Edited by

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NEUROBLASTOMA

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PREFACE

Although neuroblastomas have been intensively studied and have fascinated clinical investigators for more than 100 years, they still remain an enigma as far as effective treatment. Except for acute leukemia and brain tumors, neuroblastoma is the most common malignancy in children. Neuroblastoma is a tumor of early life; its incidence is highest during the first two years and decreases rapidly thereafter. More than 80 percent of cases occur before the age of five years. There is no predilection for either sex or for any race.

Neuroblastomas originate from primitive sympathetic neuroblasts of the neural crests. Recognition of the wide distribution of these primitive sympathetic cells in the embryo helps to explain the widely variable clinical behavior of this tumor. The tumors may arise from any site where one would normally find elements of the sympathetic nervous system. Thus, the spectrum of clinical manifestations of neuroblastoma is vast.

In spite of the fact that neuroblastoma in its usual behavior is the most malignant of human cancers, it also shows the highest rate of spontaneous regression. This peculiarity of frequent spontaneous regression has tantalized and frustrated several generations of clinical investigators.

In 1864 Virchow described a "glioma" in a child with a malignant abdominal tumor. In 1880 Parker described a similar case and called it a "congenital sarcoma." In 1885 Dalton described a child with an abdominal tumor with similar histology who also had massive metastases to the liver. Marchand in 1891 pointed out the relationship between the sympathetic nervous system and adrenal medullary tumors. Pepper in 1901 and Hutchison in 1907 described their famous syndromes which we now know were neuroblastomas with differing patterns of metastasis. But neither clinically nor anatomically are these eponymic designations justified. It was not until 1910 that Wright demonstrated convincingly that neuroblastomas originate from embryonal sympathetic neuroblasts; this conception of the histogenesis is now the accepted one. In 1927 Cushing and Wolbach described their case of neuroblastoma which subsequently showed complete maturation to a histologically proven ganglioneuroma.

In this book I have tried to organize the extensive literature on neuroblastoma into a workable and easily understood scheme. It is recognized, of course, that for such a vast and complex literature, any one scheme of presentation may not be appropriate for the most lucid

discussion of all aspects of this disease. One chapter is devoted to neuroblastomas in infancy, since the neonatal manifestations of this tumor are particularly intriguing. Following this are chapters on the various clinical and laboratory manifestations. For convenience, the clinical discussions deal with each region of the body separately. There are also discussions of catecholamine metabolism in neuroblastoma and the various histopathological patterns of this tumor. The in vitro behavior and immunological phenomena associated with this tumor are discussed in separate chapters. Another chapter is devoted to ganglioneuroma, which is a closely related tumor. Finally, extensive discussions are devoted to the various modes of therapy and to the interpretation of the several parameters used in assessing prognosis. Hopefully, these discussions will enable the modern pediatrician and oncologist to see possibilities where his predecessors saw only doom.

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Carl Pochedly, M.D.

CONTENTS

1 Neuroblastoma in Infancy

Carl Pochedly, M.D.

Introduction
1. Locations of primary tumors and metastases
2. Differential diagnosis
3. Neuroblastoma in the fetus
4. Peculiarities of neuroblastomas in infancy
   a. Skin metastases
   b. High incidence of liver metastases
   c. High rate of spontaneous cure
5. Role of nerve growth factor in neuroblastoma regression
6. Neuroblastoma in situ
7. Familial neuroblastoma
8. Neuroblastoma in animals

Summary and conclusions

Neuroblastoma is probably the most fascinating tumor of childhood. The unique and intriguing features of this tumor are mainly those manifested when the tumor occurs in children during the first few months of life.

