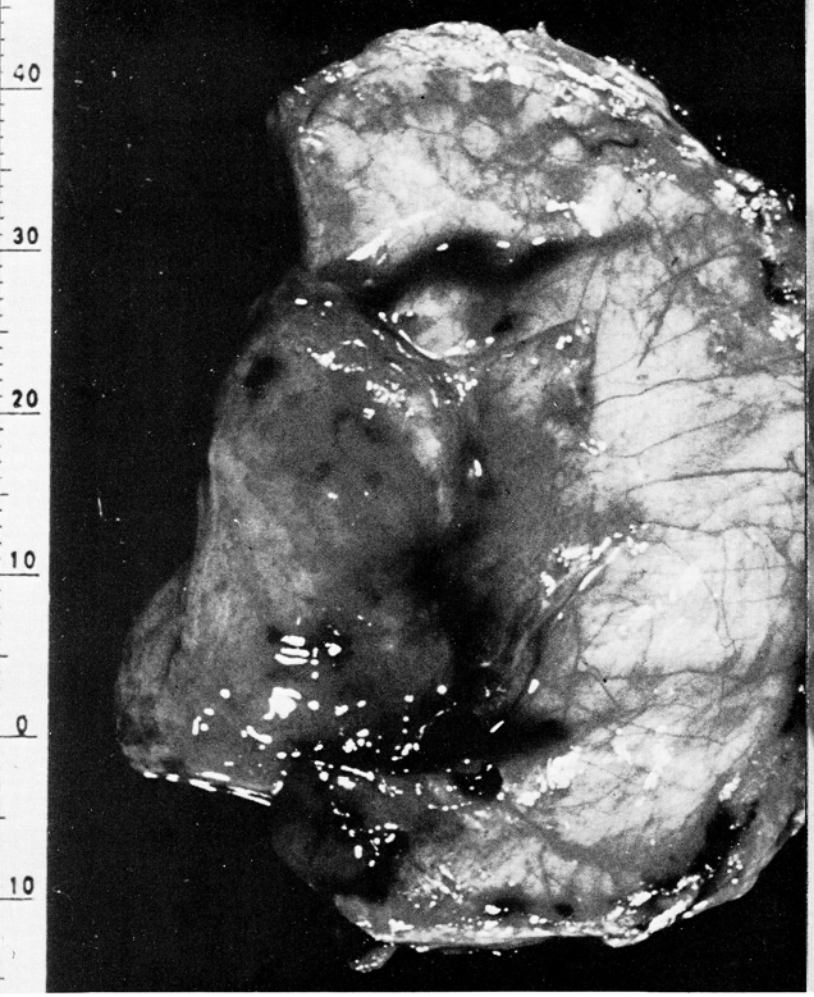

Fig. 2—Surgical specimen of right nephrectomy.

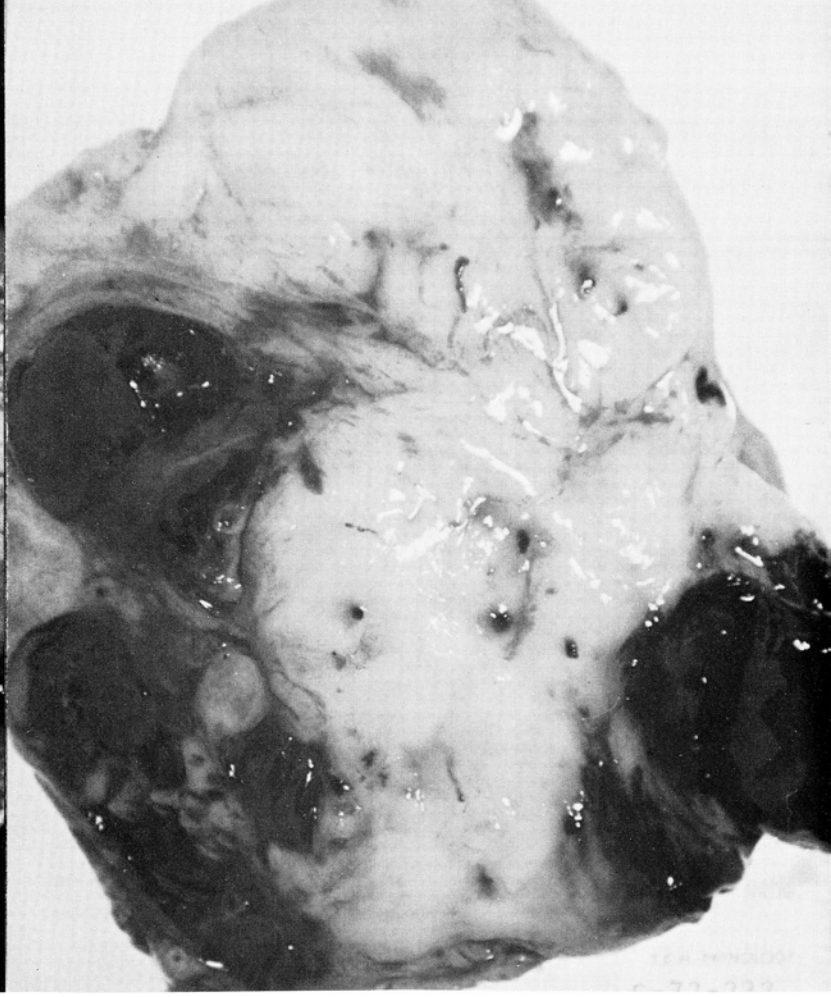

Fig. 3—Most of the kidney has been replaced by a large white unencapsulated tumor marked by extensive fresh hemorrhage.

In the present case several features are atypical for mesoblastic nephroma. The tumor not only invaded through the renal capsule but extended into the perinephric fat appearing in a biopsy of the perinephric connective tissue. The undifferentiated elements are more extensive than usual. At five months of age this infant is at the upper limits of age for the usual patient with mesoblastic nephroma.

The nature of the lesion has been variously ascribed to a fibrous variant of Wilms' tumor or a benign hamartomatous or fibroproliferative disorder involving the kidney. Although a malignant potential has been acknowledged, malignant behavior with metastases has not been recorded.

Management is generally recommended as surgical excision without the subsequent use of radiation or chemotherapy. In one case described to me by Dr. H. J. Wigger, an incomplete removal resulted in a local recurrence of a fibrous tumor but not metastases.

In summary this lesion is interpreted as a mesoblastic nephroma with aggressive potential but without the capacity for generalized dissemination to be expected in a Wilms' tumor.

Dr. Rosenberg's diagnosis: MESOBLASTIC NEPHROMA.

Histopathologic diagnoses submitted by mail:

Leiomyosarcoma	52
Fetal hamartoma	24
Wilms' tumor	13
Angiomyolipoma	9
Fibrosarcoma	8
Mesoblastic nephroma	6
Others	13

Dr. Rosenberg: Leiomyosarcoma I can sympathize with but I would not really agree with since I do not feel that this has the malignant potential of this tumor. I would feel that Wilms' tumor is not warranted, particularly in the absence of any of epithelial component.

Dr. Regato: Dr. J. B. Frerichs, of El Paso, also diagnosed congenital mesoblastic nephroma. Dr. W. C. Bauer, of Saint Louis, Missouri, made a diagnosis of fetal hamartoma of the kidney. Dr. R. E. Stanford, of Denver, offered a designation of atypical leiomyomatous hamartoma, whereas Dr. K. Hallman, of El Paso, reverted the terms and called it a hamartomatous fibroleiomyoma. Dr. L. J. Clowry, of Milwaukee, preferred leiomyosarcoma in a renal hamartoma. Dr. L. Lowbeer, of Tulsa, proposed a diagnosis of nephroblastoma, leiomyosarcomatous type. Dr. R. W. Wahl, of Fort Sam Houston, Texas, wondered if it was a leiomyosarcoma arising from a Wilms' tumor. Drs. M. J. Demeo, of San Rafael, California, and R. D. Schultz, of Sioux Falls, South Dakota, simply called it a leiomyosarcoma. Dr. P. W. Gikas, of Ann Arbor, Michigan, preferred spindle-cell sarcoma.

Subsequent history: Following operation the patient received Dactinomycin and radiotherapy. In October, 1972, she was reported living and well.

Dr. Ternberg: The problem here is to work out the most logical approach for treating this child. I think there is a morbidity associated with arteriography particularly in the smaller children and in the infants; an arteriogram is, as somebody said, a road map, but we work on a three dimensional system and it isn't always that much help. I

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The cellular nests have a considerable variation. Many of these nests contain mature ganglion cells with an abundant bright eosinophilic cytoplasm and a single vesicular nucleus with a prominent nucleolus. Some of the ganglion cells are very large with ballooning degeneration consisting of peripheral accumulation of the Nissl granules with central clearing of the cytoplasm. Other cells are less well differentiated ganglion cells with considerably less cytoplasm, more compact nuclei, and inconspicuous nucleoli. Binucleate and multinucleated forms are abundant. In addition to these relatively well differentiated ganglion cells, the cellular nests contain smaller cells with a similar cytoplasm but relatively large nuclei. These are embedded within a feathery, finely fibrillar stroma, occasionally mixed with the more mature ganglion cells. Mitoses are not identified.

The stroma contains focal deposits of amorphous calcification and islands of lymphocytes and few plasma cells. An estimated 50% of the tissue consists of well differentiated ganglion cells or fibrous tissue while the remainder consists of the smaller, poorly differentiated elements embedded within the feathery fibrillar stroma.

In the differential diagnosis of this lesion, a neurofibroma involving a sympathetic ganglion would not accompany an increased urinary excretion of vanilmandelic acid. The ganglion cells of a normal ganglion would not have either the immaturity, the degeneration, or the multinuclear configuration identified here.

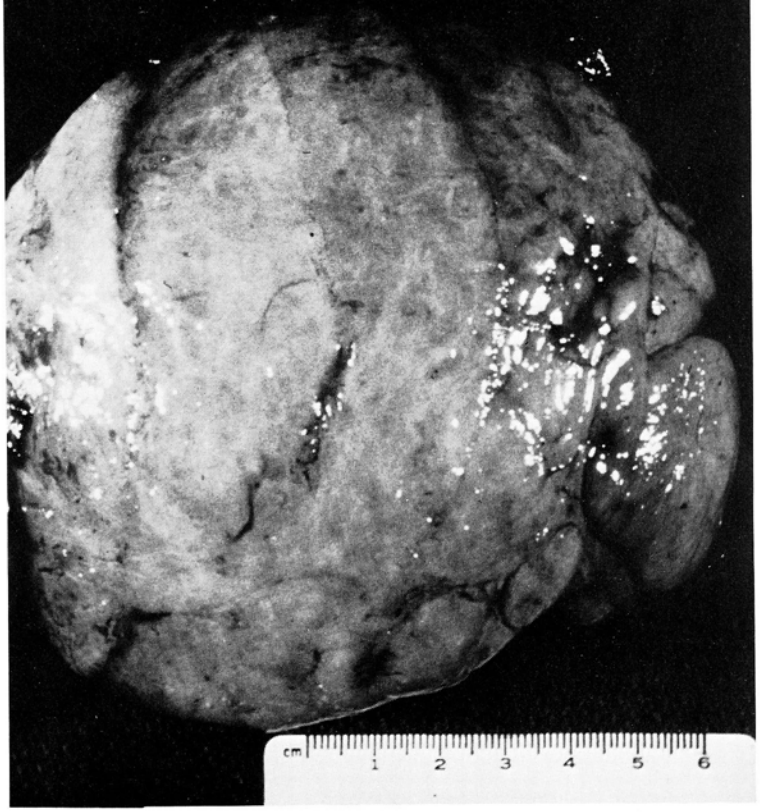
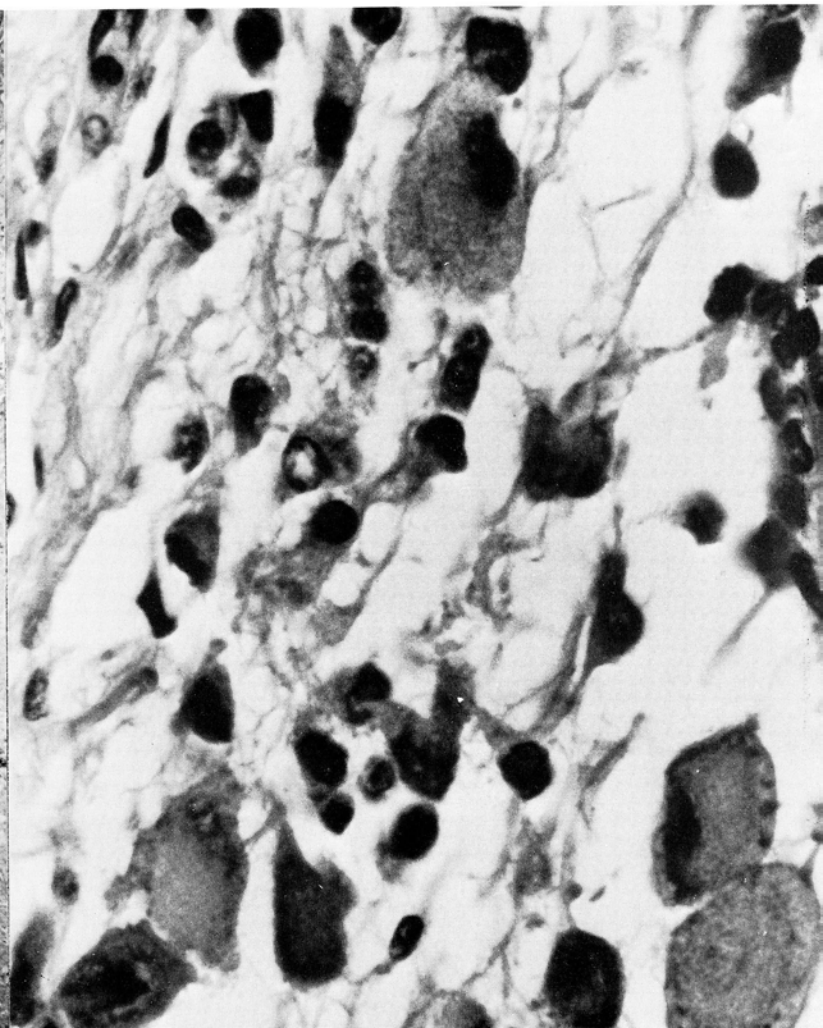


Fig. 2—Fragment of gross specimen of retroperitoneal mass.

Fig. 3—The basically fibrous tumor contains cellular nests, clusters of lymphocytes, and focal calcification. (Hematoxylin-eosin, X13).

Fig. 4—The cellular elements range from small compact immature cells to large well-differentiated ganglion cells. (Hematoxylin-eosin, X160).



specified that these tumors can have a great deal of atypia in them, but are nevertheless benign. We had occasion to review his paper and verified that in two out of the 5 cases reported there was a great deal of cellular atypia much as we saw in today's case; those two cases were post-operative deaths and had absolutely no followup; the cases without the atypia, the other three cases, all had long term survival. In the literature there are many cases like this, with a six-month follow-up or no follow-up at all; I am not really sure that we yet have good evidence that this type of lesion with this degree of atypia is benign in terms of long term follow-up.

Dr. Rosenberg: I think your observations are very well taken. I think I could do no better than to repeat what Robert Bolande has said about this. He does hold out the possibility that these may have a malignant potential although none has ever been described. There is a current controversy: Crocker-Vernier have done some interesting tissue culture studies on several tumors of this mesoblastic nephroma variety and in the tissue culture in which they used mouse brain as an inducer, they found the presence of renal tubules; on that basis it was suggested that the lesion that we are describing is really just a potential Wilms' tumor which has not yet reached its potential. As you might suspect, Dr. Bolande has taken great offense at this and has suggested that this isn't the case, the tubules that they were looking at are really mouse ependymal cells. For practical purposes it really doesn't make that much difference. As of this moment I am prepared to subscribe to the concept that this fibrous type variant is a potentially benign lesion and malignancy has not yet been demonstrated.

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9. *Hepatocarcinoma*

Contributed by **C. Perez-Mesa, M.D.** and **C. M. Waggoner, M.D.,** Columbia, Missouri

THE PATIENT was a 6-month old baby boy in Febuary, 1949, when he was presented because of an abdominal mass. The baby had become less active, irritable and pale. Examination revealed a large, smooth, firm mass in the right side of the abdomen extending beyond the midline. CBC, serum proteins, bilirubin and urinalysis were all within normal limits.

Dr. Dunbar: There is a huge, non-calcified right sided abdominal mass which extends across the midline to the left side. There is a mild scoliosis, but the visible bones of the area show no destructive or metastatic lesion, though they show some osteoporosis, particularly in the proximal femora. The right kidney is ill-defined, and slightly enlarged, and its collecting system slightly enlarged and distorted. The right psoas shadow is obliterated. The right flank bulges.

In the partially visible lower thorax, there is no evidence of lung or pleural disease, and the heart is not enlarged. The lower pole esophageal line may be slightly displaced to the left. The urinary bladder is poorly seen but intact. The left kidney collecting system and ureter, though incompletely visualized, appear normal. The gut, though markedly displaced, is not evidently invaded or obstructed. The mass extends well across the midline to the left, partially overlying the left kidney, and contains within it, at least one area of reduced density suggesting but not proving some fat content. The mass is rather ill-defined, and the liver not defined at all.

It is almost certain that this is a malignant tumor; the child's condition is poor in spite of evidence of gut or urinary obstruction, and the mass is ill-defined and probably involves the liver. The diagnostic possibilities include retroperitoneal sarcoma, neuroblastoma, malignant teratoma, and Wilms' tumor. The suggestion of some fat content in the tumor is not valid unless confirmed by a plain film of the abdomen, since it might represent an area of hemorrhage or necrosis which becomes relatively radiolucent in the course of the total body opacification produced by the excretory urogram. Further investigation should include chest radiographs, a liver scan, and a skeletal survey. An arteriogram would be of little value, but an inferior vena cavagram should be done pre-operatively.

A Wilms' tumor cannot be excluded, since it can sometimes arise from the anterior surface of the kidney, and produce exactly the findings described. A retroperitoneal sarcoma usually presents in the neonatal period rather than at age six months, but cannot be excluded on the present evidence. A retroperitoneal sarcoma, particularly rhabdomyosarcoma, is possible. A primary tumor of the liver is less likely than a retroperitoneal primary lesion because the right kidney is displaced upwards slightly rather than downward.

Dr. Dunbar's impression: 1) MALIGNANT RETROPERITONEAL TUMOR 2) TUMOR OF THE LIVER.

Roentgenologic impressions submitted by mail:

Hepato(blasto)ma	23
Neuroblastoma	20
Mesenteric cyst	15
Teratoma	5
Wilms' tumor	2
Others	19

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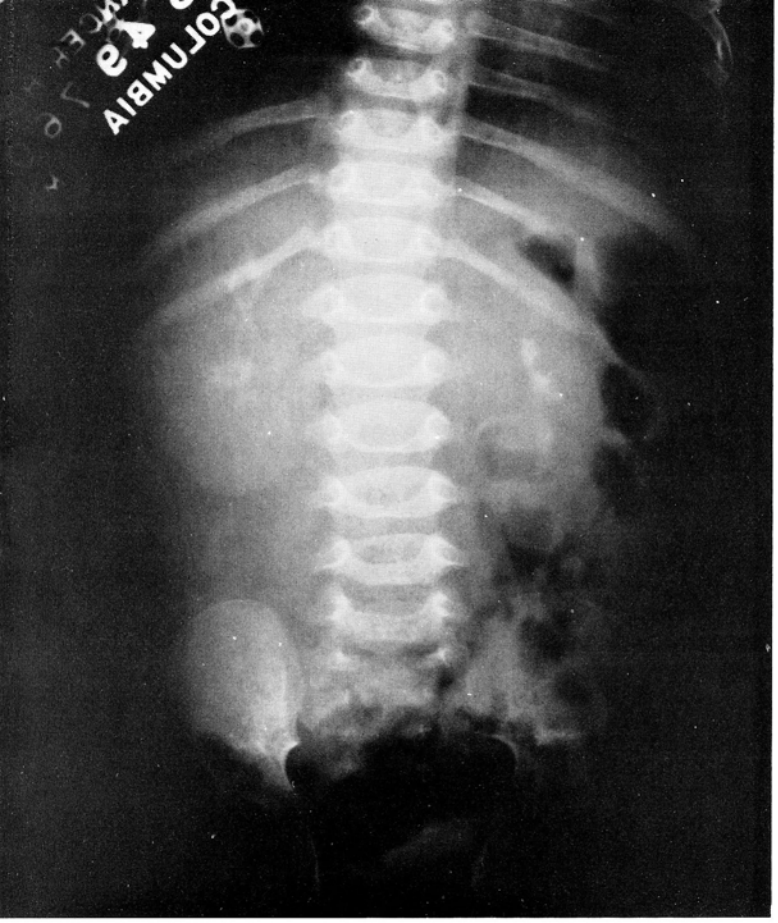
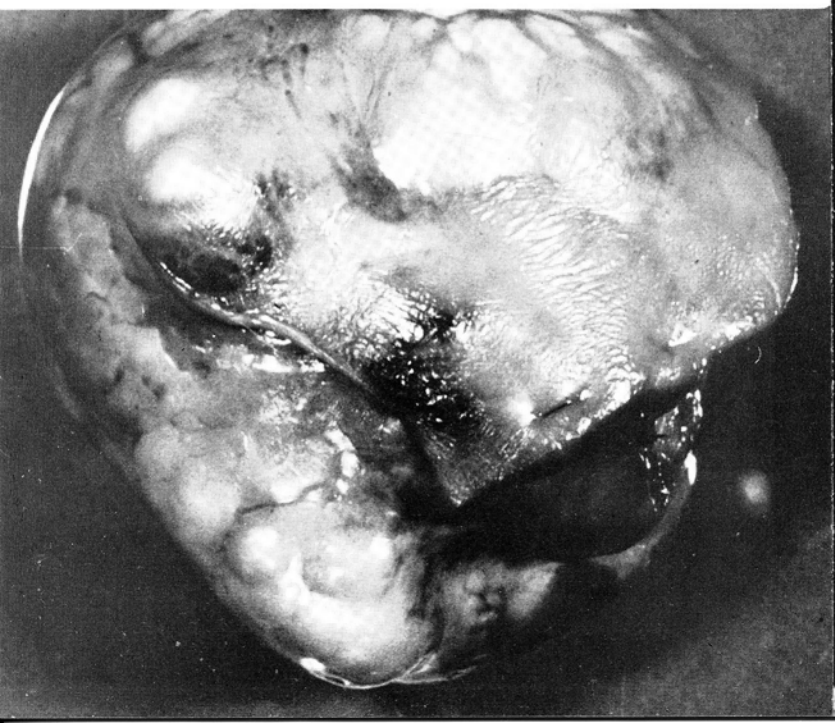


Fig. 1—Large right-sided abdominal mass.

