TUMORS OF THE NEWBORN AND INFANT

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To my dear wife and children, who have wholeheartedly supported me in my endeavors throughout the years.

PREFACE

Neoplasms that affect the newborn and infant differ in several respects from those seen at later ages. These tumors are perhaps the most likely causes of difficulty in diagnosis for pathologists. This book presents the gross pathologic and histopathologic features of these tumors as well as some clinical aspects of both neoplastic diseases and tumorlike conditions in these young patients. For the past 27 years I have been intensely interested in this subject, and this work is based to a large extent on my own experience at Children's Hospital Los Angeles. Most of the illustrations are taken directly from cases I personally examined, including more than 5,000 surgical and autopsy tumor specimens obtained from infants and children during this quarter century.

Although this work is intended primarily for pathologists, its content is appropriate for clinical application. Pediatricians, pediatric surgeons, and radiologists may find it of interest and benefit. To illustrate the various tumors of the neonate and infant as comprehensively as possible, I have used the case presentation method in many instances. I hope this provides correlation between a given tumor, its clinical presentation, and its pathologic findings. Treatment can then be planned.

The selection of tumors is based on what I believe a pediatric pathologist engaged in routine hospital work may expect to see. This includes tumors that must be diagnosed by biopsy or by postmortem examination. References are given for the more unusual, exotic tumors not discussed in detail in this text.

Comprehensive reviews and textbooks on the genetics, molecular biology, and treatment of tumors are available, and I have not attempted a complete presentation of these subjects. This book does provide a basis for the study of neoplasms in the newborn and infant and the opportunity for familiarization of the clinician and pathologist with these unique tumors and tumorlike conditions. The ultimate goal is to help both pathologist and clinician achieve an accurate diagnosis and to clearly understand these lesions so that proper treatment can be initiated.

I wish to acknowledge the secretarial assistance of Miss Renee Brown and the photographic assistance of Mr. Darkin Chan.

Hart Isaacs, Jr., M.D.

CONTENTS

CHAPTER 1

Introduction

Neoplasms occurring in the neonate and infant are not entirely the same as those observed in the adolescent or adult. They differ in type, incidence, clinical features, behavior, and response to treatment (see references 1–8, 12–16, 18–26, 28–30, 35–38, 40–47).

Sometimes it is difficult, if not impossible, to distinguish between certain tumors, congenital malformations, and hamartomas.[4, 8, 16, 35, 45] Teratoma, melanocytic nevi, and benign soft tissue vascular lesions are good illustrations of this dilemma. Whether lymphangiomas and hemangiomas, the most common congenital soft tissue masses, represent tumors, hamartomas, or congenital malformations has not yet been completely settled.[17] A *hamartoma* is defined here as a benign mass lesion composed of cells not cytologically abnormal for those ordinarily found at the site of origin. On the basis of this definition I believe that most hemangiomas represent hamartomas rather than true neoplasms. Furthermore, many nonneoplastic conditions mimic tumors. The numerous and varied entities that are seen as abdominal masses in the newborn infant are a good example of this diagnostic problem (Table 1–1).

Generally pathologists make the diagnosis of malignancy based on certain microscopic criteria, but these are not always helpful or valid in young children. Several factors must be considered. First, normally developing organs and tissues display significant mitotic activity and contain immature or embryonic-appearing structures that may mimic malignancy. Second, lesions not histologically malignant may cause death simply because of their location; for example, a large lymphangioma, mature teratoma, or fibromatosis may involve vital structures in the neck or mediastinum. For these and other reasons the pathologist must be familiar with tumors and tumorlike conditions in the infant so that the correct diagnosis is made and the proper treatment begun.

Both benign and malignant tumors display unique clinical and pathologic features in the newborn infant. Correlation between these clinical and pathologic findings is necessary not only to diagnose the tumor accurately but also to predict its behavior. Some neoplasms diagnosed in the first year of life show an unexpectedly benign behavior, although they appear malignant microscopically.[5–10] A lesion with

TABLE 1–1.
Differential Diagnosis of Abdominal Masses in the Newborn*

Gastrointestinal
- Imperforate anus
- Meconium plug
- Meconium ileus (cystic fibrosis)
- Meconium cyst
- Intestinal duplication
- Mesenteric cyst
- Lymphangioma
- Intussusception
- Pyloric stenosis

Liver and bile ducts
- Hemangioma
- Mesenchymal hamartoma
- Hepatoblastoma
- Cystic disease
- Choledochal cyst
- Subcapsular hematoma
- Metastatic neuroblastoma, leukemia