Neuroblastoma is not uncommon in the neonate—more than 60 such cases have been described.[1,2,3] Neuroblastomas present at birth differ in certain respects from those that appear later in childhood, and a larger proportion of infants are cured of their disease. The location of "metastases" varies in the infant, with liver and subcutaneous involvement more commonly found.[4,5]

According to classical descriptions, abdominal neuroblastomas occur in two types. The *Pepper* type[6] (adrenal-hepatic) is characterized by distension of the abdomen from enlargement of the liver, mesenteric lymph node metastases, rapid loss of weight and strength, and anemia (Figure 1). Metastases to the bones of the skull are

seldom seen. This type occurs almost exclusively in children less than 6 months of age. The *Hutchison* type[7] (adrenal-skeletal-orbital) is characterized by the peculiar onset of ecchymosis of the eyelids, proptosis, and enlargement of the preauricular, submaxillary, and upper cervical lymph nodes on the same side. These symptoms are caused by metastases in the bones of the skull, which have an unexplained predilection for the region of the orbit. Cases with the Hutchison type almost always occur in children *over* 6 months of age. But on close examination, many patients have features suggestive of both the Pepper and Hutchison types. Thus, these terms, although hallowed by tradition, are of little clinical use. The new staging system, to be described later, offers a more meaningful classification and description of children with neuroblastoma. The terms Pepper type and Hutchison type should be considered obsolete.

The clinical diagnosis of neuroblastoma in infancy is often difficult because the primary tumor may be inconspicuous, and the symptoms are mainly determined by the localization of metastases. X-ray examination is often very useful. But the diagnosis can be made only on the basis of the histological picture of these tumors, in combination with the results of assay of urinary catecholamines[8,9,10] and cystathionine.[11,12]

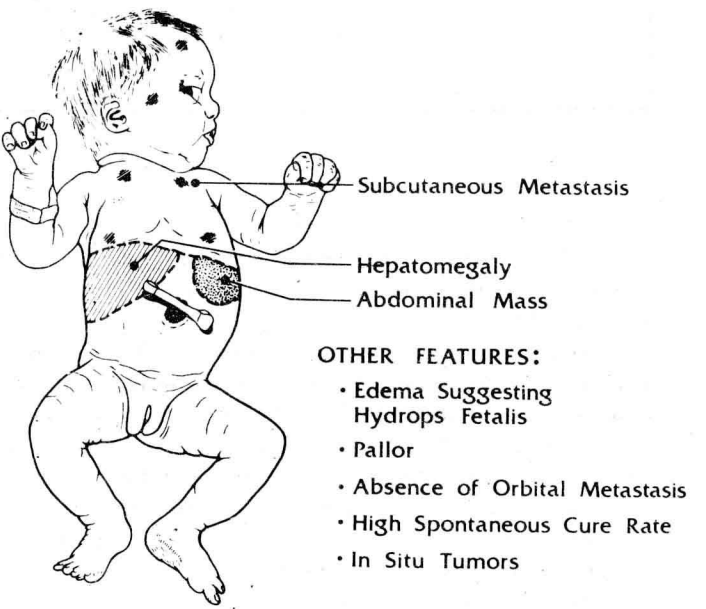

Figure 1. Special features of neuroblastomas in infancy.

The newborn infant with neuroblastoma may be edematous, jaundiced, anemic, and have a distended abdomen.[13,14] Thus, many cases of congenital neuroblastoma resemble severe erythroblastosis fetalis. Similarities in the gross and histological appearance of the placenta in congenital neuroblastoma and in erythroblastosis fetalis are also present.[15]

LOCATIONS OF PRIMARY TUMORS AND METASTASES

Neuroblastoma can arise from sympathetic nervous system tissue in any area of the body. In all age groups, the adrenal gland is the most common site of origin of neuroblastoma. It may, however, be a slightly more frequent site in the newborn than in older children. In 1,303 children of all ages with neuroblastoma, 65.5 percent of the tumors arose from the adrenal; 72.1 percent of neuroblastomas in neonates were of adrenal origin[2] (Table 1). In 7 newborns, tumor was found within both adrenals. This represents metastases from one adrenal to the other, or multiple sites of origin. The frequency of neuroblastoma arising in the thorax or pelvis is the same in all age groups.[1,16]