Dr. Dunbar: I would be very much opposed to mesenteric cyst because it doesn't do these bad things to the patient generally, nor to the liver. Teratoma I cannot exclude. When neuroblastoma makes the child pale, irritable, listless, it begins to show either paravertebral enlargement or widening of the soft tissues or skeletal metastasis; as a matter of probability, a neuroblastoma, in my opinion, is very much less likely.

Fig. 2—Right lobe of the liver almost entirely occupied by tumor.



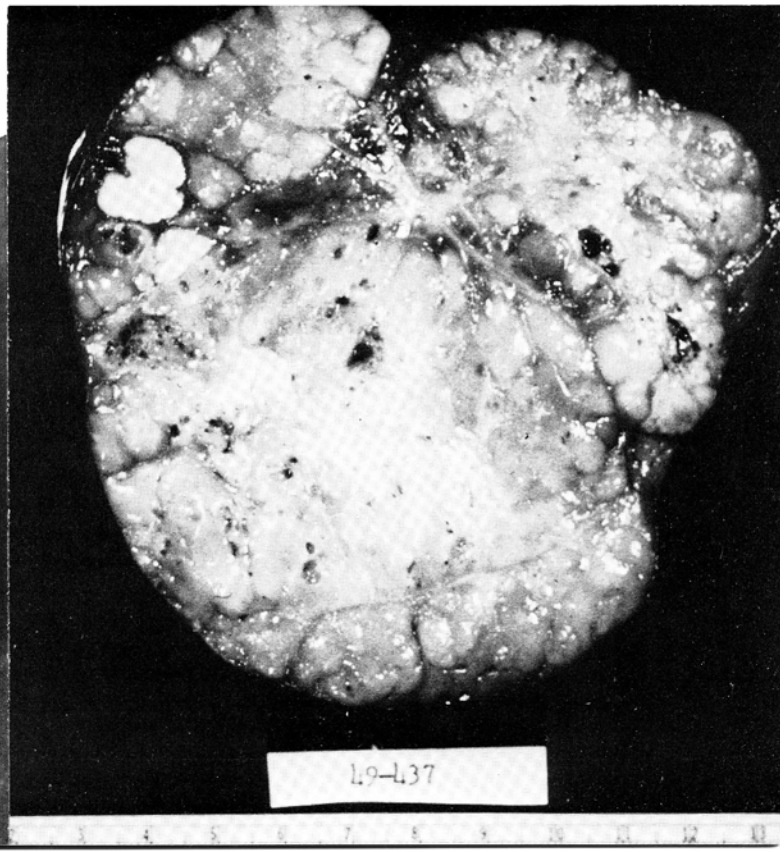
Dr. Regato: Drs. C. A. Poole, of Miami, P. H. Riemenschneider, of Santa Barbara, and B. Felson, of Cincinnati, all offer an impression of hepatoma.

Operative findings: On March 2, 1949, a tumor was found occupying the major portion of the right lobe of the liver and extending to the region of the right hepatic artery and portal vein. A complete resection was done between the right and left lobes. Signs of severe shock developed during the operation; the patient received whole blood administered by syringe at the angle of the great saphenous vein. The surgical specimen, 12 x 11 x 8 cm consisted mostly of tumor with a rim of normal liver.

Dr. Rosenberg: A thin incomplete fibrous capsule separates an intrahepatic tumor from the overlying Glisson's capsule with a thin rim of parenchymal elements between the tumor and the superficial capsule. Within the tumor, broad irregular fibrous strands and irregular necrotic zones interrupt the basically cellular architecture. Three basic patterns not sharply demarcated from each other make up the tumor. The first consists of dense sheets of uniform polygonal cells arranged about sinusoids. These cells have an abundant, poorly stained, cytoplasm, a single rounded or angular nucleus and a prominent nucleolus. Mitoses are not identified. In the second pattern, aggregates of smaller cells with a much more dense cytoplasm have a less obvious arrangement along sinusoids. Nucleoli are inconspicuous, otherwise the nuclei are similar to those in the first pattern. The third pattern consists of large cells with an abundance of eosinophilic cytoplasm and large nuclei with prominent nucleoli. Some of these cells are giant forms and some are multinucleated. In the large pleomorphic cells, the nuclear chromatin is very loose and sometimes granular. No discrete inclusions are identified in either the nucleus or the cytoplasm.

The large and small fibrous trabeculae contain small acinar arrangements resembling bile ducts, some of which

Fig. 3—Cross section of surgical specimen showing only a rim of normal liver.



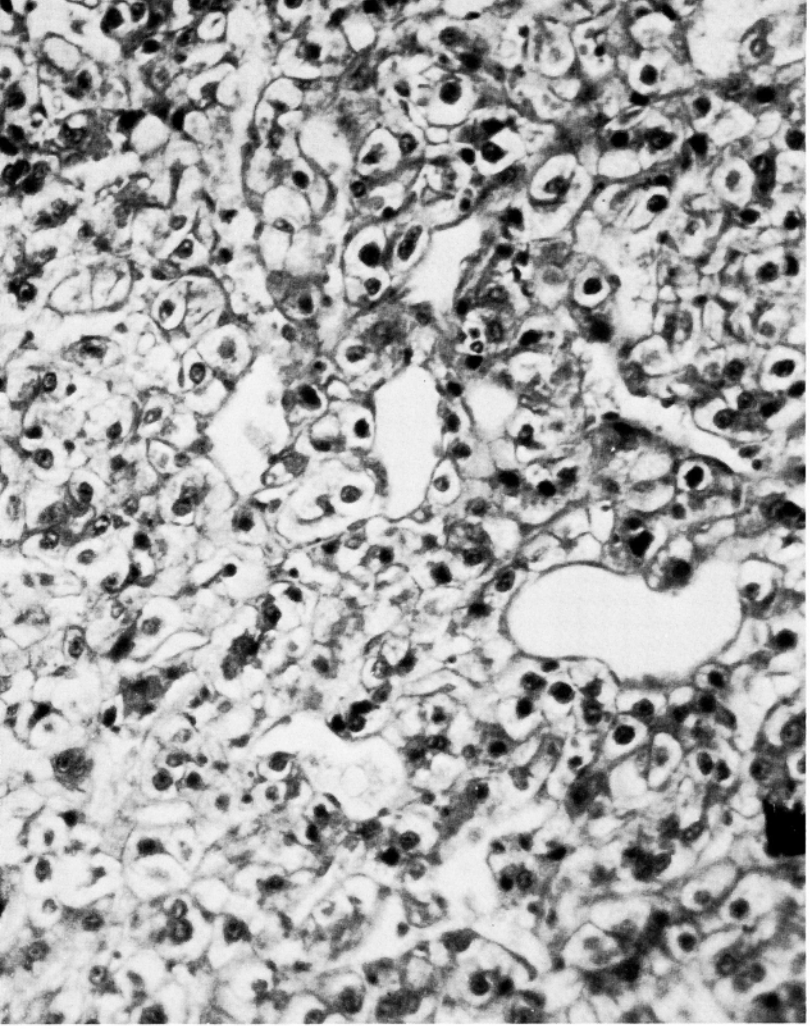


Fig. 4—In one portion of the tumor, small cells with abundant, clear cytoplasm have an orderly arrangement in thin plates, oriented along vascular sinusoids. (Hematoxylin-eosin, X64).

lie in lacunae presumably representing artifactual shrinkage. Clusters of small mononuclear cells infiltrate the trabeculae without evidence of either immature erythroids or megakaryocytes. These are interpreted as inflammatory, not extramedullary hematopoiesis.

In several areas the tumor contains large foamy histiocytes oriented individually or in sheets. Focally, the tumor elements surround large vascular lakes some of which are filled with blood and some filled with eosinophilic granular material resembling lymph. No bile formation is definitely identified. A few isolated cells contain PAS positive granules. No undifferentiated mesenchymal elements are identified in the broad fibrous areas.

Primary epithelial tumors of the liver in infancy and childhood fall into two major groups: hepatoblastoma and hepatocarcinoma. Histologically, hepatoblastomas consist of relatively small cells resembling embryonal or fetal liver. These are further classified as epithelial or mixed depending on the presence of undifferentiated mesenchymal elements which appear in the mixed type. Hepatocarcinomas, in contrast, consist of large, pleomorphic, frequently multinucleated and grotesque cells with a pattern identical to that of primary carcinomas of the liver in the adult. The fairly good clinical separation on the basis of age usually obviates the need for a histologic differential diagnosis. Some classifications use a six year age boundary defining epithelial or mixed hepatoblastomas occurring in infancy, and hepatocarcinoma occurring later in childhood. This classification on the basis of age has been challenged by the rare examples of hepatocarcinomas in infancy. Since the prognosis of both lesions is not good, a distinction could be considered impractical and of little value. From the experience at Texas Children's Hospital and the experience recorded by others, epithelial hepatoblastomas have a somewhat better prognosis, with some instances of survival after simple lobectomy. Survival of patients with hepatocarcinoma after any management has been rare.

Considering the present case, an infant male under one year would most likely have an epithelial hepatoblastoma. Unfortunately, the histology does not conform to that pattern. Although some of the elements could pass for fetal parenchymal cells, the large cells, the clusters of giant forms with multinucleation, and the broad cellular trabeculae characterize hepatocarcinoma.

Having made this distinction a hedge is necessary. Cellular tumors with histologic patterns of malignancy during the first year of life do not necessarily conform to the same biologic behavior as tumors of similar configuration occurring later in life. The mechanisms are not clear but parallels are found in sacrococcygeal teratoma, neuroblastoma, Wilms' tumor, adenocarcinomas of the testis and others.

This lesion is interpreted as a hepatocellular carcinoma occurring atypically in an infant with a guarded prognosis in light of the infant's age.

Dr. Rosenberg's diagnosis: HEPATOCARCINOMA

Histopathologic diagnoses submitted by mail:

Hepatocarcinoma	33
Hepatoma	24
Hepatoblastoma	33
Pheochromocytoma	9
Adrenocortical carcinoma	6
Others	12

Dr. Rosenberg: Hepatoma is all right but it doesn't help too much; hepatoblastoma I think we have already discussed. Adrenocortical carcinomas and hepatic carcinomas do share something in common. They are both present in a high association with infants who have congenital malformations, namely, hemihypertrophy. Wilms' tumor, hepatoblastomas and adrenocortical carcinomas all share what is apparently a dysontogenetic basis; that is, they are probably determined, at least in some, by a genetic configuration.

Dr. Regato: Drs. Prapont Piyaratn, of Bangkok, and L. P. Dehner, of Saint Louis, Missouri, also made a diagnosis of hepatocellular carcinoma. Dr. E. Bemis, of Milwaukee, offered mixed hepatocellular and cholangiocarcinoma. Dr. L. B. Henley, of Fort Sam Houston, called it an embryonal hepatoma. Dr. L. Lowbeer, of Tulsa, proposed adrenocortical carcinoma from either the adrenal or the intrahepatic adrenal cell nests. Dr. R. M. Sherwin, of Colorado Springs, and Dr. C. Maso, of Chicago, offered pheochromocytoma and Dr. F. Cabanne, of Dijon, France, chemodectoma.

Subsequent history: In March, 1972, twenty-three years after his operation, the patient was reported in good health and working normally; he was described by his family as "fat and sassy."

Dr. Ternberg: This is a case in which I would like to have an arteriogram because if we are going to think about resection of the liver, I think that I would like to have some idea what the blood supply to the other lobe is and that we don't see evidence of involvement in that side.

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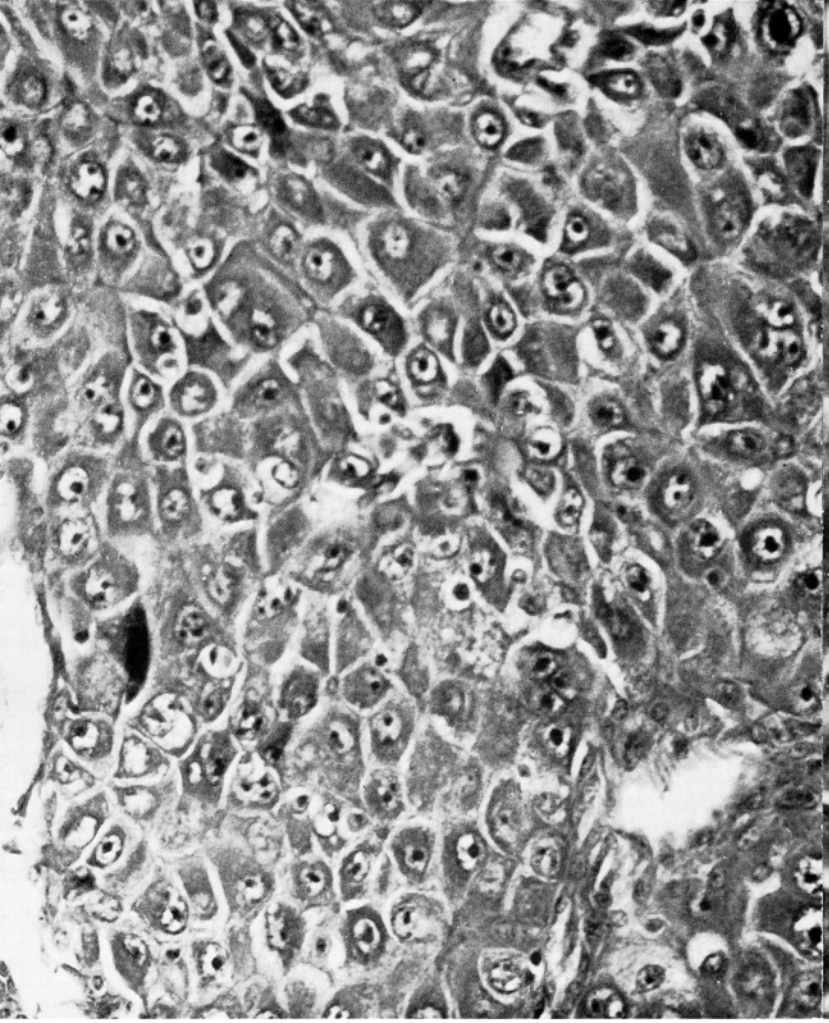

Fig. 5—In another portion of the tumor, the large, occasionally multinucleated cells have dark cytoplasm and an arrangement in thick sheets with no sinusoidal pattern. (Hematoxylin-eosin, X64).

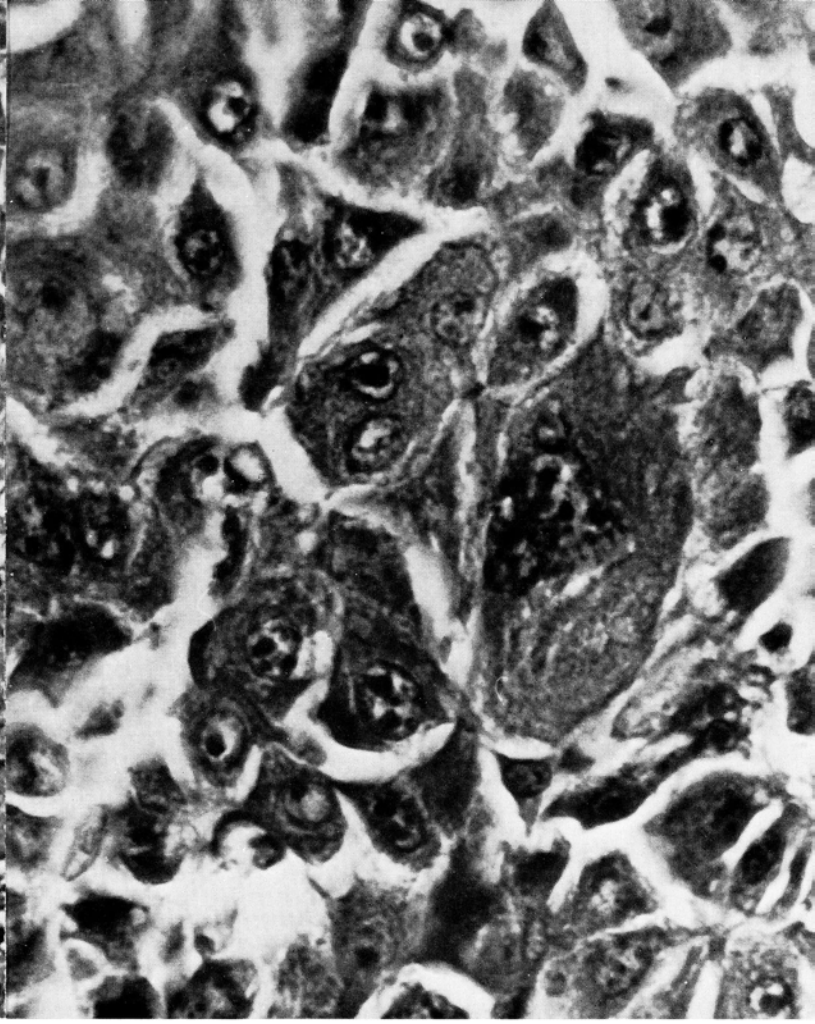

Fig. 6—In the most pleomorphic areas, cells have one or more nuclei or large bizarre giant shapes. (Hematoxylin-eosin, X160).

There is another word of caution that probably should be mentioned. This child might suddenly receive both radiotherapy and chemotherapy following the resection; it has been noted at Boston Children's that this combination is particularly lethal following resection, unless you give the liver a chance to regenerate first. Apparently what you do is to stop or prevent that regeneration from occurring and you can have a dreadful period of morbidity if this is done; so that just as a word of caution, following a major liver resection, I think that chemotherapy-radiotherapy should be withheld for the initial period of time. You can follow regeneration with liver scans quite well.

Dr. Dunbar: You will remember that I was impressed that the baby was sick and had osteoporosis and this among other things convinced me it was a malignant tumor, either retroperitoneal or of the liver. I had not personally observed nor had I heard about a correlation between tumors of the liver and osteoporosis; that is a fascinating possibility. I just was not aware of it.

C. Perez-Mesa, M.D., Columbia, Missouri: In 1949, I was still a medical student in Cuba; I discovered the story of this case later by pure accident. At the time of surgery it was obvious that the tumor was infiltrating the vessels and the surgeon was ready to close and declare himself defeated by trying to remove the lesion. However, the pediatrician insisted that this baby's only chance was to have his surgery performed. Apparently she was so successful in her plea that the surgeon did a total right lobectomy. In 1967, I discovered this case and contacted the patient who, to our surprise was still alive. The patient was in such a physical condition that he was called to serve with the Marines; on physical examination they discovered the scar. So I received a letter from the office of induction and sent them some slides. Anyway, a week ago I had the pleasure to see the patient again and now he is 23 years old, 220 pounds and playing football.

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10. *Undifferentiated-cell Malignant Lymphoma of the Terminal Ileum and Cecum*

Contributed by **B. E. Favara, M.D.** and **W. S. Davis, M.D.,** Denver, Colorado

THE PATIENT was a 9-year old baby boy in April, 1968, when he complained of lower left abdominal pain. On examaination there was some slight periumbilical tenderness but no palpable abdominal masses. The hemoglobin was 10.4%, the urinalysis revealed 2+ Ketons and the bone marrow aspiration was normal.

Dr. Dunbar: There is a non-calcified well-defined mass in the cecum and/or proximal ascending colon. The mucosal folds are stretched over it. Superior to it, in the proximal colon, are many irregular filling defects which may either be extensions of the mass of fecal material. There is a linear shadow in the upper ascending colon which is likely insignificant, though it could possibly represent a long pedicle. The appendix is not visualized. There is slightly dilated small bowel in the right lower quadrant which may represent partial small bowel obstruction.

The liver may be enlarged, because the hepatic flexure is flattened and slightly displaced infero-medially, but one cannot be sure of this. The spleen appears normal, as does the colon distal to the hepatic flexure. The regional bones are intact.

There may be a calcification overlying the right ileopectineal line of the pelvis, but is not recognizable with certainty on this single barium enema radiograph. There are two lytic defects in the right proximal humerus, the upper, which is in the metaphysis just contiguous to the zone of provisional calcification, is faint, moderately well-defined, slightly lobulated, about 1 cm in diameter, and partially filled with bone. The lower, with irregular shape, is about 2 cm in diameter, immediately deep to the lateral cortex, with some adjacent sclerosis of bone. The contour of the upper humerus and metaphysis and epiphysis are normal. The cortex overlying the lower of the two defects is slightly thin but otherwise intact. There is no soft tissue mass. The regional bones are intact, with the possible exception of some subperiosteal new bone formation on the inferior aspect of the right distal clavicle.

An ileocolic intussusception at this stage would have to be considered, and if present, would be due to a polypoid lesion of the ileum, since the "ideopathic" ileocolic intussusception of infancy virtually never occurs at this age. A mucocele of the appendix may produce just such changes, and its possibility is somewhat increased by the lack of filling of the appendix by the barium enema, (though it may have been previously removed).

Lymphosarcoma of the ileal region may produce ileocolic intussusception, but the appearance suggests a filling defect in or immediately involving the ascending colon rather than an intussusception. An intussusception of the appendix of which there are several types, may produce such a defect, but the stump of the appendix is likely present and thus its being intussuscepted is unlikely.

Benign mesodermal tumors such as fibroma, myoma, lipoma and angioma all have very low incidence in this age group, as does carcinoid tumor.

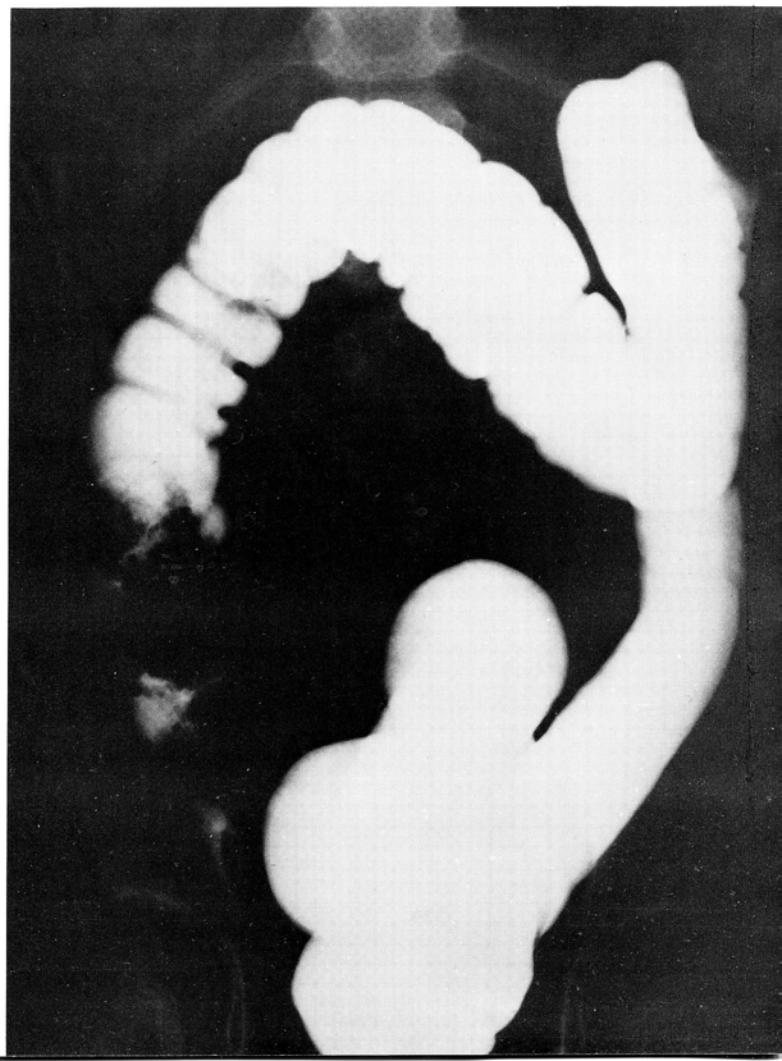
Dr. Dunbar's impression: 1) MUCOCELE OF APPENDIX 2) LYMPHOSARCOMA OF THE DISTAL ILEUM.

Roentgenologic impressions submitted by mail:

Malignant lymphoma	26
Carcinoma of cecum	13
Tuberculosis	12
Intussusception	10
Abscess	9
Regional enteritis	9
Others	12

Dr. Dunbar: Carcinoma of the cecum would be extremely rare; this very well defined lesion with the mucosal pattern stretched over it is not characteristic of such a specific malignant lesion in the cecum. Tuberculosis pro-

Fig. 1—Well-defined mass of cecum and ascending colon.



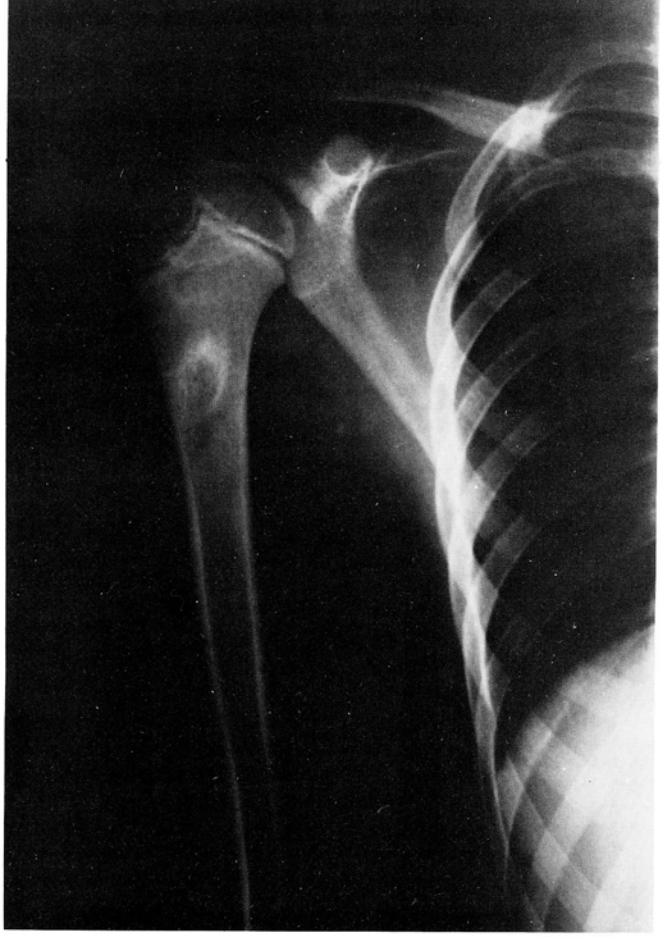


Fig. 2—Benign lytic defects of the proximal humerus.

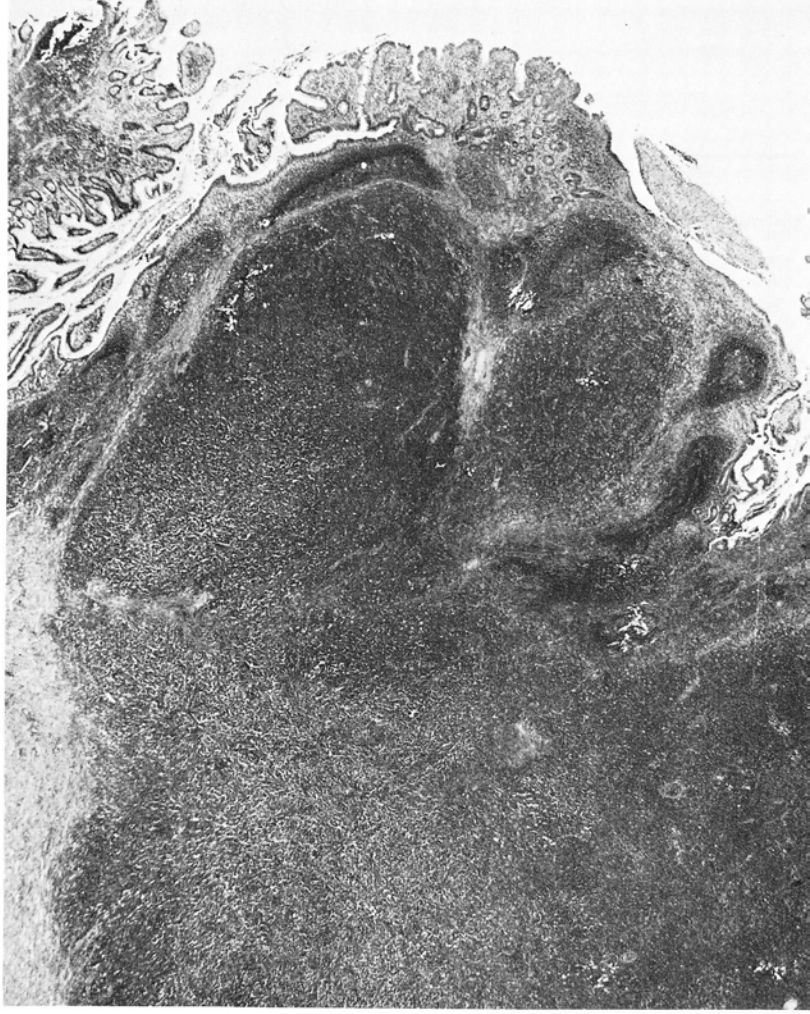


Fig. 3—A broad, cellular monotonous sheet of tumor extends superficially from the submucosa, compressing and distorting the normal landmarks. (Hematoxylin-eosin, X20).

duces circumferential changes with spasm of the cecum and I do not believe we have them here. Intussusception, I have discussed. Abscess is possible in view of the pain, but generally an abscess produces much more in the way of diffuse changes with spasm of the bowel and perhaps movement of the bowel away from the flank; I don't think it is a very good possibility. Regional enteritis I don't believe is a good possibility at all, unless it were considered to be the cause of an ileocolic intussusception and I just think it is very unlikely.

Dr. Regato: Drs. D. H. Kersey, of Colorado Springs, and P. H. Riemenschneider, of Santa Barbara, offered an impression of lymphosarcoma of the ileo-colon. Dr. B. Felson, also suggested malignant lymphoma with intussusception.

Operative findings: In April, 1969, an abdominal exploration was done; an intramural mass, 5 cm in diameter was found in the terminal ileum. The terminal ileum, the cecum and part of the ascending colon were resected. The surgical specimen presented a tumor 4 x 3 cm partially obliterating the lumen of the cecum and apparently infiltrating the serosal surface; a large mass of paracecal nodes was also resected.

Dr. Rosenberg: A broad sheet of lymphoid elements occupies the mucosa and submucosa of the ileum near the ileocecal valve. The lymphoid tissue extends from the mucosa into the muscular coat destroying the landmarks of the submucosa with isolated lymphoid nests deeper within the muscle but without apparent extension into the serosa. Superficially, a small amount of fibrinopurulent exudate covers the eroded mucosa. Peripherally, the mucosa contains a few distorted glands and blunted villi.

The lymphoid tissue has a neoplastic pattern with no nodules or germinal centers, interrupted only by a few blood vessels and fragments of connective tissue from the invaded intestinal wall. The compressed adjacent structures of the ileum contains normal lymphoid nodules. The tumor cells are arranged in a broad sheet with no characterizing architectural pattern. The fairly uniform cells have scanty or inconspicuous cytoplasm and oval nuclei with finely clumped chromatin and a single nucleolus. The small amount of reticulin appears to be the remnant of the invaded tissue. The cells are not pyroninophilic. A few pyknotic forms, a moderate number of cells in mitosis, and a small number of eosinophils provide the only interruption of the monotony.

Very few cell types produce tumors in the small intestine in children. Epithelial lesions are extremely uncommon, consisting almost entirely of papillary structures accompanying the Peutz-Jegher syndrome. Nodular inflammatory infiltrates accompany granulomatous entercolitis but present little difficulty in histological differentiation from neoplasm.

The differential diagnosis of the cytologic type presents a little more difficulty. Using the classification of Rappaport and Gall, only three of the four lymphoma types occur in childhood, always in a diffuse pattern. Well differentiated lymphocytic lymphoma is extremely uncommon in children. Of the remainder, histiocytic lymphomas rarely occur as a primary tumor in the intestine. The remaining

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Fig. 4—At this level, the tumor occupies the submucosa and invades and compresses the muscularis mucosa. A small amount of normal mucosa lies superficially including a lymphoid nodule with a germinal center. (Hematoxylin-eosin, X25).

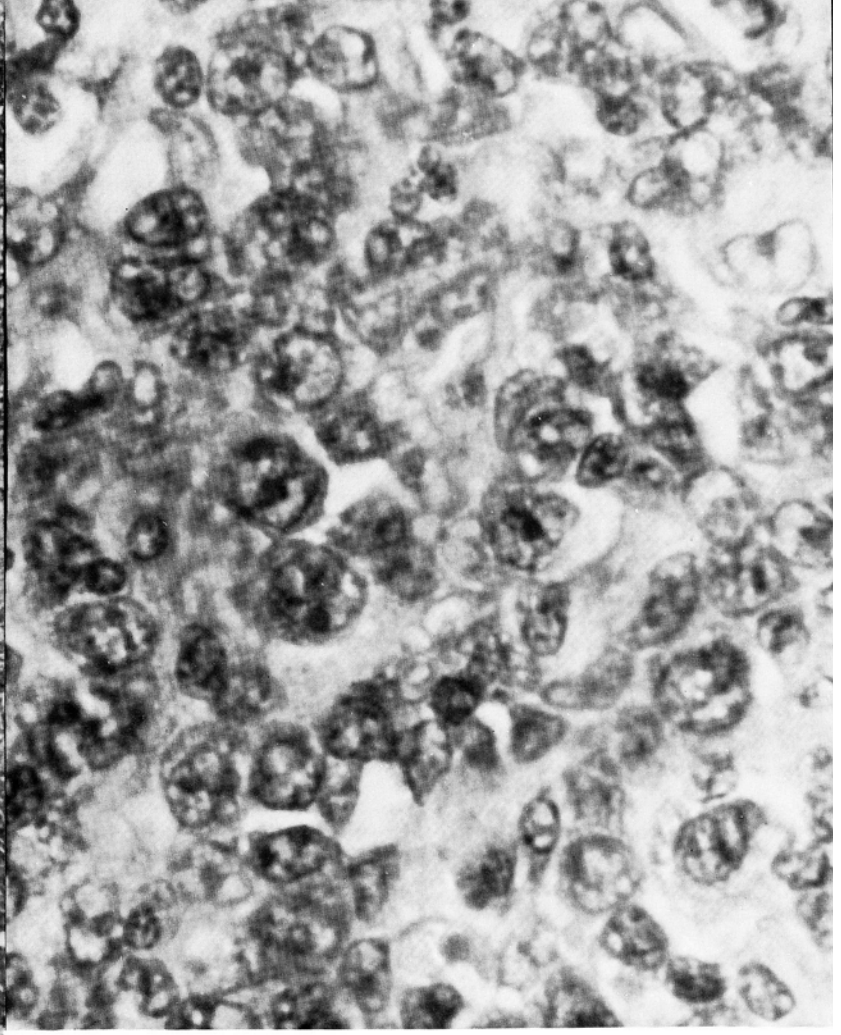

Fig. 5—The tumor cells have a uniform appearance with a thin rim of cytoplasm and a rounded nucleus with finely granular chromatin and a single nucleolus. (Hematoxylin-eosin, X160)

two tumor cell types: stem or undifferentiated cell, and poorly differentiated or lymphoblastic lymphoma may each involve the intestine. The uniformity of cell appearance, the finely granular chromatin, and the prominent nucleoli identify the tumor as stem cell lymphoma. This is the cell type encountered in each of the six examples of intestinal lymphoma identified at the Texas Children's Hospital.

Stem cell lymphoma in an extra nodal site suggests a relationship to Burkitt's lymphoma. The similarity to Burkitt's is restricted to the location in the abdomen and the uniformity of the immature lymphoid elements. More characteristic of Burkitt's lymphoma and lacking in this case are the "Starry sky" distribution of histiocytes and tumor cell pyroninophilia.

Malabsorption syndrome has been described in 25% of patients with lymphoma of the small intestine and, in one series, 16% of patients with non-tropical sprue developed lymphoma. Neither the clinical history nor the structure of the intestinal villi suggest malabsorption in this patient.

Intestinal lymphoma has a geographic distribution and has been described in the Middle East as apparently different from the typical Burkitt's lymphoma. Reports from Israel, Iran, and Lebanon describe the relatively high incidence of small intestinal lymphoma in native born children of that area.

The most common sites of intestinal lymphomas are the distal ileum and cecum; involvement of the proximal ileum, jejunum, and the duodenum is rare. The gross patterns of intestinal lymphoma has been described as aneurysmal, polypoid, constrictive or ulcerative. At Texas Children's Hospital there have been six intestinal lymphomas, five in the terminal ileum and one in the cecum, all either aneurysmal or polypoid. Children with polypoid lesions presented with intussusception, characterizing intussusception after two years of age as associated with a specific lesion contrasting with the lack of specific lesion in idiopathic intussusception of infancy.

The prognosis in the cases of intestinal lymphoma at Texas Children's Hospital has been poor. One surviving child was operated in the last six months, the status of one patient is unknown to me, and the remaining four patients have died. Fu and Perzin report 18 children with primary lymphoma of the intestine with six surviving beyond five years.

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Dr. Rosenberg's diagnosis: UNDIFFERENTIATED-CELL MALIGNANT LYMPHOMA.

Histopathologic diagnoses submitted by mail:

Malignant lymphoma	121
Stem-cell type	2
Reticulum-cell type	25
Histiocytic type	12
Lymphoblastic type	15
Lymphocytic type	21
Burkitt's	8
Straight	28
Others	6

Dr. Rosenberg: Perhaps someone would care to comment on the different terminology that pathologists use. I don't think that I will go into it. We all do agree that this is a lymphoma.

Dr. Regato: There was almost complete unanimity in the diagnosis of malignant lymphoma but quite a melee in reference to the cell that the individual expert decided upon as the type, or cell of origin. Dr. Vogt-Hoerner, of Tunisia, offered a diagnosis of Burkitt's lymphoma. Dr. J. B. Frerichs, of El Paso, predicted that many would diagnose "pseudolymphoma"; Dr. G. B. Elliott, of Vancouver, Canada, did offer such a diagnosis and hoped that Dr. Rosenberg and others at the CANCER SEMINAR might discuss the histologic features of the intestinal lymphomas, namely the scarring, vascularity and atrophic foreign body content.

Subsequent history: Following operation the patient received a number of irradiations with conventional 250 Kv. equipment to large fields of the upper and lower abdomen; the "depth dose" is said to have been of the order of 1240 R, but we have no indication of the depth nor the time of fractionation. The patient also received chemotherapy, in the form of cytoxan, vincristine and also courses of prednisone. A lesion of the humerus was biopsied and reported negative. In April, 1970, all therapy was discontinued. In March, 1972, two years later, the patient was reported well.

Dr. Ternberg: This child looked to me as though he had partial intestinal obstruction; it seems that most of the malignant lymphomas we see present as either intussusception or as an acute appendix or as an intestinal obstruction. The nicest kind are where you can resect; it looks as though you could have done it in this case and re-establish continuity. Occasionally you will see it where there is so much mesenteric involvement that it is totally impossible and you are limited at that time to doing a by-pass. It is extremely important that you do get material for histopathology and that the material is adequate, that they are going to be able to make a diagnosis from the standpoint at least of saying that it is malignant or is not malignant; there could be nothing worse than closing up this kind of an abdomen and then being faced with future therapy, radiotherapy or chemotherapy, and not having any idea what it is you are dealing with.

Editor's Note: This patient was reported well on November 15, 1972 by Dr. Holton of the Children's Hospital of Denver: he has shown no evidence of recurrence, is asymptomatic, showing normal growth and has received no further treatment..

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11. *Adenocarcinoma of the Infantile Testis (Yolk-sac Tumor)*

Contributed by **H. S. Rosenberg, M.D.** and **L. W. Able, M.D.,** Houston, Texas

THE PATIENT was a one-year old boy in December, 1962, when he was seen because of a swelling in the region of the scrotum. On examination there was a painless, rubbery mass in the scrotum. The hemoglobin was 10.6 gm%; there were 9,000 WBC with 51% lymphocytes.

Dr. Dunbar: There is diffuse osteoporosis of all the bones visualized, minimum in mid shafts and maximum in the metaphysis. In some areas, notably the distal right femur and distal left tibia, the osteoporosis is associated with pathological metaphyseal fractures. While diffuse, the osteoporosis is associated with or complicated by localized destructive bone lesions, most obvious in both lower femoral metaphyses.

The soft tissues show some muscle wasting. There is local swelling about the right knee area, likely with fluid in the joint, but this is probably caused by the fracture. A tiny amount of sub-periosteal new bone formation is present in the distal right femoral shaft. There is transverse striation of many of the metaphyses in and on the shaft side of the zone of provisional calcification in each case.

The changes in the bone films represent extensive, and indeed perhaps diffuse, malignancy involving all the bones. Such changes may be due to leukemia, though there is more localized destructive disease than is usually seen in leukemia.

There are several malignancies which can present with a painless, rubbery mass in the scrotum, but all rare. Patients being treated for leukemia sometimes develop such changes, but almost never present in this manner. Teratoma, seminoma, lymphosarcoma or embryonal carcinoma are all possible. Orchioblastoma is a characteristic tubulopapillary adenocarcinoma of the testes that occurs in infants and young children, all be it rarely. Almost all the fifty odd cases reported have been under the age of two years.