Prognosis in congenital neuroblastoma is related to the location of the primary tumor. In one series of 10 cases in which the primary tumors were both extra-adrenal and extra-abdominal in location, all survived.[3] But it is doubtful whether this is true for all age groups, since neonates have special "metastases" (i.e., the stage IV-S distribution).[17]

Table 1
Primary sites of Neuroblastomas in Neonates Compared with the Incidence in Children of All Ages

Location	Percent in Neonate	Percent for All ages
Head*	3.0	0.2
Neck	3.0	3.2
Chest	10.3	14.6
Abdomen	72.1	65.5
Pelvis	8.6	4.5
Unknown	3.0	12.0
Total cases reviewed	68	1303

Source: References 1, 2, 15, 19, 21–23, 25–27, 29, 32, 39, 41, 76, 83.
* Doubtful true neuroblastomas.

In series which include children of all ages, 60 to 70 percent will have metastases at the time of diagnosis. The location of metastases is different in the neonate, about half of whom have disseminated lesions at diagnosis. In cases of congenital neuroblastoma liver metastases are present in 64 percent, subcutaneous metastases in 32 percent, and bony metastases in only 3 percent. In children older than neonates but below 2 years of age, bony metastases are found in 35 percent.[2,18] Bony metastases occur in 66 percent of children over 2 years of age.[18] Subcutaneous metastases seem to be a method of spread unique to the newborn. Hepatic metastases are also more common in the young infant.

In recent reports neuroblastomas in newborn infants have been associated with paraplegia,[19] tumor of the vagus nerve,[20] retroorbital tumor,[21] hypoglycemia,[22,23,24] mass in the scrotum,[25] homocysteinuria,[26] cervical mass,[27] and periumbilical mass.[28]

DIFFERENTIAL DIAGNOSIS

Neuroblastomas often become manifest in the first year of life, and particularly in the neonatal period. In addition they often present as an abdominal mass which may represent either the primary tumor or frequently a liver enlarged by metastases. Thus, the problem in diagnosis lies in distinguishing the mass from other causes of a palpable abdominal tumor.

Three conditions need to be considered in the differential diagnosis: First, kidney enlargement not due to tumor, such as hydronephrosis and cystic kidney. Second, *liver* enlargement not due to tumor, such as that caused by hemolytic disease, congenital syphilis, and congestive cardiac failure due to congenital heart disease. The additional clinical features, serological tests for syphilis, and demonstration of Rh or other blood group incompatibility are obvious aids in distinguishing these conditions. The occasional occurrence of jaundice and, more frequently, a moderate degree of anemia in congenital neuroblastoma may cause initial confusion, especially when the peripheral blood smear shows many normoblasts that may be misinterpreted as evidence of hemolytic disease when seen in association with anemia, jaundice and hepatomegaly. The third condition in the differential diagnosis is *other abdominal tumors* of infancy, including Wilms' tumor, lymphosarcoma, and splenomegaly due to congenital leukemia. Blood and bone marrow examination will help to differentiate leukemia,[29] although disseminated tumor cells in the bone marrow smear may be misinterpreted and lead to an

erroneous diagnosis of leukemia. The differentiation among leukemic blasts, neuroblasts, and nonmalignant lymphoblasts may be extremely difficult. Erroneous diagnoses of acute leukemia are commonly made in these children.[30] Roentgen diagnostic maneuvers including I.V.P. and arteriogram may be virtually diagnostic, but tissue biopsy is needed to diagnose the other tumors. Massive hemorrhage into the adrenal gland of a neonate may produce a radiographic picture suggesting neuroblastoma.[31]

NEUROBLASTOMA IN THE FETUS

Since neuroblastomas can develop in utero, it might be supposed that, if much neuroblastomous tissue was present in the fetus, catecholamines might be released which could pass into the maternal circulation and affect the mother. If this occurred, it would be possible to recognize neuroblastoma in the unborn child. In one study there were signs and symptoms in six mothers in whose fetuses neuroblastomas had developed.[32] Sweating, pallor, tingling in the fingers, headaches, palpitations, and hypertension appeared during the last weeks of pregnancy. The symptoms exhibited by the mothers during pregnancy suggest that neuroblastomas within the fetuses secreted catecholamines which were responsible for the observed clinical effects. No one else has reported these findings in women who later delivered infants with congenital neuroblastoma.