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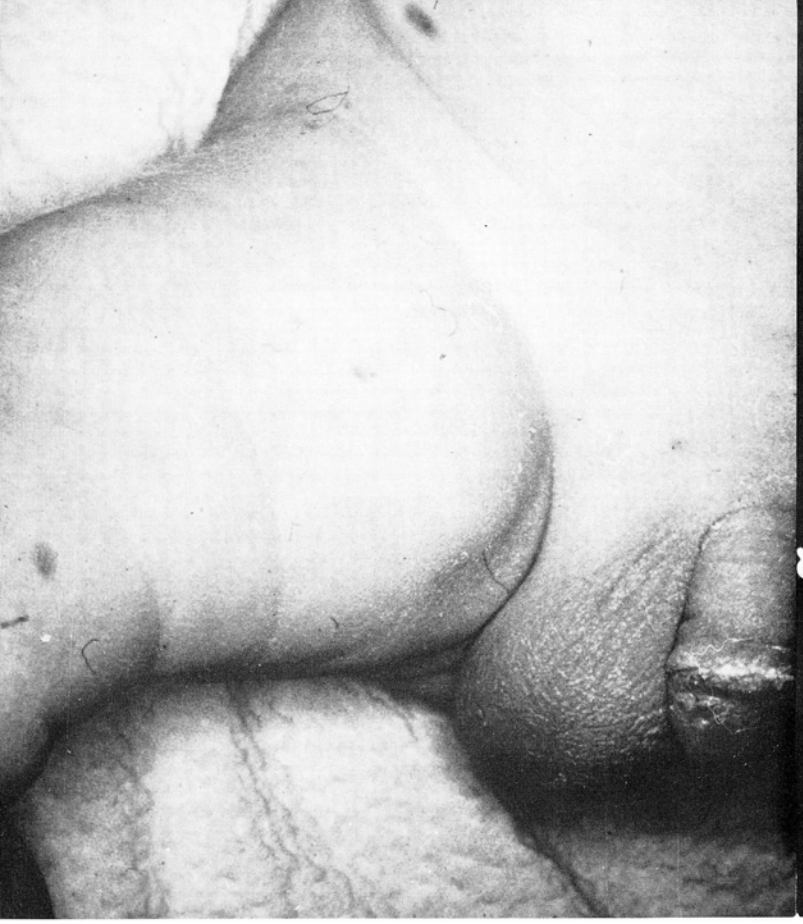

Fig. 1—Scrotal tumor.

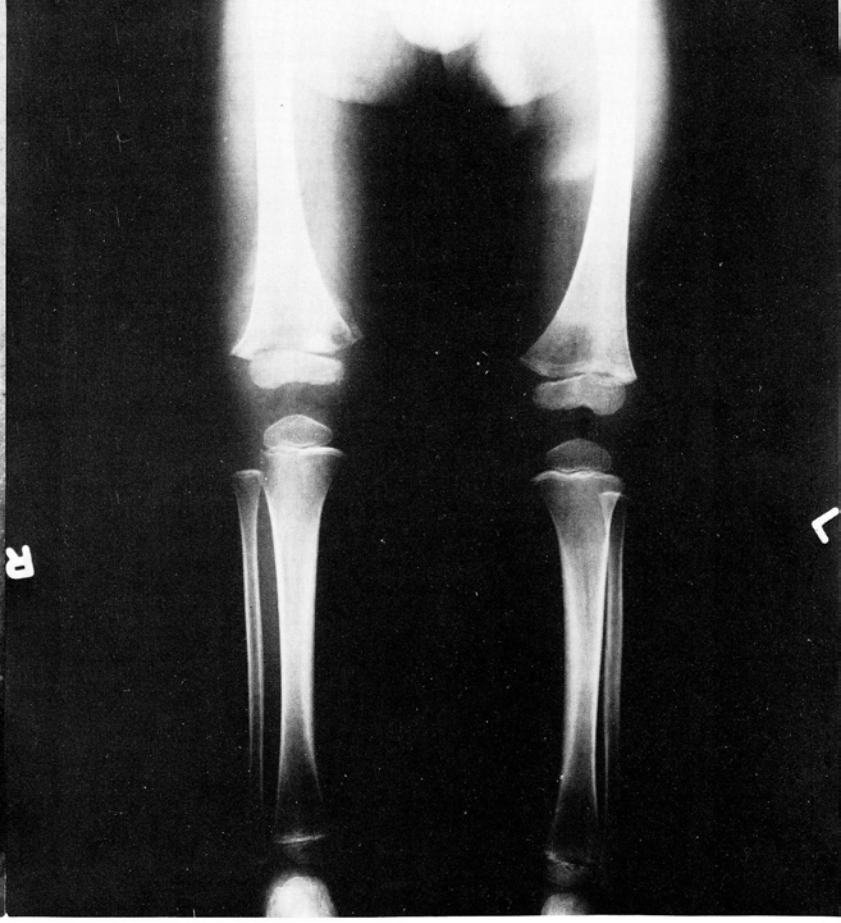

Fig. 2—Roentgenogram showing no large soft tissue mass.

Dr. Dunbar's impression: MALIGNANT TUMOR OF THE TESTIS (ORCHIOBLASTOMA?)

Roentgenologic impressions submitted by mail:

Testicular tumor	31
Acute leukemia	25
Lymphosarcoma	20
Others	15

Dr. Dunbar: This age group it does not seem to me that lymphosarcoma is likely to produce these diffuse bone destructive changes that we have seen and isn't as likely, at least, to cause the initial finding of a painless mass in the scrotum.

Dr. Regato: Drs. E. C. Hwa, of Newton, Kansas, and D. H. Kersey, of Colorado Springs, also offered an impression of testicular tumor. Dr. P. Riemenschneider, of Santa Barbara, added that it already showed metastases; Dr. B. Felson, of Cincinnati, diagnosed luetic bones. Dr. J. W. Barber, of Cheyenne, offered an impression of acute leukemia.

Operative findings: In December, 1962, the child was operated upon; a mass 5.6 x 3.5 x 2.4 cm was removed; the spermatic cord extended into the tumor but no testis could be identified.

Dr. Rosenberg: An indistinct and incomplete fibrous capsule separates a moderately cellular tumor from the adjacent immature testis. The necrotic central portion of the tumor contains a purulent exudate about the periphery. The tumor configuration has some variation with a few solid areas scattered among a loose honeycombed network of papillae, tubules, and small cystic spaces. The epithelial elements in all areas vary only moderately from cuboidal to columnar and most have a finely vacuolated cytoplasm. Flattened epithelium lines numerous small cystic spaces arranged in a festoon of channels many of which are filled with mucus. The loose vacuolated network has wide meshes lined by flattened, undifferentiated cells. Some cysts contain papillae made up of an invaginated epithelium serving as a mantle on the surface of small blood vessels. Some papillae have simple columnar epithelial mantles while others are hypercellular with inconspicuous blood vessels in a pattern resembling a cellular glomerulus. In the compact areas, the cells vary somewhat in size and shape but most have a vacuolated or poorly stained cytoplasm and nuclei which vary from small and compact to large, bizarre giant cells with finely granular nuclear chromatin and prominent nucleoli. The tumor has invaded blood vessels and extended through the capsule into the adjacent testis. Focally, the tumor surrounds small seminiferous tubules which remain fairly well preserved.

The clinical history of a hydrocele is typical and accounts for the frequent time lag between presentation of a clinical mass and the surgical excision. Following orchiectomy, this patient received chemotherapy and irradiation to his periaortic and mediastinal lymph nodes. Shortly after surgery metastases appeared first in the mediastinum followed by additional lesions in the lungs and the bones of the arms, legs, and hips. He expired at the age of 22 months. At autopsy additional metastases were identified in the liver and occipital meninges.

Some of the slides are from the testis while others are from the metastases. The pattern varies only a little depending on the concentration of the solid or papillary pattern.

The morphologic pattern characterizes the testicular adenocarcinoma of infancy also known as yolk sac tumor,

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endodermal sinus tumor of Teilum, malignant teratoma, or embryonal carcinoma. Sufficient unique characters of this lesion serve to distinguish it as an entity whatever the designation. This malignant epithelial tumor of infants only rarely occurs later in life and may involve other anatomic sites such as ovary, mediastinum, and sacrococcygeal region. Characteristically, the tumor presents during the first years of life, and when it spreads, invades directly or metastasizes by a hematogenous route.

The fairly rapid dissemination and death of this patient does not characterize the usual course of this tumor. The tumor in infants under the age of two has a survival rate of up to 89% after simple orchiectomy contrasting with a survival rate of 12.5% after the age of two.

The designation yolk sac tumor implies an origin from extra-embryonic membranes distinct from a teratoma composed of the embryonic germ layers. Teratomas and yolk sac tumors make up the principal form of germinal epithelial tumors of the prepubertal testes. Malignant behavior of a testicular teratoma in infancy or childhood is relatively uncommon. Other germinal tumors of the testis, seminoma and choriocarcinoma in infancy are even more uncommon.

Dr. Rosenberg's diagnosis: ADENOCARCINOMA OF THE INFANTILE TESTIS (YOLK SAC TUMOR).

Histopathologic diagnoses submitted by mail:

Endodermal sinus tumor of testis	27
Papillary adenocarcinoma of testis	25
Embryonal-cell (yolk sac) carcinoma	24
Orchioblastoma (infantile)	18
Adenomatoid tumor of rete testis	10
Mesothelioma (tunica vaginalis)	14
Mesonephric (papillary) carcinoma	2
Others	3

Dr. Rosenberg: There is a remarkable uniformity; we are all really talking about the same tumor. So that we are fairly well unified on the unique character of this lesion.

Dr. Regato: Drs. W. C. Bauer, of Saint Louis, Missouri, and E. Bemis, of Milwaukee, diagnosed orchioblastoma; Dr. Bemis pointed at the resemblance to papillary carcinoma of the thyroid including psammoma bodies. Dr. H. Hamperl, of Bonn, Germany, proposed papillary adenocarcinoma and questioned its possible mesonephric origin. Dr. Samruay Shuangshoti, of Bangkok, offered mesothelioma, adenomatoid tumor of the scrotum. Dr. J. Ray, Jr., of Lubbock, Texas, considered mesothelial papilloma of the tunica with low malignant potential. Dr. L. Lowbeer, of Tulsa, further designated this lesion as malignant mesothelioma of the tunica vaginalis, producing hyaluronic acid. Dr. F. Cabanne, of Dijon, France, chose the designation malignant testicular mesoblastoma and clarified that it was the equivalent of endodermal sinus tumor, yolk sac allantoic tumor or Schiller mesonephroma.

Subsequent history: During 1963 the patient presented radiographic evidence of pulmonary and bony metastases. The child died in October, 1963; at autopsy metastases were found in the lungs, bones, adrenals, lymph nodes and meninges.

Dr. Ternberg: Did this child get any therapy after the removal of the testicle?

Dr. Rosenberg: Yes, this child was treated but I don't have the regimen here and I don't know what it was.

Dr. Ternberg: Isn't it true that this is a relatively benign tumor under the age of two? I was just wondering whether it might not be smart perhaps to treat him and not stop re-

Fig. 3—The tumor focally extends through the testicular capsule into the epididymis. Although solid, the tumor has a few small cysts and a mucoid character.

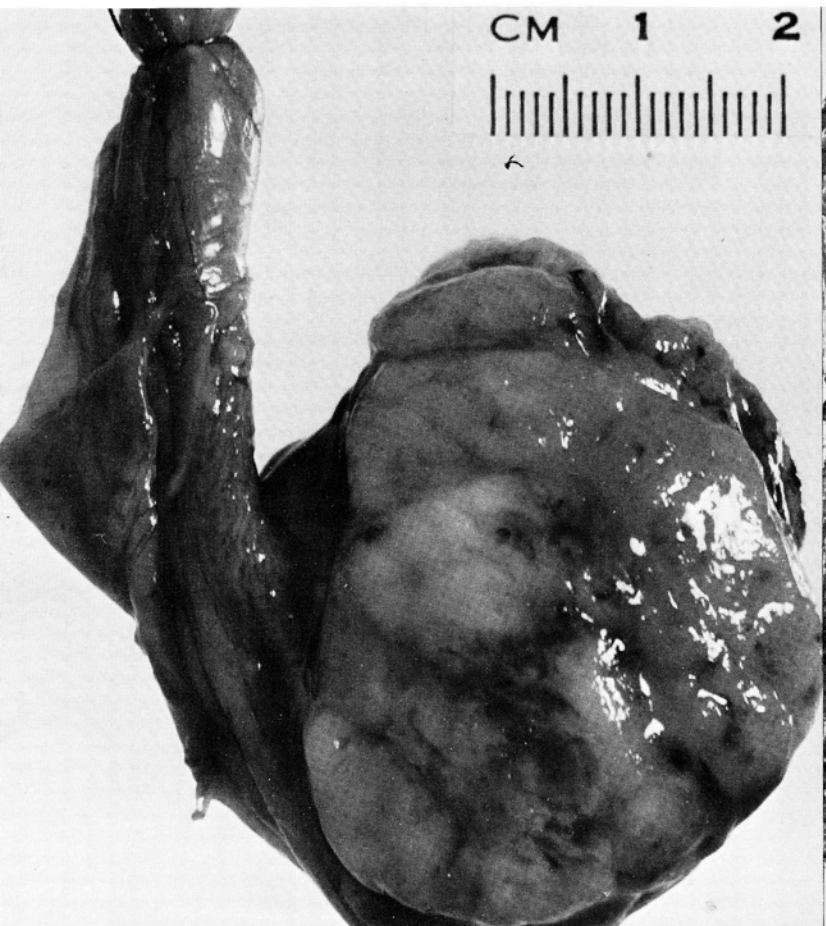
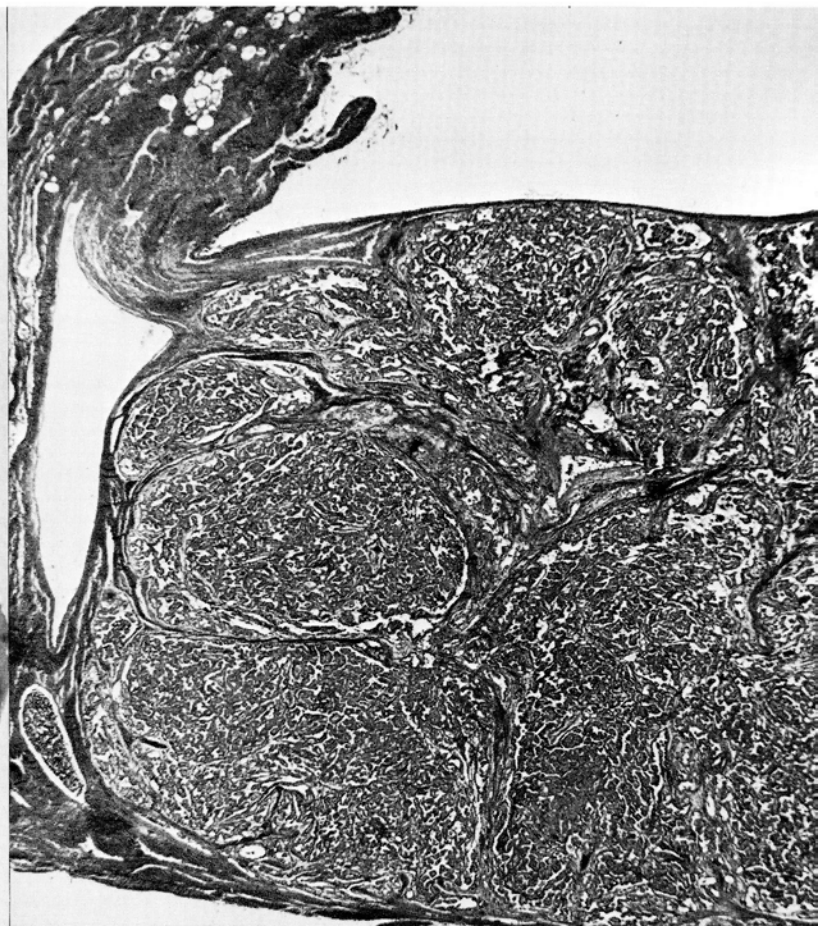


Fig. 4—The individual lobules of tumor contain a compressed network of cysts, papillae, and few solid areas. (Hematoxylin-eosin, X16).



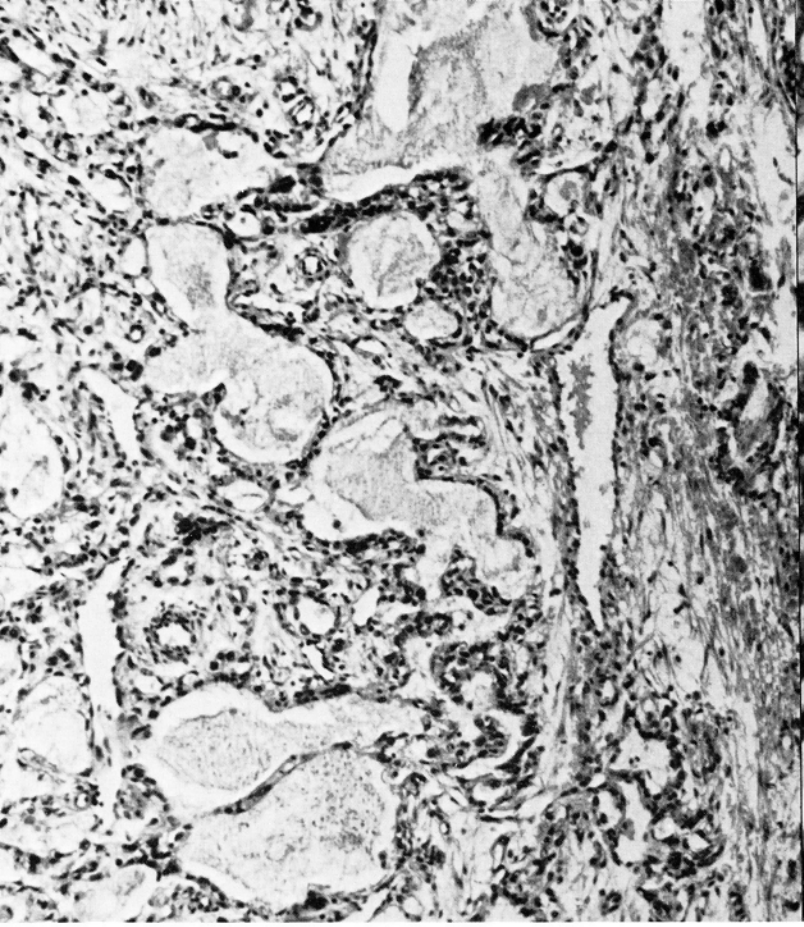


Fig. 5—In much of the tumor, a loose honeycombed network of tubules and cystic spaces is filled with mucus and lined by flattened epithelium. (Hematoxylin-eosin, X64).

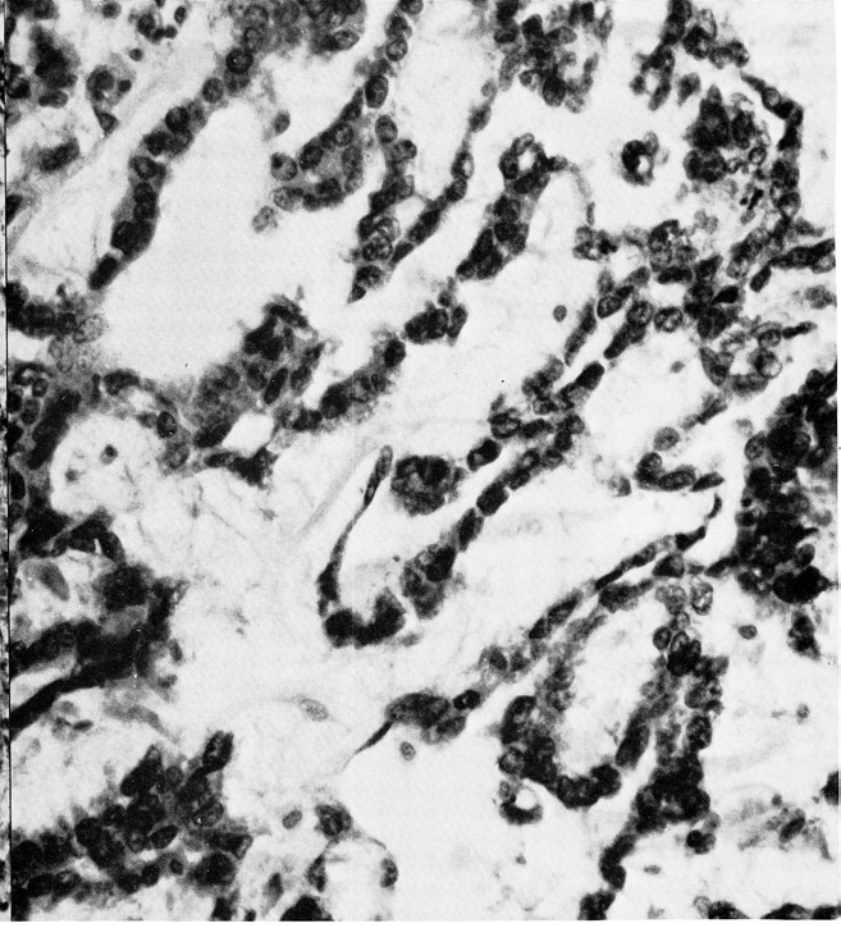


Fig. 6—Focally the channels form festoons lines by dark staining cuboidal epithelium. (Hematoxylin-eosin, X60).

Fig. 7—The epithelium forms a mantle on blood vessels invaginating glomerulus-like into small cystic spaces. These are the Schiller-Duval bodies characterizing Yolk sac tumor. (Hematoxylin-eosin, X160).

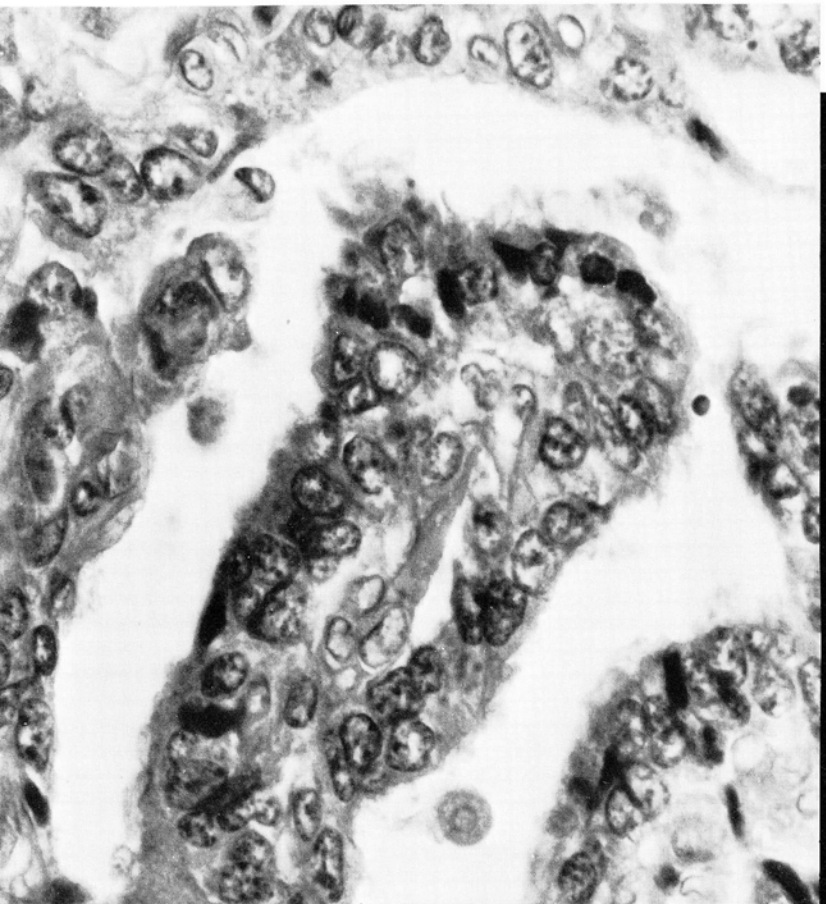
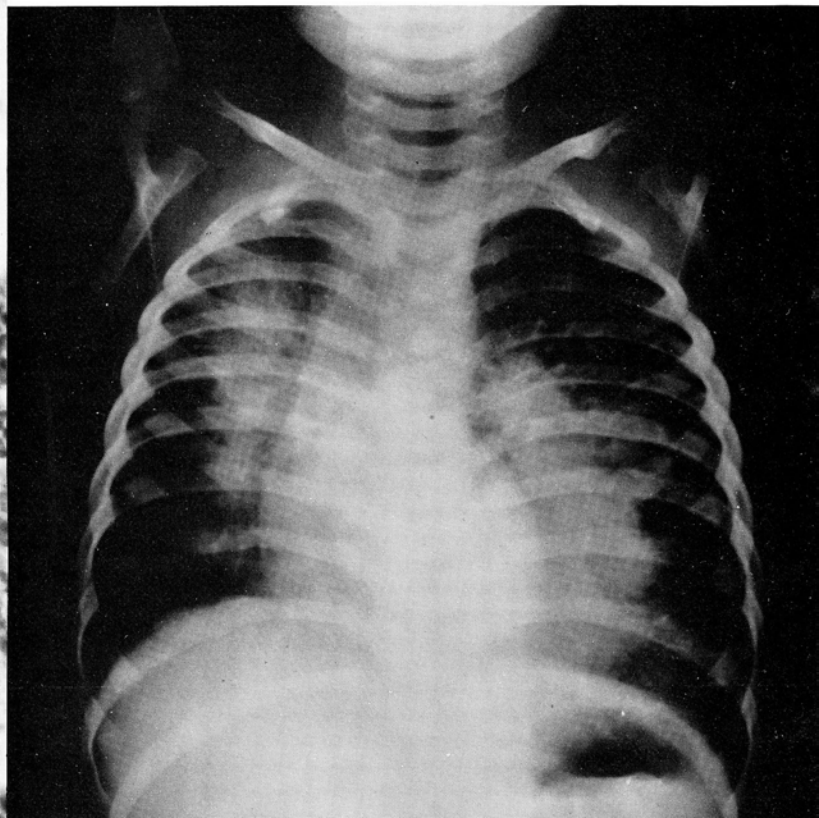


Fig. 8—Pulmonary metastases.



garding it as benign because even a 25% mortality seems rather steep.

E. B. Price, Jr., M.D., Denver, Colorado: I would agree with everything that Dr. Rosenberg said except that this tumor does occur in adults. It is very rare but a few of the so-called embryonal carcinomas of the adult do have this pattern.

Dr. Dunbar: The chest radiograph made six weeks before the bone film shows a bilateral consolidation of the medial portion of each lung, with bilateral hilar lymph node enlargement and with, on the left side, multiple Kerley's B Lines. The left lung is over-inflated, the mediastinal structure displaced to the right, and the left main bronchus likely narrowed.

Since the chest radiograph was made relatively early in the course of the disease, and since the bones of the thorax and the shoulders show little malignant change on the chest radiography, I choose to regard the chest findings as manifestations of the diffuse malignancy rather than a complicating infection or hemorrhage. This concept is strengthened by the partial obstruction of the left main bronchus and the enlargement of the hilar lymph nodes. So all these things fit into a picture of diffuse disseminated malignant disease at the time the child was first seen.

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12. *Embryonal Rhabdomyosarcoma of the thigh in an infant.*

Contributed by **F. P. Bornstein, M.D.** and **J. A. Backus, M.D.,** El Paso, Texas

THE PATIENT was a 4-month-old baby girl in November, 1971, when she was seen because of a mass noted in the right thigh. On examination there was a palpable mass in the area of the quadriceps muscle. The hemoglobin was 10 gm%.

Dr. Dunbar: The right quadriceps muscle shows a smoothly outlined fusiform enlargement without significant edema or increased vascularity of the overlying soft tissues. The underlying femur and all the regional bones visualized are intact, as are the joints.

The commonest malignant tumor of the somatic structures of the head and neck in childhood is rhabdomyosarcoma. Of the three commonly recognized histologic variants, the adult, the embryonal, and the alveolar, the embryonal has the highest incidence in early life. Malignant mesenchymoma is rare but may occur in somatic soft tissues. Sarcoma of alveolar soft parts is a distinctive lesion of unknown histogenesis, also known as a malignant granular cell myoblastoma or peripheral chemodectoma. It occurs as a lentiform or plaque-like mass usually in soft tissues of an extremity, but generally in adolescents or young adults.

Dr. Dunbar's impression: EMBRYONAL RHABDOMYOSARCOMA.

Roentgenologic impressions submitted by mail:

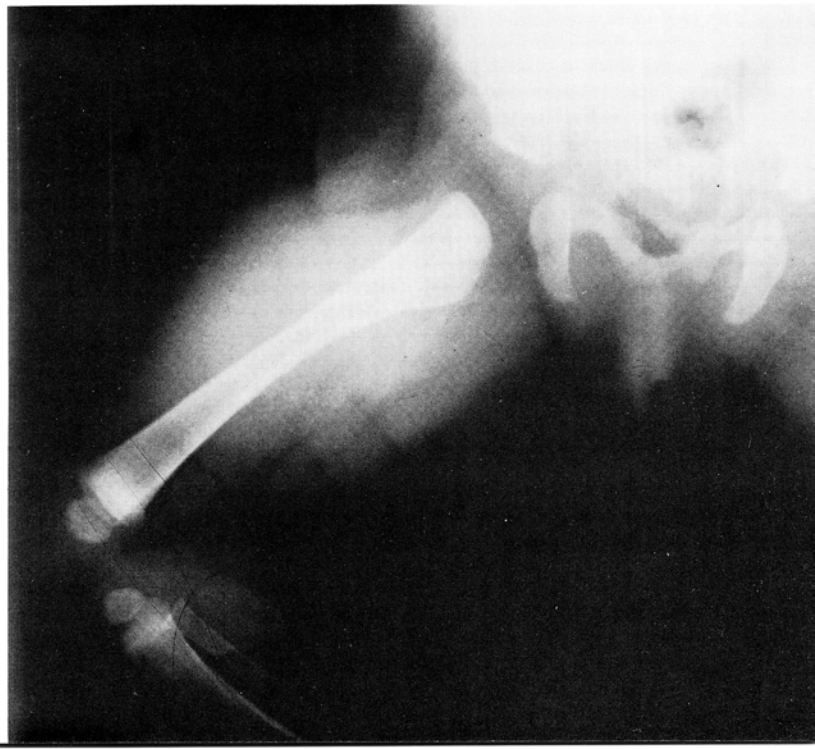
Rhabdomyosarcoma	49
Fibrosarcoma	17
Other soft tissue sarcomas	15
Others	12

Dr. Dunbar: Rhabdomyosarcoma was the favorite; fibrosarcoma and other soft tissue sarcomas would be equally tenable. I know of no valid way to distinguish them.

Dr. Regato: Dr. E. J. Keeffe, of Pontiac, and Dr. M. Daves, of Denver, offered an impression of fibrosarcoma. Dr. J. W. Barber, of Cheyenne, Wyoming, suggested rhabdomyosarcoma.

Operative findings: On November 12, 1971, a surgical exploration revealed the presence of a jelly-like mass between the muscles and the periosteum of the femur which

Fig. 1—Smoothly outlined fusiform enlargement within the right thigh.



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appeared intact, but the mass could not be removed completely. The surgical specimen consisted of several fragments of pink-yellow tissue to an aggregate of 8 cc.

Dr. Rosenberg: Interpretation of this lesion from the thigh of a five-month-old infant tests the self esteem of the pathologist and his feelings of omniscience in interpreting the destiny of primitive mesenchymal tissue. This densely cellular tumor has multiple widely spaced areas of necrosis and scanty stroma composed of thin strands of irregularly dispersed collagen. Focally, abundant collagen surrounds clusters and individual cells while it is absent in other areas of broad cellular sheets. In some areas the compact cellular sheets resemble the formless monotony of a lymphoma but in other areas parallel elongated elements form a pattern of interlacing bands.

The configuration of the individual cells is best defined in the few loosely cellular areas. Elsewhere the compact pattern obscures individual cell borders. In the loose areas, the cells are rounded or occasionally elongated with a scanty eosinophilic cytoplasm. A few cells are very large or multinucleated and a few are elongated bipolar cells with a centrally placed nucleus. The cytoplasm occasionally contains vacuoles and some granules but neither longitudinal nor cross striations. The nuclei vary considerably in size although most are rounded and have a finely granular chromatin pattern and a prominent nucleolus. Mitoses are abundant.

In the differential considerations of a primitive mesenchymal tumor such as this, consideration must be given to the various cell types that may arise from mesenchyme: fat, muscle, bone, cartilage, and so forth. Since none of these differentiated tissues present themselves in this tumor, attention must be given to the pattern of poorly differentiated cells and their corresponding tumors. Of all mesenchymal malignant tumors, liposarcoma is most common in the adult and rhabdomyosarcoma is most common at younger ages. Of the various patterns in which rhabdomyosarcomas appears, the embryonal form presents as the first consideration in this case by virtue of the age, location, and morphology. Given the general incidence of soft tissue malignant tumors, rhabdomyosarcoma is the most likely lesion in the extremity of any infant or child.

In establishing the identity of an embryonal rhabdomyosarcoma, one must accept the inability to identify striations as no deterrent to the diagnosis. Having leaped the hurdle, the diagnosis of embryonal rhabdomyosarcoma comes easier. In the group of malignant mesenchymal tumors in the files at the Texas Children's Hospital, only two were not rhabdomyosarcomas. Of the rhabdomyosarcomas, most were embryonal and most had no cross striations.

The list of tumors with a similar histological pattern may be quite long and studies other than light microscopy may be necessary for an ultimate decision. Even after examination of the ultrastructure, some tumors defy identification and these have been designated as primitive mesenchymal tumors or, embryonal sarcoma with no indication as to their cell line maturation.

Embryonal rhabdomyosarcoma occurs principally in infants and children, usually in the first decade but may present at birth. Other sites of involvement than the extremity include the head and neck and the pelvic organs.

Several observers have commented on the reluctance of individual pathologists to label a tumor embryonal rhabdomyosarcoma when the compact cell pattern resembles a lymphoma as much as a connective tissue sarcoma. Reliance on isolated areas of pleomorphism, alveolar arrangements, or spindle cells may be of value but, as in the present case, these areas may be sparse. Pragmatically, identification of a specific cell type may not add a great deal to the concept of mesenchymal or embryonal sarcoma since these tumors carry an exceedingly poor survival rate with the best response following extensive surgery and chemotherapy.

Fig. 2—Compact cellular sheets form much of the tumor but the remainder has a loose formless monotony. (Hematoxylin-eosin, X22).

One's faith in prognosticating on these lesions is shaken by anecdotal experiences. One infant at Texas Children's Hospital had a lesion interpreted as a rhabdomyosarcoma of embryonal type only to make an uneventful recovery without sequelae after local and presumably incomplete excision. Similar experiences recorded by others are by far the exception and may be concluded as peculiar tumor variant, unique host resistence, or faulty interpretation by the pathologist.

Dr. Rosenberg's diagnosis: EMBRYONAL RHABDOMYOSARCOMA.

Histopathologic diagnoses submitted by mail:

Rhabdomyosacoma	32
Soft tissue sarcomas	50
Hemangiopericytoma (malignant)	21
Hemangiosarcoma	8
Malignant lymphoma	10
Others	12

Dr. Rosenberg: I didn't recognize the vascularity that I have identified in the other hemangiopericytomas. Hemangiosarcoma, I know the word, but I don't know the disease. Kaposi's sarcoma I recognize, but if there is such a lesion as a sarcomatous blood vessel disease in infancy or childhood, then I have not seen it nor have any awareness of it. Malignant lymphoma is certainly, from a cyto-

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logic basis, not a difficult lesion to accept, although I certainly have not seen one with this extent in soft tissues.

Dr. Regato: Dr. G. Gricouroff, of Paris, Dr. A. O. Severance, of San Antonio, and Dr. P. Piyaratn, of Bangkok, also made a diagnosis of rhabdomyosarcoma. Dr. D. M. Lang, of Sioux Falls, South Dakota, proposed undifferentiated sarcoma. Dr. J. McQuaid, of San Diego, California, offered fibrosarcoma. Dr. F. B. Askin, of Saint Louis, Missouri, suggested a possible synovial sarcoma. Dr. D. Assor, of Columbus, Ohio, preferred malignant pericytoma. Dr. J. M. Kissane, of Saint Louis, Missouri, considered this the most difficult case of the CANCER SEMINAR, a tumor of undifferentiated mesenchyme with no apparent histogenesis. Dr. W. C. Bauer, of Saint Louis, wondered as to the possibility of leukemic infiltration. Dr. R. Marcial-Rojas, of San Juan, Puerto Rico, hesitated between malignant histiocytoma and hemangioendothelial sarcoma.

The AFIP rendered a report prepared by Dr. F. M. Enzinger (Accession number 1395152): Sarcoma, type undetermined. Dr. J. Kuzma, of Milwaukee, offered a diagnosis of questionable fibroxanthosarcoma.

Subsequent history: The parents of the child refused any further treatment of any kind. The child expired in March, 1972; no autopsy was done.

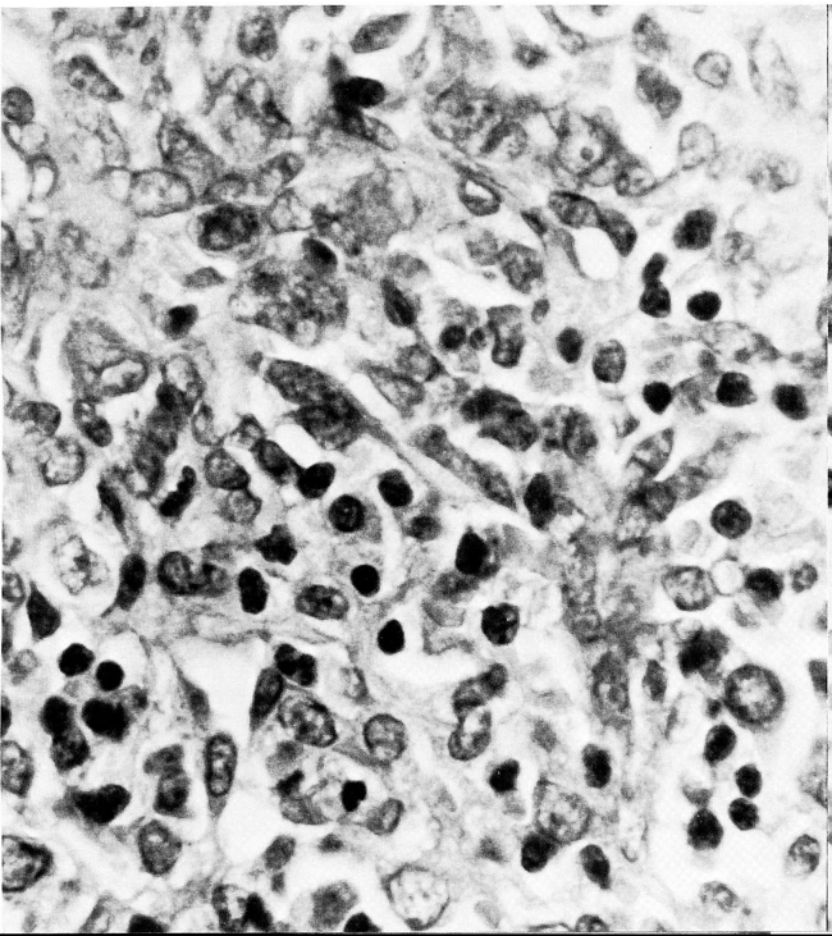
Dr. Ternberg: Soft tissue tumors in children are extremely difficult problems. Once the child has been worked up with a radiographic examination, et cetera; that the next thing that should be done is a biopsy, unless the mass is situated in such a way that it can be easily excised, not disturbing functional components, et cetera; most times this is not true. Once you have the incisional biopsy, you are dependent upon your pathologist to tell you whether this is something that needs more radical treatment or something that you can reasonably consider benign. If the tumor is malignant you are going to have to approach the family afterwards to suggest that amputation is going to be required. There is no way to radically resect and have a functional limb left. This is the reason why it is important to have this information before you go into the operating room as far as therapeutic surgery goes. There would be some instances when you might be willing to do something less than amputation, but I doubt that the diagnoses that were submitted on this one, that you would offer anything less.

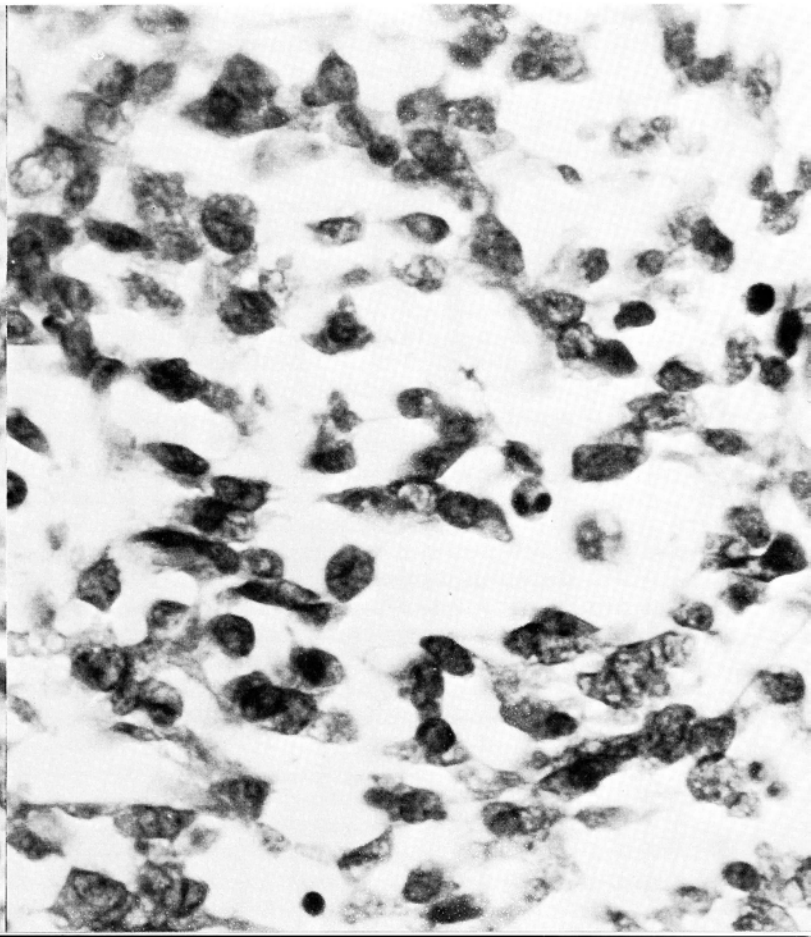
F. P. Bornstein, M.D., El Paso, Texas: We were especially interested to get a roentgenogram of the chest with the metastatic lesions because one of the consulting letters suggested that this case had a relatively good prognosis; at least now we know and can take another look at the histology on the light of a very bad prognosis.