Neuroblastoma in the fetus may show multiple sites of origin. A mature stillborn fetus was described in which a small, well-encapsulated neuroblastoma of the left adrenal gland was the only gross finding. Microscopic examination, however, revealed diffuse neoplastic involvement of the liver, adrenals, spleen, kidneys, and lungs. It appears that multicentric proliferation of undifferentiated sympathetic cell groups occurred in these organs.[33] Neuroblastoma may be the cause of antenatal death.[34,35]

Four cases of placental involvement by congenital metastasizing neuroblastoma have been reported. The diagnoses were made upon histological examination of the placenta. Numerous emboli with malignant cells were found in the vessels of the chorionic villi of the placenta. The primary neuroblastomas were located in the adrenal glands with massive spread to the liver in all cases.[14,15] While transplacental metastasis of tumor cells from mother to fetus is known to occur, the reverse has not been encountered. In one case of congenital neuroblastoma and placental metastases, fetal red blood cells

were found in the maternal circulation. It is possible in this case that fetal tumor cells entered the maternal circulation via the placenta, although the mother was found to be well one year post-partum.[15] The explanation for this failure of metastases from the fetus to become established in the mother is probably related to immunological mechanisms.[14]

PECULIARITIES OF NEUROBLASTOMAS IN INFANCY

Nodular Skin Lesions

Neuroblastoma with subcutaneous metastases occurs most frequently in the neonatal period.[8,23,36] The appearance and characteristic feel of the subcutaneous lesions may be described by the term "blueberry muffin." This term, usually associated with the rubella syndrome, is borrowed to describe the infant's appearance. Similar skin lesions may be seen in congenital leukemia.[37]

Subcutaneous nodules are observed in nearly one-third of neonates with congenital neuroblastoma. The nodules are usually scattered randomly over the entire body and vary from a few millimeters to several centimeters in diameter. The nodules are firm, nontender, bluish-tinged and mobile within the subcutaneous tissue. These nodules represent disseminated disease but are not necessarily associated with a fatal prognosis, as with bony metastases. Presence of nodules should not alter the usual methods of treatment.[23] In fact, aggressive chemotherapy, X-ray therapy, or deforming surgery may be both unnecessary and dangerous in these cases.[38]

Persistent blanching in and around the cutaneous metastases of a neuroblastoma was observed in a newborn infant with neuroblastoma.[39] The skin had many firm, blue subcutaneous nodules approximately 0.5 to 1 cm in diameter located over the thorax, abdomen, and lower extremities. When palpated, these lesions initially became erythematous for 2 to 3 minutes; the lesions and a circle of the surrounding skin, 2 to 3 cm in diameter, then blanched and remained blanched for 30 to 60 minutes. Catecholamines were demonstrated in the tumor cells from a skin metastasis by electron microscopy and fluorescence histochemistry. The blanching is believed to result from local vasoconstriction following release of catecholamines from the tumor cells. The blanching phenomenon may be a useful diagnostic sign characteristic of the skin metastases of neuroblastoma.[39]

High Incidence of Liver Metastases

The distribution of liver metastases in the infantile type of neuroblastoma (Figures 2 and 3) may be explained on the basis of the anatomy of the fetal circulation.[40] Tumor emboli have less opportu-