L. L. Lowbeer, M.D., Tulsa, Oklahoma: We saw a tumor somewhat similar to that in a 50-year-old man, surrounding the fibula, but the fibula radiographically seemed to be embossed by it. There was then an amputation performed and the tumor had a variety of structures. In the soft tissues it had a structure similar to this one here, some others resembling a Ewing's sarcoma, but within the fibula it had a structure of osteogenic sarcoma with areas of hemangioma. In other words, it resembled these tumors

Fig. 3—In the few loose areas, the pleomorphism becomes apparent. Some few cells are rounded and "lymphoma-like" while others are elongated and spindle shaped. (Hematoxylin-eosin, X160).

Fig. 4—A few cells have a central round nucleus with unipolar or bipolar cystoplasmic extensions. No cytoplasmic striations are identified. (Hematoxylin-eosin, X160).





which had been designated at the Memorial Hospital, as purely potential sarcomas which can differentiate into various directions or remain indifferentiated. The patient died two years later from multiple metastases.

J. D. Cox, M.D., Washington, D.C.: Could you repeat again what treatment was given to this patient?

J. A. Backus, M.D., El Paso, Texas: Vincristine, actinomycin and cytoxin.

Dr. Cox: If we will assume that the patient has some sort of a rhabdomyosarcoma or soft tissue sarcoma of infancy, the experience has been that an operative procedure is not the only treatment of choice for these people and that if for some reason a reasonable operative procedure cannot be utilized that these patients should be offered radiotherapy with the likelihood in an increasing number of long term control. So the fact that the patient could not be treated without sacrifice of the limb or perhaps even treated adequately at that rate, you shouldn't leave us with the idea that there was no treatment available at all.

Dr. Ternberg: In essence, I agree with what has just been said, but I think that the statistics that are available indicate that so-called triple therapy will give you the best result if you are dealing with this rhabdomyosarcoma.

Dr. Regato: What are the results?

Dr. Ternberg: With triple therapy there are two series. There is a series from Columbus Children's Hospital, from Pittsburgh, where there has been surgery combined with radiotherapy and chemotherapy and there is a pretty good comparison for this with a series that comes out of the Mayo Clinic where the triple therapy was not used. There is a real difference between the two series; at the M. D. Anderson Hospital they do recommend the use of radiotherapy and chemotherapy in the ones where it is impossible to do surgery. I think that if it is possible to add surgery, and this would include amputation, that the results are better.

Dr. Cox: The comment I was making was actually pertaining to the local tumor alone and I really do not have any disagreement particularly if there is a high likelihood of dissemination, but we know now that with adequate radiotherapy reaching reasonable dose levels of the order of 5,000 Rads in 5 weeks, that local control can be obtained in approaching a hundred percent of cases; this has been demonstrated now for several different sites, including orbit and soft tissues of extremities.

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13. *Neurilemoma of the Leg*

Contributed by **J. F. Wilson, M.D., M. L. Wilson, M.D.** and **V. R. Condon, M.D.,**
Salt Lake City, Utah

THE PATIENT was a 3-month old baby girl in August, 1971, when she was examined because of a history of a mass in the right leg which had been growing since birth when it was first noted. On examination a moveable, non-tender mass was palpated in the calf of the right leg measuring about 3 cm in diameter. The patient had another smaller soft tissue mass in the right cheek.

Dr. Dunbar: There is a soft tissue mass in the right upper calf muscle, presumably involving or arising in the gastrocnemius. The tibia at and below this level is thinned, curved, possibly elongated, and with irregular sclerotic cortex throughout its circumference. There is more marked thickening of the mid tibial cortex anteriorly, where there is also slight irregularity. The fibula is likely somewhat elongated and is thin and curved, particularly distally. The femur, the knee joint, the ankle joint and the posterior foot are intact.

This lesion is characteristic of neurofibromatosis involving the tibia. While it usually produces or is associated with a pathologic fracture, it can sometimes present in this manner, with thin, curved tibial shaft (called kyphoscoliosis of the tibia), and thickening, sclerosis and irregularity of the involved mid shaft cortex. More often, a pseudofracture or ununited fracture is present when the lesion is first radiographed. If the bone is intact, as in this case, and it does undergo fracture, or if an attempt at osteotomy correction is made, healing of the fracture or osteotomy is very unlikely.

There may or may not be evidence of neurofibromatosis elsewhere in the body in infancy, or developing later in life. Histologic examination of the bone itself and related soft tissues does not necessarily show well defined neurofibromatous changes. An associated soft tissue mass, as in this case, is rather unusual.

Dr. Dunbar's impression: NEUROFIBROMATOSIS.

Roentgenologic impressions submitted by mail:

Neurofibromatosis	58
Soft tissue sarcoma	16
Hemangioma	7
Others	10

Dr. Dunbar: I don't believe that hemangioma is worth considering here, because it doesn't usually produce this rather characteristic and unique appearance in bones and because the vascular tissue show no evidence of increase in vessels in the area.

Dr. Regato: Drs. C. A. Poole, of Miami, and B. Felson, of Cincinnati, also offered a diagnostic impression of neurofibromatosis.

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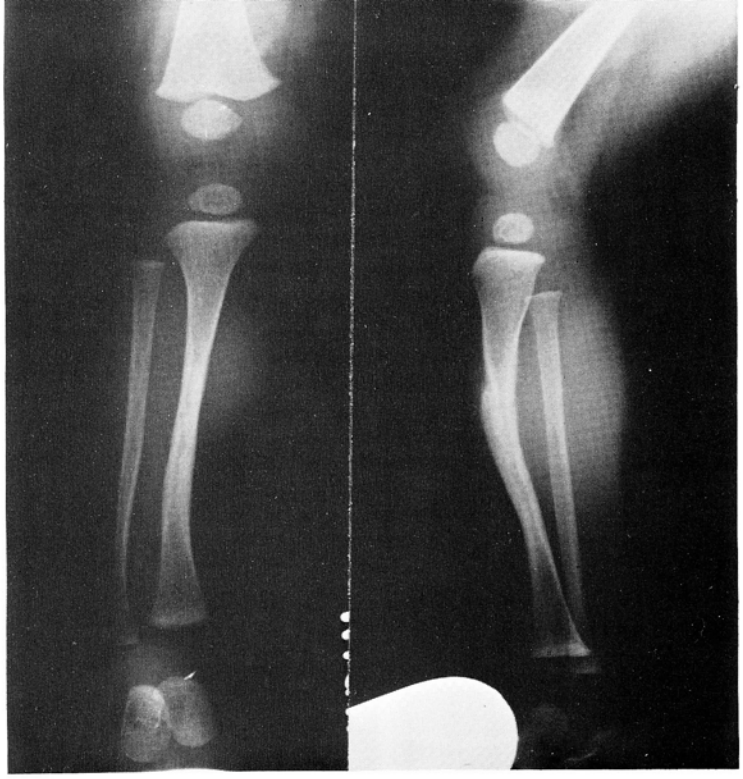


Fig. 1 and 2—Soft tissue mass of the right calf with curving of the tibia.

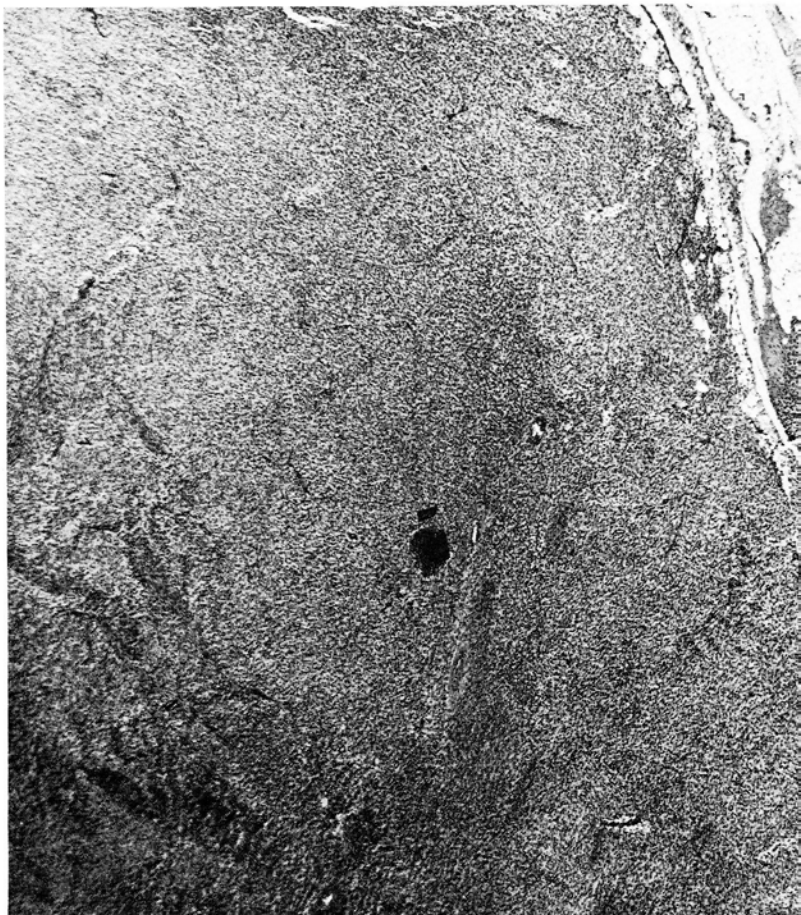
Operative findings: In December, 1971, a surgical excision was done. The specimen measured 2.5 x 3 x 1.5 cm; the tumor appeared encapsulated; on cross section it was tan in color and presented hemorrhages and necrosis but no calcifications.

Dr. Rosenberg: While interpreting the microscopic pattern of the lesion in the leg of this three-month old child, the clinical description of an additional soft tissue mass in the cheek and radiologic evidence of anterior tibial bowing must be kept in mind. This lesion has some aspects of localization, but a capsule is not apparent and focally the cellular components are not sharply defined from the adjacent fat. The tumor has a compact pattern with only isolated areas of relative looseness reflecting the quantity of intercellular collagen. In the cellular areas, fibrous bands course in an interlacing, sinous fascicular pattern with focal palisading of nuclei. Only a few compact blood vessel channels are scattered through the structure. Most of the cells are elongated spindle forms with an inconspicuous cytoplasm and elongated nuclei with rounded ends. Some fascicles are pleomorphic with large, rounded cells containing nuclei with coarse chromatin, some with nucleoli and a few cells in mitosis. Although the architecture focally has a loose pattern, there is no necrosis and no infiltrate of inflammatory cells. No distinct nerve fibers are identified. Generalized collagen deposition occupies some space between individual cells or clusters of cells in every portion of the tumor. In a few areas abundant collagen deposition forms focal small hyalinized areas.

A fibrous tumor in the soft tissue of a three-month old infant requires consideration of an aggressive fibromatosis of infancy sometimes called congenital fibrosarcoma. The exceptionally low rate of metastasis and the cure rate after local excision suggests a closer relationship to the cellular fibromatoses than with malignant, potentially lethal connective tissue sarcoma. Morphologic distinction between cellular fibromatoses and fibrosarcoma is difficult, if not impossible. Even the nuclear atypism and the number of mitoses do not reflect on the metastatic potential of this tumor. Morphologically, these tumors are characteristically large, occur in the extremities, do not metastasize, but do have a tendency for local recurrence.

How does an aggressive fibromatosis conform to the clinical pattern in this child? The description of two lesions, one in the leg and one in the cheek requires confirmation. Multiple soft tissue lesions appear in the syndrome of congenital disseminated fibromatosis. Histologically they are highly vascular and prone to broad areas of hyalinization and subsequent calcification. Bone lesions in congenital generalized fibromatosis, are fibroproliferative. The tibial bowing in this patient, plus two soft tissue lesions, one of which is fibrous, suggests generalized neurofibromatosis. Neurofibromatosis frequently presents in the first year of life and establishing a specific diagnosis may be difficult because of the incomplete presentation of symptoms. The absence of a family history and cafe-au-lait spots does not inhibit the diagnosis of neurofibromatosis. Histologically, the interlacing cellular bundles, the absence of nerve fibers, and the suggestion of Verocay bodies are consistent with a neurilemoma. The presence of mitoses in cellular nerve sheath tumors is a potent indicator of a malignant potential. Neurofibromas bear a malignant potential at a rate estimated as 5 to 15% which is rarely achieved until early adult life although the incidence in preadolescent children has been reported as 7%. The rarity of neurofibrosarcoma in the neonate need not have any bearing on the interpretation. For prognostic purposes we may invoke the concept of Kauffman and Stout that congenital mesenchymal tumors rarely behave malignantly and probably differ biologically from those in older age groups

Fig. 3—The solid, collagen-rich, cellular tumor is well-circumscribed, but does not have a capsule. At the periphery, tumor cells merge with the adjacent fat. (Hematoxylin-eosin, X23).



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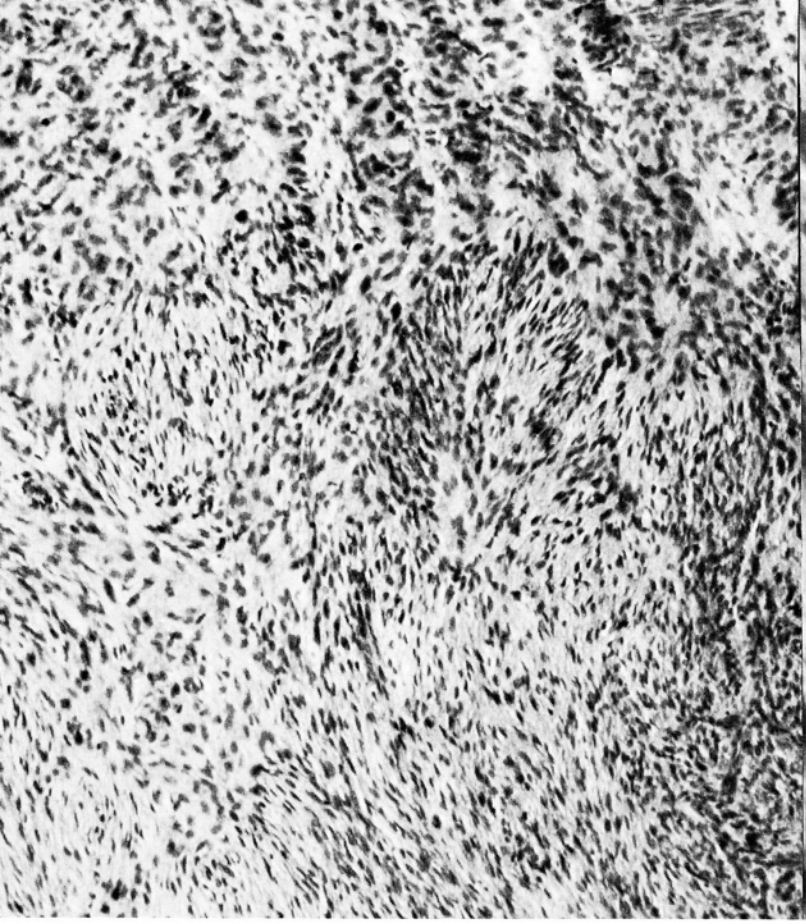


Fig. 4—In the more cellular areas, the nuclei of the elongated spindle cells lie parallel, forming palisades. (Hematoxylin-eosin, X64).

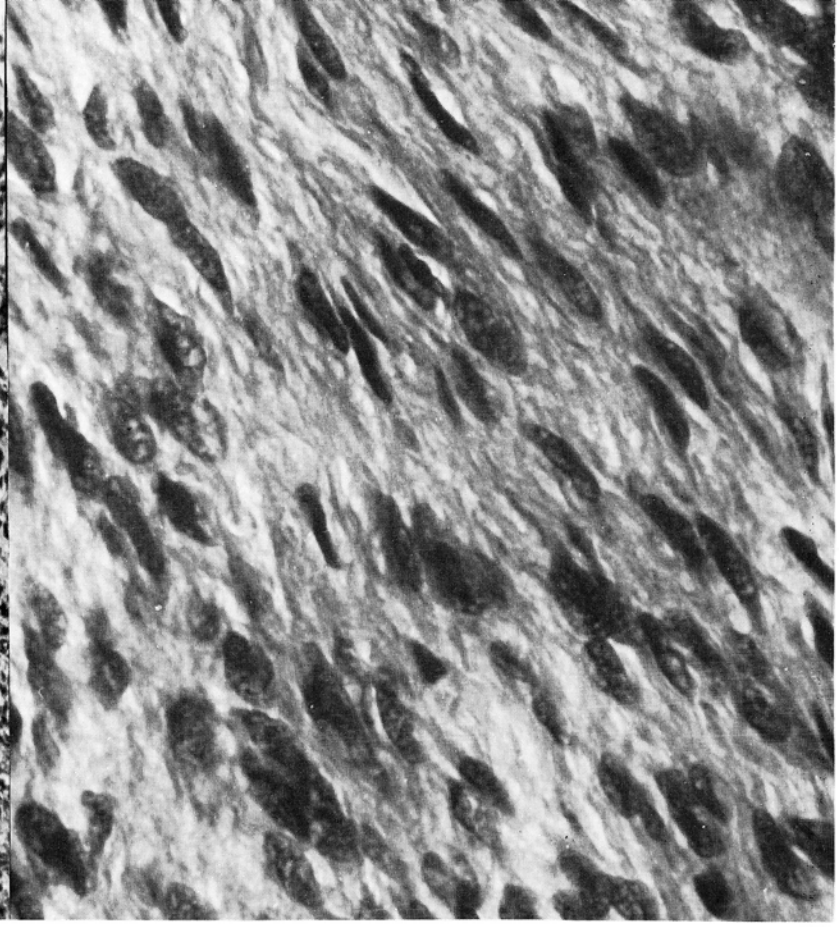


Fig. 5—Most of the tumor cells have a spindle shape with elongated nuclei with rounded ends. The cells are separated by strands of collagen. (Gomori's trichrome, X160).

which they resemble histologically. Histologically this lesion is interpreted as a neurilemoma, possibly part of generalized neurofibromatosis which must be qualified by other data including a family history, cafe-au-lait spots, and the histologic identification of the cheek tumor.

Dr. Rosenberg's diagnosis: NEURILEMOMA

Histopathologic diagnoses submitted by mail:

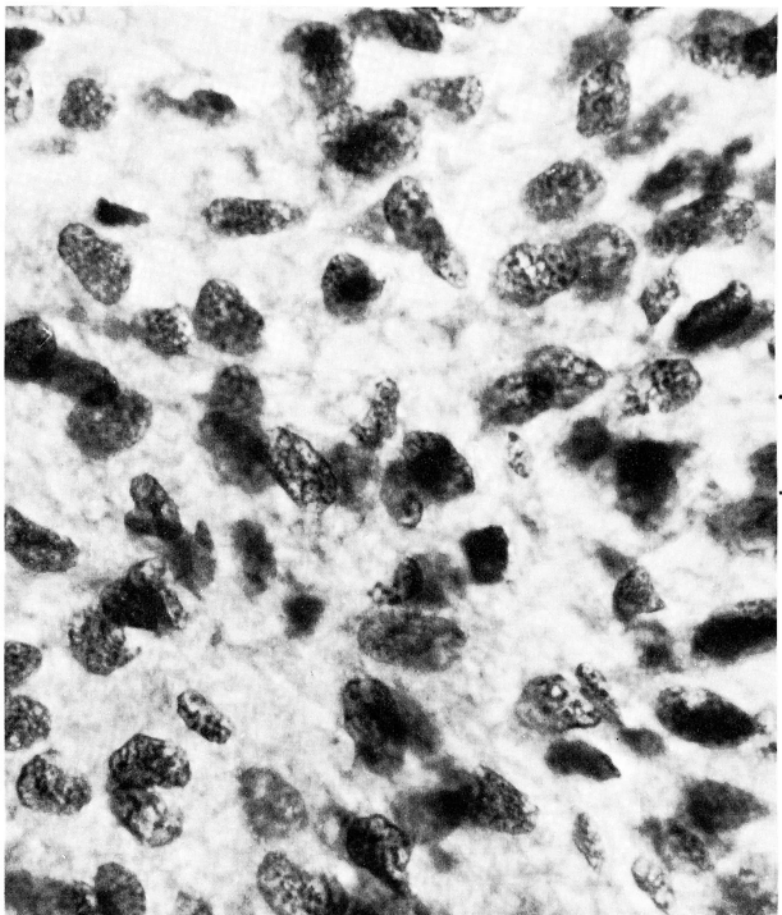
Neurofibroma(tosis)	60
(Neuro)fibrosarcoma	33
Malignant Schwannoma	20
Various sarcomas	8
Others	7

Dr. Rosenberg: There has been only a single case of a malignant Schwannoma in an infant. This was reported by the late Martin Bodian a few years ago; the primary tumor looked like a neurilemoma and then metastasized. But it is the only one that I am familiar with.

Dr. Regato: Dr. C. E. Berry, of Colorado Springs, and Sister Joseph Ignatius, of Cincinnati, also made a diagnosis of neurilemoma. Dr. A. Mazabraud, of Paris, considered its prognosis guarded. Dr. R. Marcial-Rojas, of San Juan, Puerto Rico, and Dr. A. O. Severance, of San Antonio, made a diagnosis of outright malignant Schwannoma. Dr. W. C. Bauer, of Saint Louis, Missouri, offered a pseudosarcomatous fasciitis. Dr. L. P. Dehner, also of Saint Louis, preferred congenital fibrosarcoma. Dr. M. Berthrong, of Colorado Springs, also diagnosed fibrosarcoma. Dr. R. D. Schultz, of Sioux Falls, South Dakota, offered leiomyosarcoma and Dr. M. J. Demeo, of San Rafael, California, malignant Schwannoma.

The AFIP offered a diagnosis of fibrosarcoma (Accession number 1397629), rendered by Dr. F. M. Enzinger. Dr. Benjamin Landing, of Los Angeles, was also consulted;

Fig. 6—Plump oval cells with a mild pleomorphism make up small portions of the tumor. (Hematoxylin-eosin, X160).



he felt that the lesion was compatible with fascial fibromatosis.

Subsequent history: In April, 1972, there was a local recurrence. A radical excision was done; a nodule in the region of the right cheek was also removed. In October, 1972, there was no evidence of recurrence; there was good function of the limb and there has been an apparently spontaneous regression of other subcutaneous lesions of the cheek.

J. F. Wilson, M.D., Salt Lake City, Utah: The lesion that was removed, was removed from the eyebrow; it was an inclusion cyst. The larger of the two lesions that were in the cheek was in very close the distribution of the facial nerve and the surgeon was reluctant to go after it; this is the one that appears to be regressing spontaneously.

Dr. Dunbar: No cafe-au-lait spots and no family history?

Dr. Wilson: No sir, and no family history.

Dr. Ternberg: I just wonder whether the subsequent course would make you think more that this might be a so-called congenital fibrosarcoma rather than a neurofibroma, because of the regression of the face lesions. Did the tibia straighten out?

Dr. Regato: The tibia did not straighten out.

Dr. Rosenberg: I still am not sure that I want to put my name on the bottom of the page in relation to those tibial changes because not only Dr. Dunbar, but our own radiologists assured me that this is pathognomonic, for neurofibromatosis.

Dr. Dunbar: Characteristic.

F. P. Bornstein, M.D., El Paso, Texas: It seems to me that there hangs a miasmic cloud over our diagnoses of malignant tumor every time that the patient lives long. Nobody seems to believe that malignant tumors can be cured; just because a patient survives is really not a reason to change your diagnosis afterward.

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14. *Congenital Fibromatosis*

Contributed by **H. S. Rosenberg, M.D.** and **A. J. Rudolph, M.D.,** Houston, Texas

THE PATIENT was a newly born baby boy in February, 1972, when a tumor was felt in the deltoid region. On examination a subcutaneous mass 4 x 3 cm was felt in the left deltoid region; there were other reddish subcutaneous lesions in the abdomen and extremities. Hemoglobin was 10.5 gm%; 13,000 WBC with 53% lymphocytes.

Dr. Dunbar: I was given two chest radiographs, made five days apart. On both radiographs, all the bones are slightly thin, indicating failure to thrive. There is a noncalcified ill-defined soft tissue mass in the left deltoid area, without erosion, invasion or destruction of the underlying humerus. The heart is moderately enlarged. There are multiple lesions, 1 to 5 mm in diameter approximately, uniformly distributed throughout both lungs, but a little larger in the upper lobes. The lungs are moderately over-distended. The liver is not obviously enlarged. The radial heads appear to be dislocated anteriorly bilaterally.

On the second radiograph, the heart is no longer enlarged, the lungs are not over-distended, and the deltoid mass has either diminished in size or is at least visible, than previously. The lung lesions are essentially unchanged. They may contain tiny foci of calcification in their centers. The liver is smaller than average, and the spleen is not enlarged. The abdominal gas pattern is within normal limits. Some of the bones contain irregular lucencies in their metaphyses but these are not well shown and are hard to assess.

I am aware of only two diseases which produce multiple soft tissue subcutaneous masses, fibromatosis of the newborn and hemangiomatosis. Both are rare, and neither characteristically involves the lungs. Neither is associated with dislocation of the radial heads.

The cardiac enlargement and pulmonary over-distention suggest heart failure, which increases the suspicion of hemangiomatosis, as does the description of the subcutaneous lesions as being "reddish." On the other hand, if there is calcification in the lung lesions, a perinatal or prenatal infection such as tuberculosis or histoplasmosis becomes more likely. Either can produce disseminated lung lesions, and in the case of tuberculosis, the lesions are amenable to chemotherapy, and may undergo calcification.

A family history of hemangiomatosis or Osler-Weber-Rendu syndrome (multiple telangiectasis) would be useful, as would the presence or absence of known maternal tuberculosis, histoplasmosis or even rubella infection.

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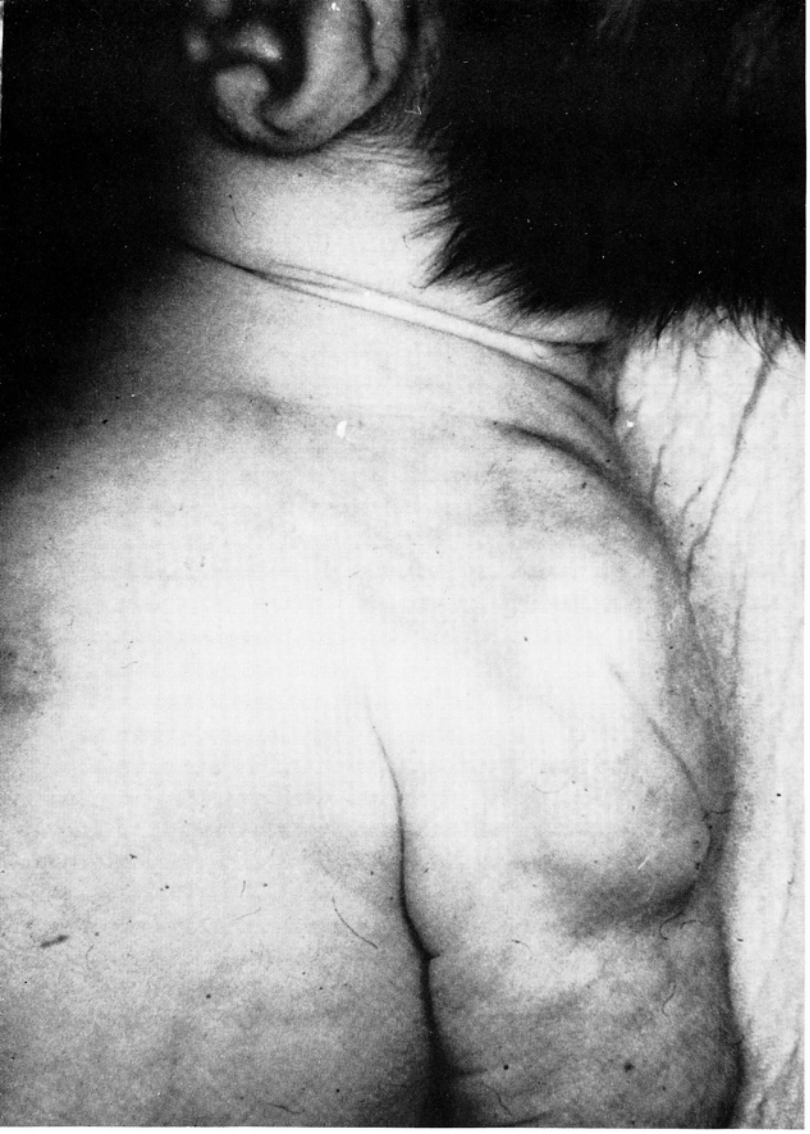


Fig. 1—Clinical appearance of soft tissue mass on left shoulder.

Dr. Dunbar's impression: HEMANGIOMATOSIS (possible OSLER-WEBER-RENDU SYNDROME)

Roentgenologic impressions submitted by mail:

Hemangiomatosis	31
Hemangiosarcoma	22
Rhabdomyosacoma	15
Neurofibromatosis	5
Various, malignant	19
Others	5

Dr. Dunbar: In preparing for this CANCER SEMINAR I made a good effort to look up hemangiomatosis in the newborn with lung involvement and there is no such thing recorded. But other radiologists seem to come to the same general impression, probably influenced as I was very strongly, by these multiple reddish lesions in the skin and subcutaneous tissue. Hemangiosarcoma I would have to pass on for I don't know anything about it and whether it occurs in the newborn and produces multiple lesions of this kind. Rhabdomyosarcoma doesn't fit because there are multiple lesions. I have no roentgen evidence to support neurofibromatosis in early life; there is none of the bone or soft tissue malformations ordinarily present.

Dr. Regato: Drs. M. Daves, of Denver, and E. C. Hwa, of Newton, Kansas, also made a diagnosis of hemangiomatosis. Dr. R. E. Wesenberg, of Denver, offered congenital fibromatosis.

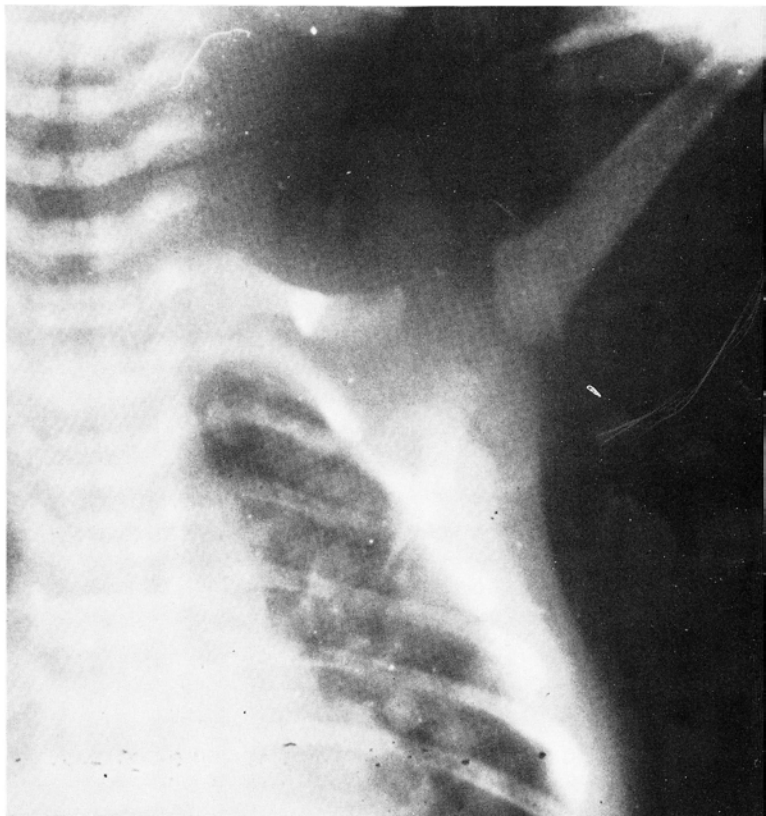
Operative findings: In February, 1972, a biopsy was done; the specimen consisted of a well encapsulated 1 cm nodule.

Dr. Rosenberg: A poorly localized fibrous tumor extends without circumscription into the adjacent connective tissue, striated muscle, and fat. Isolated strands of muscle encompassed by the tumor are interpreted as remnants of the invaded muscle rather than components of the tumor. Although the tumor presents a variety of patterns, the variety depends on the quantity of intercellular collagen. Some portions consist of interlacing cellular bands of elongated spindle cells while other consist of broad hyalinized areas with only a few cells. The cellular element in all areas are fairly uniform consisting of elongated spindle cells with plump nuclei with blunted ends. Mitoses are very few. The cytoplasm of the spindle cells has a red, sometimes granular, stain with Gomori's trichrome. One hyalinized area contains a deposition of amorphous calcium. In several other areas a loose myxomatous stroma contains a few mononuclear inflammatory cells.

Based on the generalized distribution of fibroblastic lesions, this lesion is interpreted as congenital generalized fibromatosis. Distinction of the individual lesion from an aggressive fibromatosis may be impossible, although the trichrome preparation suggest the presence of smooth muscle. Hyalinization and calcification seem a component of most cases of congenital generalized fibromatosis but this could conceivably occur in other fibromatoses as well. An arrangement about blood vessels in some cases gives a resemblance to a collagen rich hemangioma.

Subsequent to this biopsy, the infant did fairly well with regression in size and firmness of the dermal lesions. At the age of two months respiratory difficulty increased in severity and the infant expired of respiratory insufficiency at 93 days of age. At autopsy, nodules similar to those in the skin occupied the myocardium, lung, liver, pancreas, lymph nodes, striated muscle and the medullary space of

Fig. 2—Roentgenogram barely showing soft tissue mass of shoulder and pulmonary nodules.



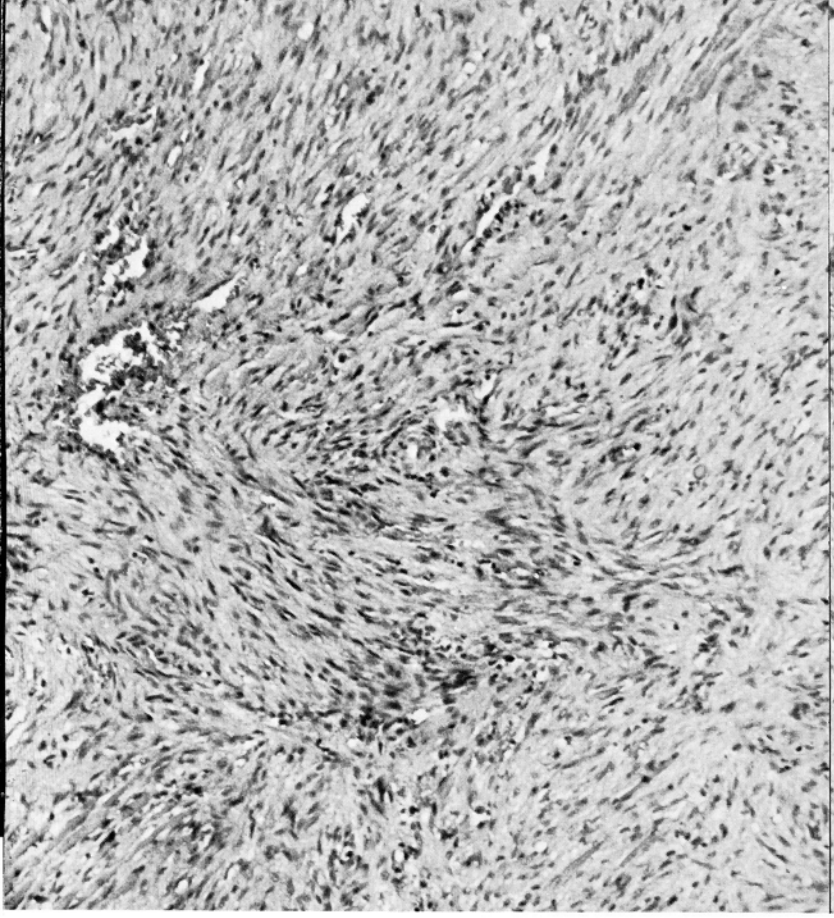


Fig. 3—Many small vascular spaces lie within the pattern of interlacing cellular bundles. (Hematoxylin-eosin, X64).

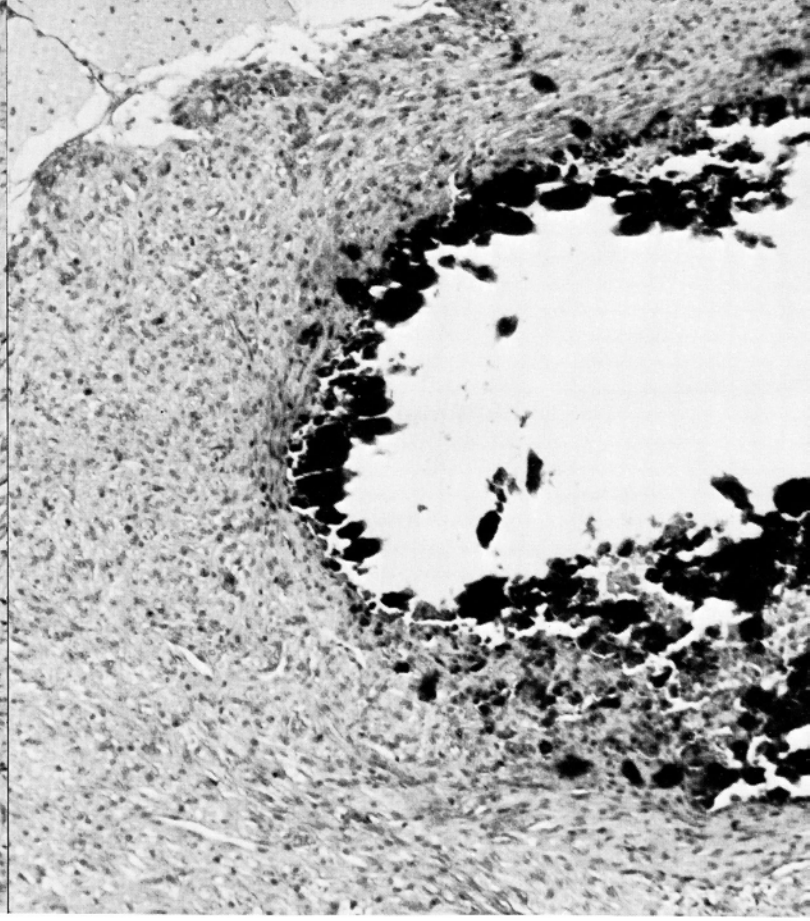


Fig. 4—Amorphous calcific deposits lie within the cellular tumor with no associated inflammation. (Hematoxylin-eosin, X64).

vertebra and long bones. A special feature of the pulmonary infiltrate was the localization of many of the fibrous nodules within the lumen and walls of pulmonary arteries and veins. The systemic vessels did not have this same character of infiltrate.

Because of the good differentiation of the fibrous elements in the individual nodules the lesions are interpreted as multiple primary nodules in discrete loci, distinct from a fibrosarcoma with metastases. The concept of multiple individual lesions is supported by the natural history. Of 25 cases reported, 12 have resolved with subsequent survival of the patient. An interesting clinical facet is the age at the time of death. Of all infants who died of the disease, each was less than 100 days of age. It would seem that if the patient can survive to 100 days the lesions will regress with survival of the patient.

The prognosis of congenital generalized fibromatosis depends on the sites of involvement. Two patterns of distribution and their related difference in survival rate are recognized. Of those infants in whom the lesions occupy the skin, subcutaneous tissue, muscle, and occasionally bone, the natural progression includes resolution of the lesion and a high survival rate. In those infants with visceral infiltrates as well as soft tissue infiltrates, the survival rate is very poor. Particularly when the lung is involved, survival rarely occurs.

Dr. Rosenberg's diagnosis: CONGENITAL FIBROMATOSIS.

Histopathologic diagnoses submitted by mail:

Juvenile fibromatosis	40
Leiomyoma (vascular, calcified)	25
Neurofibromatosis	12
Nodular fasciitis	11
Hamartoma (fibrous, leiomyomatous)	10
Benign mesenchymoma	6
Malignant Schwannoma	3
Hemangiopericytoma	3
Others	20

Dr. Rosenberg: We can agree that using Dr. Stout's original designation that this certainly does fall within the general group of juvenile fibromatosis; leiomyoma is also a good designation since even though we were unable to prove smooth muscle, others in similar lesions have. I don't believe that fasciitis is valid; only by generic relationship would this be a nodular fibrosis.

Dr. Regato: Drs. J. B. Frerichs, of El Paso, and D. L. Dawson, of Colorado Springs, diagnosed juvenile fibromatosis. Dr. K. Hallman, of Fort Sam Houston, Texas, designated the lesion as fibrous hamartoma of infancy. Dr. G. B. Elliott, of Vancouver, offered venous angiomyoma.

Subsequent history: On May 20, 1972, the baby expired. At autopsy fibrous nodules were found in the lungs, liver, pancreas, myocardium and subcutaneous tissues.

Dr. Ternberg: I would like to say that my experience with this is nil, at least as described in this case. But I would like to ask some questions. Suppose that you didn't have a total picture of that baby, Dr. Rosenberg, and we just gave you a piece of the tissue, would you come up with the same diagnosis?

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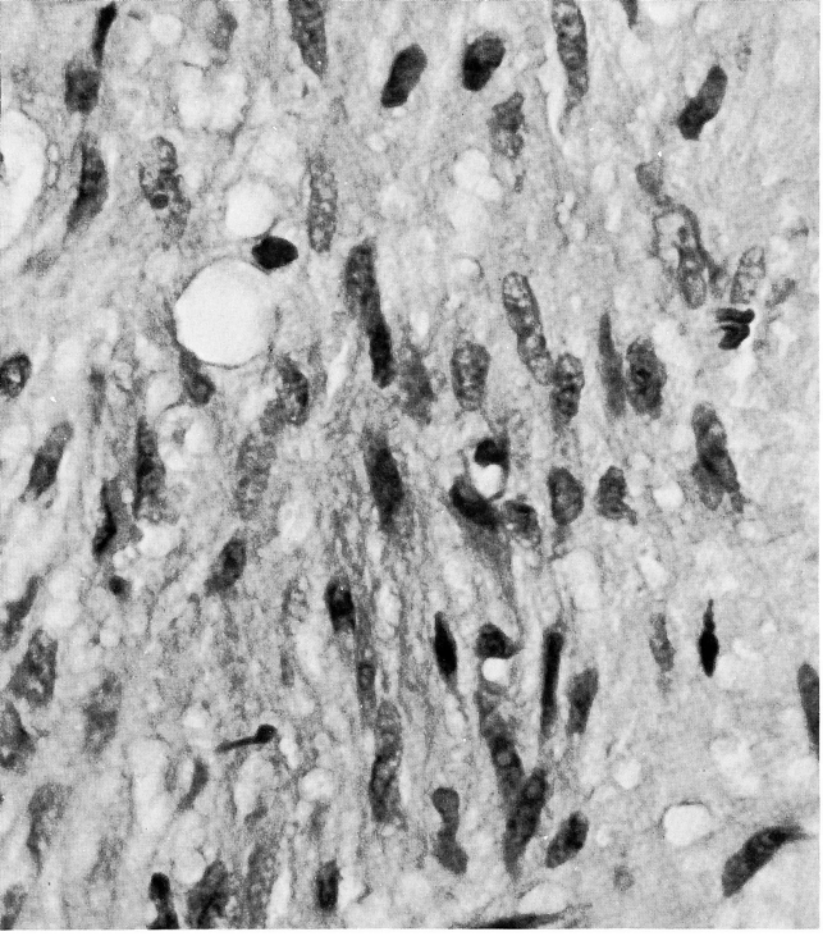

Fig. 5—The tumor cell cytoplasm is finely granular and the nuclei are elongated with blunt ends. (Gomori's trichrome, X160).