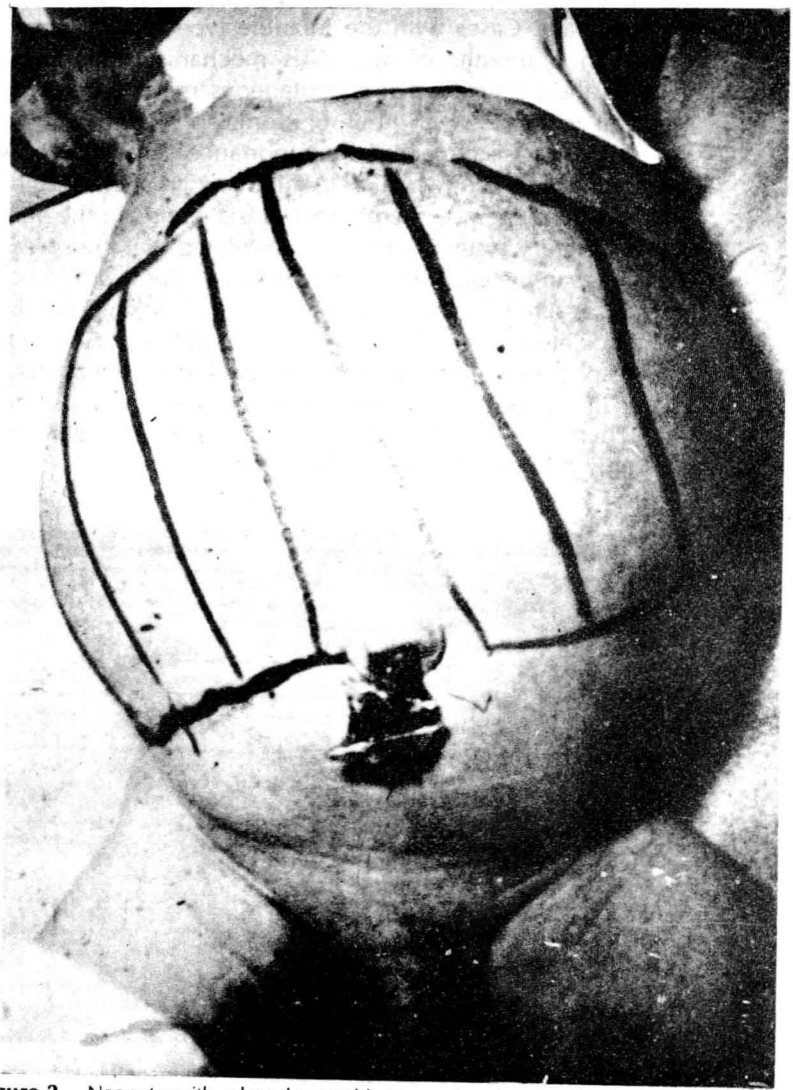

Figure 2. Neonate with adrenal neuroblastoma showing massive hepatomegaly due to liver metastases. (Courtesy of Dr. Alan H. Bennett)

nity of reaching the lung in the fetus because the foramen ovale and ductus arteriosus shunt blood past the lungs (Figure 4). Tumor emboli readily pass through the coarse filter presented by the placenta and re-enter the fetal circulation. The dictus venosus carries a large proportion of the blood directly to the liver, accounting for the greater incidence of hepatic metastases in any neoplasm in the fetus or young infant. Cases with the infantile type usually occur in infants less than 6 months of age. This mechanism does not, however, explain the occurrence of subcutaneous metastases, which are also peculiar to infants with neuroblastoma.

In metastasis of cancer the importance of mechanics is shown by the routes of spread, which determine to a great extent the location of metastases. Generally, hemic metastasis begins in the venous part of the circulatory system. It may be postulated that the spread of cancer cells ends in the capillaries of the organs, which would act, to a great extent, as filters for tumor emboli. So the "linkage" of the organs in the circulatory system plays a decisive part in hemic metastasis. In this respect conditions before and after birth differ vastly. This might result in the peculiarities of metastasis seen in fetal tumors.[40]

There are three important differences between the vascular anatomy before and after birth (Figure 4).