Dr. Rosenberg: I think that one would legitimately say that this was a fibromatosis, yes. Probably would be more likely to suggest an aggressive fibromatosis if one were to just look at this blindly.

Dr. Ternberg: I also gather that this is almost like a Presbyterian predestination, that the baby either has the worst or he doesn't; if he has the worst there is not much that you can do about it.

Dr. Rosenberg: I fear that is the case. As frequently happens, there is some magnetism about lesions as this. My experience with this disorder as of 15 months ago, was probably of the same order as yours. Namely, that I knew of it because Dr. Enzinger and Dr. Stout had written about it, and then I heard about this case; while we were finishing working up this case, a second one came and that other child is in our institution as of this moment.

Dr. Ternberg: I was just about to ask, did they have pulmonary involvement similar to the ones that you showed?

Dr. Rosenberg: The only child with visceral involvement who survived did not have pulmonary involvement.

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15. *Pigmented Neuroectodermal Retro-Orbital Tumor.*

Contributed by **W. C. Speers, M.D.** and **L. O. Gates, M.D.,** Denver, Colorado

THE PATIENT was a 3-year old boy in March, 1972, when he was examined because of a tumefaction on the left side of his head which had grown slowly since three months after birth when it had been first noticed. On examination there was a hard, non-tender and non-movable mass, 2 x 3 cm in diameter in the left temporo-parietal region.

Dr. Dunbar: There is a sclerosing mass supero-lateral to the left orbit. The sclerosis is dense, with a few radiating radiolucencies throughout its stucture. The lesion is well-defined. There is no other evidence of cranial or intracranial disease, and specifically, no evidence of increased intracranial pressure.

The lesion does not have the roentgen appearance of a malignancy and this impression is reinforced by its slow growth since the age of three months.

None of the usual tumors of infancy or childhood would seem to be compatible with this lesion. The only suggestion that I can entertain is that of an ossifying fibroma.

Dr. Dunbar's impression: OSTEOGENIC FIBROMA

Roentgenologic impressions submitted by mail:

Fibrous dysplasia	54
Meningioma	20
Osteosarcoma	9
Neuroectodermal tumor (melanotic progronoma)	5
Others	8

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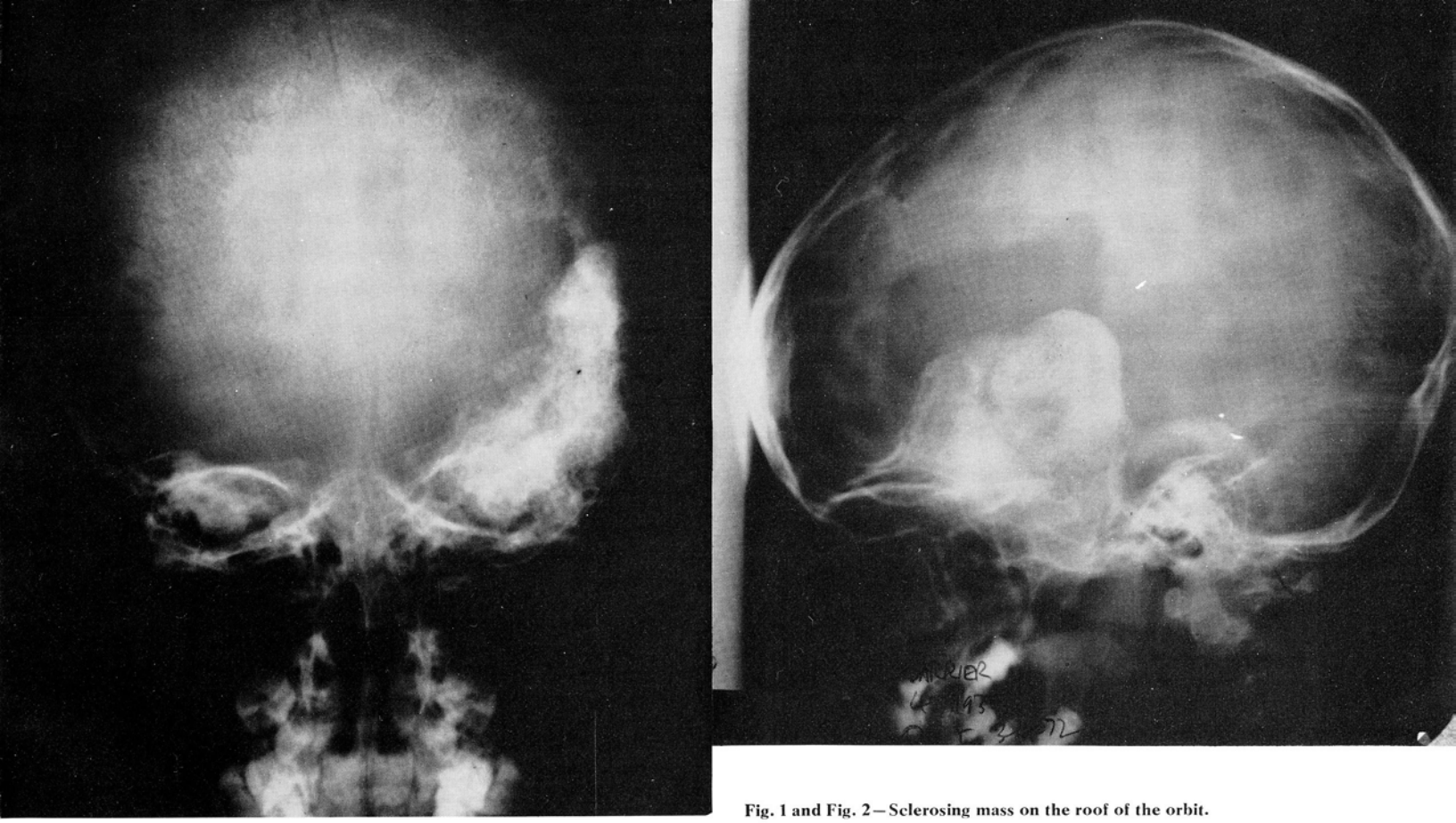

Fig. 1 and Fig. 2—Sclerosing mass on the roof of the orbit.

Dr. Dunbar: You can see that there was a predominance of opinion favoring fibrous dysplasia, meningioma. It is very hard for me to imagine an osteosarcoma doing this at this age and lasting for three months without dissemination. A neuroectodermal tumor I really don't feel I can comment on.

Dr. Regato: Drs. E. J. Keeffe, of Pontiac, J. W. Barber, of Cheyenne, and Colonel R. Hagen, of Fort Sam Houston, offered an impression of fibrous dysplasia.

Operative findings: On March 21, 1972, a left frontotemporal craniotomy was done with resection of the roof and lateral wall of the left orbit; the involved dura was resected but the tumor was stripped away from the bone in some areas; there was no difficulty with hemostasis. The surgical specimen weighed 70 gm; it consisted of yellowred to black material with bone fragments and some friable gray-brown tissue 3.5 x 2 x 1 cm.

Dr. Rosenberg: Within a dense fibrous stroma numerous irregular spaces are lined by epithelium so densely pigmented that the landmarks of the individual cells are obscured. The pigment does not take the stain reaction for iron, but does stain dense black with the Fontana preparation. Most of the small spaces are vacant, but a few contain clusters of unpigmented cells of different sizes in a non-cohesive arrangement embedded in a loose fibrillar network. The largest cells have an abundant acidophilic cytoplasm giving the appearance of ganglion cells. The epithelial cells lining the spaces are small and cuboidal with a rounded or oval nucleus frequently obscured by the pigment granules in the cytoplasm. Other pigmented cells lying free within the dense stroma are elongated, compressed spindle shaped cells. A few fragments of bone also occupy the dense fibrous tissue but with no apparent relationship to the pigmented epithelium lined spaces.

The morphologic features identify a lesion variously known as melanotic progonoma or retinal anlage tumor, among other designations. This tumor most frequently occupies the anterior maxilla, but may involve the bones and soft tissues of the head, the fourth ventricle, the mediastinum, the soft tissues of the shoulder, and the epididymis.

Although recurrence of the lesion has been described after incomplete surgical excision and at least one case has been multifocal, the lesion usually behaves in a benign fashion without capacity for either invasiveness or metastases. The tumor characteristically appears in infancy and most are first identified in the first six months of life. The tumor remains confined to bone, has a rapid growth spurt, but does not extend into the overlying skin or the mucosa and rarely presents with symptoms other than those of swelling.

In contrast to the uniform presentation of these lesions, the terminology and the concepts of origin have a broad divergence. The tumor was incorrectly considered to have been previously undescribed when, in 1947, Halpert and Patzer described the lesion as a Retinal Anlage tumor based on the infoldings of pigmented epithelium into the cystic spaces suggesting the ciliary process of the eye. The name Melanotic Progonoma was devised by Stowens who suggested an atavistic origin (pro-before, gonos-germ). More recently, a neuroectodermal origin has been suggested on the basis of neurofilmamentous structures identified by electron microscopy and at least one case which was associated with an increased urinary excretion of vanilmandelic acid. Although the lesion occurs frequently in association with the deciduous teeth, an origin from dental structures receives little support, particularly when considering the extra-maxillary tumors.

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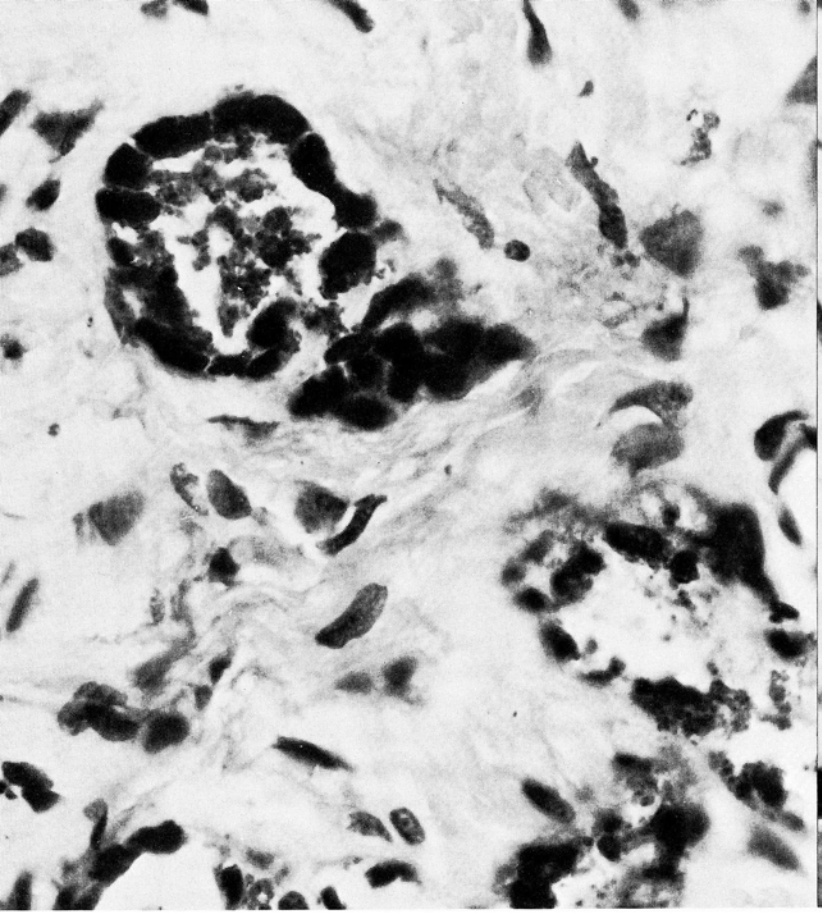


Fig. 3—The small spaces have a cuboidal epithelium whose cellular detail is obscured by the intense deposits of cytoplasmic pigment granules. (Hematoxylin-eosin, X160).

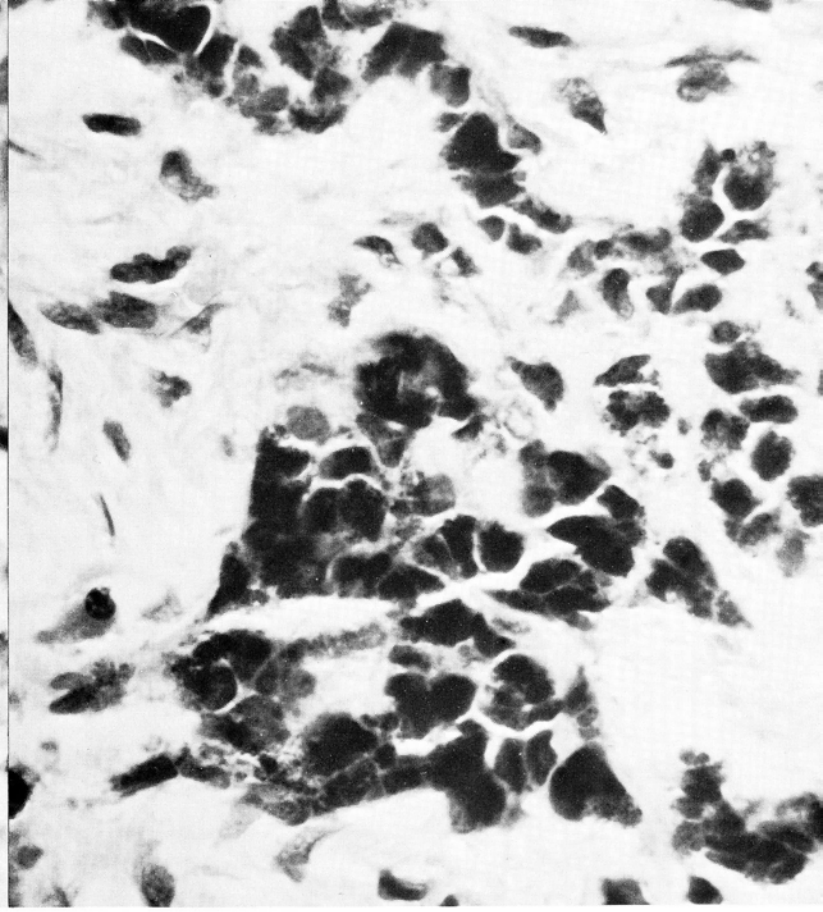


Fig. 4—Pigment granules are present in stromal spindle cells as well as the epithelial cells. (Hematoxylin-eosin, X160).

Dr. Rosenberg's diagnosis: PIGMENTED NEUROECTODERMAL TUMOR (melanotic progronoma).

Histopathologic diagnoses submitted by mail:

Retinal anlage tumor	25
Melanotic progronoma	24
Pigmented neuroectodermal tumor	23
Melanotic neural crest tumor	10
Hamartoma	8
Melanomatous hemangioma	7
Others	28

Dr. Rosenberg: It would seem, with the exception of the hemangioma that there is a unanimity about the nature of this lesion.

Dr. Regato: With very few exceptions, but with great variations in nomenclature, our experts agreed to a diagnosis of *pigmented neuroectodermal tumor of infancy,* also known as *melanotic neural crest tumor, pigmented progronoma, retinal anlage tumor, hamartoma,* or *pigmented heterotopic retinoblastoma.* Dr. M. E. Williamson, of Palm Desert, California, offered adamantinoma, pigmented type.

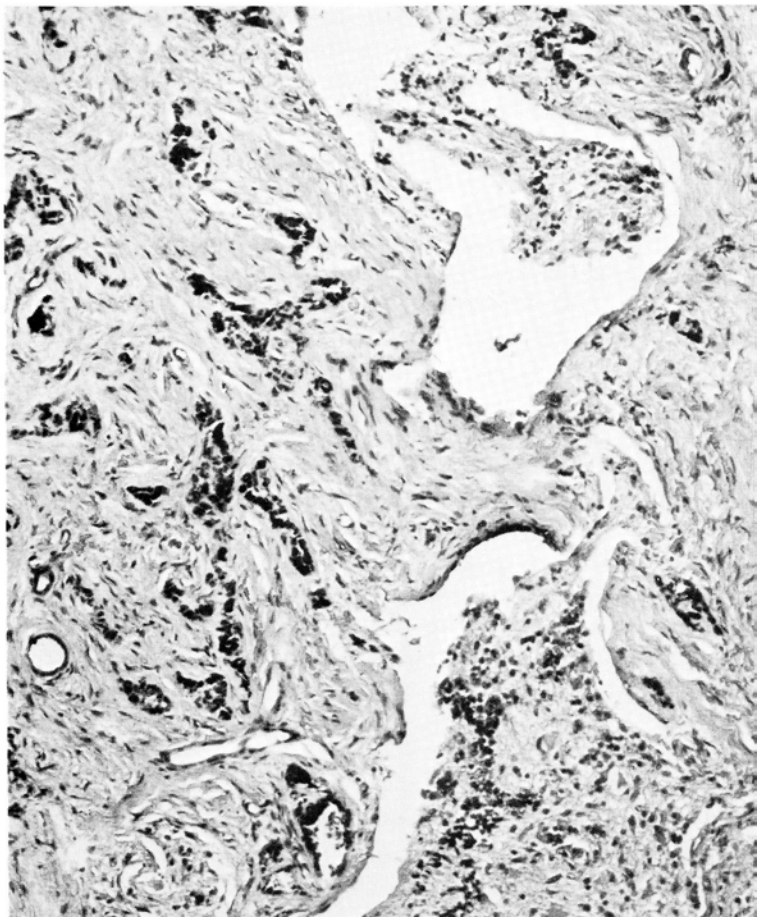
Subsequent history: In June, 1972, the patient had a cranioplasty and recovered uneventfully.

Dr. Ternberg: Isn't this one of the tumors that will put out VMA?

Dr. Rosenberg: That is true, which conforms to the possibility of this being a neuroectodermal tumor.

W. C. Speers, M.D., Denver, Colorado: We submitted some tissue for electromicroscopy. There have been three other reports that we have found of the electromicroscopy of this tumor. One describes microvilli in the lumen which this does not have; there were no desmosomes or other

Fig. 5—Some of the larger cysts contain unpigmented cells of various sizes and shapes arranged in a fibrillar stroma. Some of the larger cells resemble ganglion cells. (Hematoxylin-eosin, X64).



junctional apparatus identified. Fairly common cells in this tumor were in small ill-defined clusters or lying freely, contained numerous pigment granules and were characterized by abundant fine cytoplasmic processes somewhat reminiscent of dendritic melanocytes. The cytoplasm of these cells contained numerous mitochondria and large amounts of rough endoplasmic reticulin. The pigment granules were generally round to cigar-shaped and showed the lamellar internal structure in some; premelanosomes were identified in some of these cells. What I consider degenerated elements were fairly common throughout this tumor. The clinical history, the histological appearance and the electromicroscopy suggest to me that this is a mature and possibly degenerating lesion.

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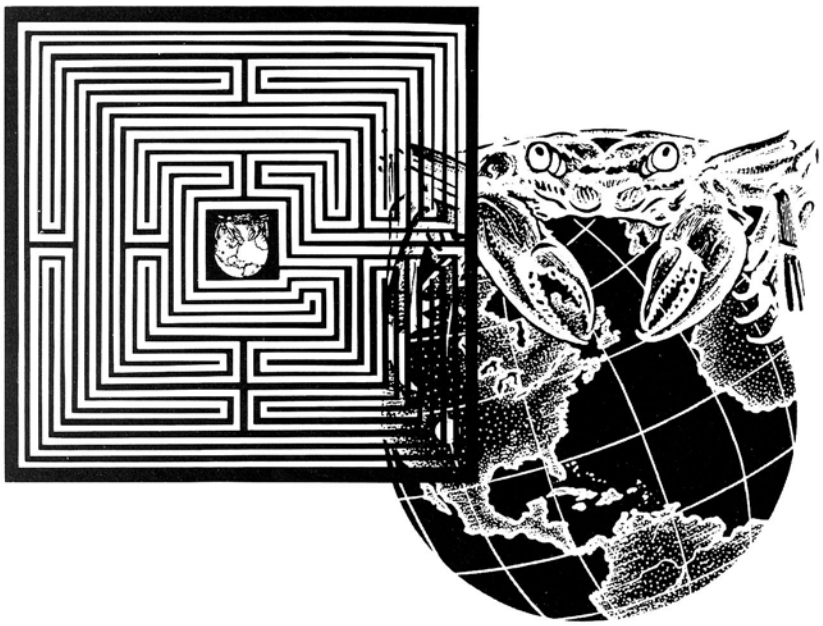

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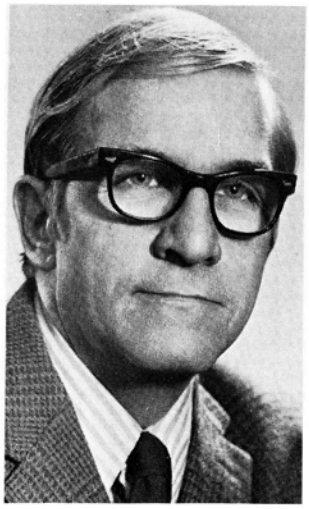

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