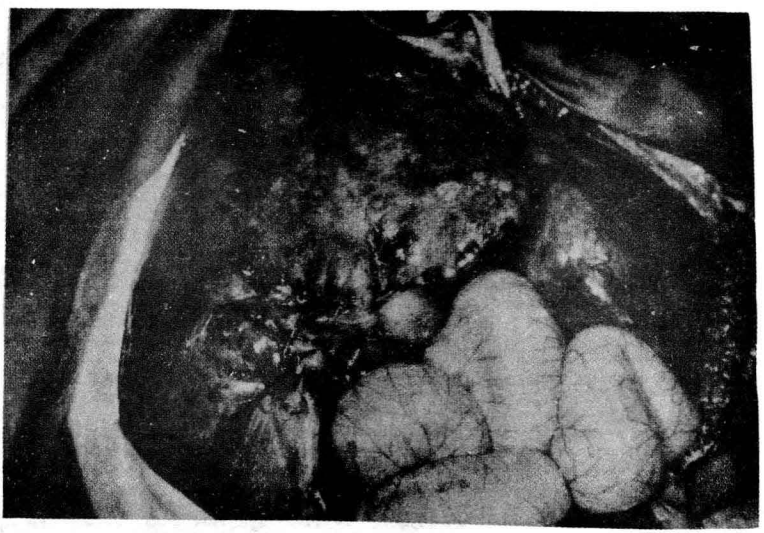

Figure 3. Markedly enlarged liver of an infant with neuroblastoma showing numerous focal metastases. X-ray therapy and chemotherapy resulted in prolonged survival. (Courtesy of Dr. Martin Winnick)

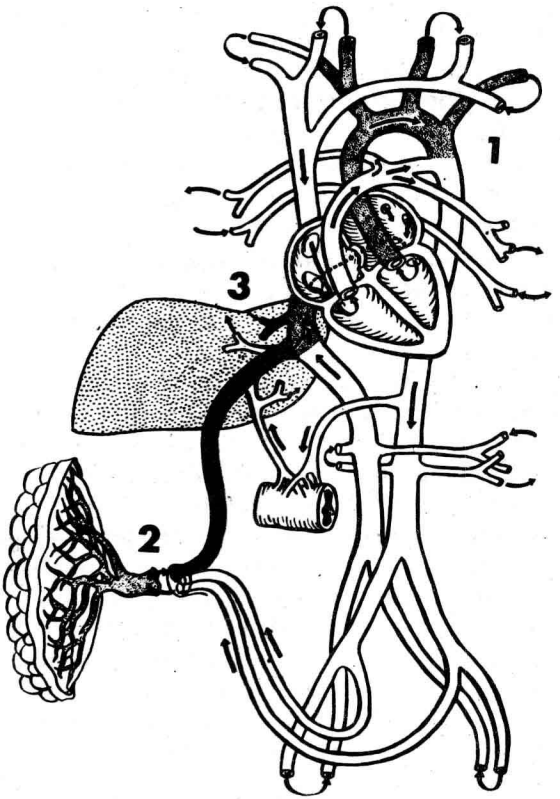

Figure 4. Diagram showing anatomy of the fetal circulation. (1) Bypassing the lungs through the foremen ovale and ductus arteriosis minimizes the likelihood of pulmonary metastases, (2) coarse filtration of the systemic blood through the placenta makes placental metastases rare, and (3) allows circulating tumor cells to lodge mainly in the liver.

1. Short circuits of the pulmonary circulation via foramen ovale and ductus arteriosus These short circuits can convey tumor emboli directly from the venous into the arterial part of the systemic circulation, thus avoiding arrest in the lungs. The ductus arteriosis reaches the aorta distal to the branches to myocardium, head, neck, and arms. Therefore, these parts of the body receive "unfiltered" blood only via the foramen ovale, whereas trunk, intestines, legs, and placenta receive unfiltered blood via both short circuits. In this connection it is of importance to know what percentage of the blood in the inferior vena cava (coming from adrenal glands, liver, placenta, and other organs) passes outside the "lung-filter" into the descending