Adrenal
- Neuroblastoma
- Hematoma

Urinary
- Megacystis
- Hydronephrosis
- Hydroureter
- Urachal cyst
- Urachal diverticulum
- Multicystic kidney
- Polycystic kidney
- Renomegaly (renal vein thrombosis)
- Mesoblastic nephroma
- Wilms' tumor
- Rhabdoid tumor

Genital
- Hydrocolpos
- Ovarian cyst
- Ovarian teratoma
- Ovarian torsion

Miscellaneous
- Sacrococcygeal or retroperitoneal teratoma
- Anterior meningomyelocele
- Splenic hematoma
- Splenic cyst

*Modified from Koop EC: *N Engl J Med* 1973; 289:570.

similar histologic features found in an adult conceivably could be fatal. Prime examples of this group are stage IV-S neuroblastoma, infantile fibrosarcoma, and nephroblastomatosis (see references 6, 7, 11, 18, 19, 36). On the basis of this observation and other findings, Bolande[5] suggested the hypothesis that an "oncogenic period of grace" exists in utero and in the first few months of life; during this time the fetus and the infant are supposedly resistant to a malignant tumor's full expression and metastases. Other theories have evolved to explain the different biologic behavior of tumors in these young patients (see references 9, 10, 29, 32, 33, 36), but as yet a full explanation has not been elucidated.

On the opposite side of the coin are those tumors with markedly worse prognoses in the newborn or infant, for example, acute lymphocytic leukemia.[13, 14, 20, 25, 36, 37]

Some tumors occurring in the newborn differ in clinical signs and symptoms from those found in older patients. For example, maternal dystocia may be the first sign of a large space-occupying congenital tumor, such as a giant intracranial or retroperitoneal teratoma. Fetal hydrops is another rare, unique manifestation; according to Keeling,[27] several causes of fetal hydrops relate to neoplasms, including (1) shunts with high-output cardiac failure produced by a large hemangioma involving an extremity, the brain, or the liver; (2) loss of protein from abnormal vessels into the interstitial space, as from a lymphangioma; (3) vascular obstruction to the main fetal circulation caused by a mediastinal teratoma; and (4) obstruction of placental villous capillaries by tumor emboli from a neuroblastoma (see Fig 5–2). Rupture of a large tumor, such as a hepatoblastoma or neuroblastoma, during delivery, with fatal exsanguination of the fetus, is a dramatic illustration of another unusual presentation.

A few terms must be defined to ensure accurate communication in this book.

Neoplasms noted at birth and during the first month of life are defined as *congenital;* the term *infancy* includes only the first year of life, and *neonatal* the first month after birth. Obviously, the distinction between a congenital and an acquired tumor during this first year is unclear. The term *tumor* is applied loosely throughout the text to both true neoplasms and to tumorlike conditions such as hamartomas (e.g., mesenchymal hamartoma of the liver) and hemangioma.

Malignant tumors of infants and children in general are termed *embryomas* (or embryonic tumors), as proposed by Willis[45] and later advocated by Bolande,[6] Morison,[31] and Wigglesworth.[44] This is based on the microscopic resemblance of these tumors to early phases in the development of either the organ or the tissue of origin. Embryomas, specifically Wilms' tumor, retinoblastoma, hepatoblastoma, neuroblastoma, medulloblastoma, and rhabdomyosarcoma, are the malignancies most frequently encountered in early childhood. According to Bolande, some members of this group exhibit a high rate of cytodifferentiation, regression, and benign tendencies.[5–8] Furthermore, most embryomas are not observed at birth or in the first 2 months of life, as suggested initially by Willis, but are found also later in childhood. It is conceivable that neoplastic transformation could occur during embryogenesis and endure. This might explain the relationship of certain embryonic appearing lesions such as Wilms' tumor in situ (nephroblastomatosis) or neuroblastoma in situ to the development of their respective malignant counterparts later.[8, 39]

Blastoma is another term used to denote an "embryonic tumor." For example, pulmonary blastoma is primarily a pediatric lung tumor composed of both primitive appearing malignant epithelial and mesenchymal elements.

Chemotherapy in the newborn and infant is hindered by poor drug tolerance in this age group.[4, 12, 15, 36, 40] The detrimental effects of radiation on immature, growing tissues are well known,[36] and mutilating surgery is absolutely contraindicated in newborns and infants. The sequelae of therapy, rather than the tumor itself, may cause death. Therefore the potential long-term effects of surgery, irradiation, and chemotherapy must be taken into full account when considering treatment. These are additional, obvious reasons why tumors in the infant must be diagnosed correctly, thereby preventing unnecessary morbidity and mortality as a result of improper therapy. Moreover, the physician responsible for the patient's care should discuss with the parents the possible risks involved with therapy before it is begun.[13]

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CHAPTER 2

Etiologic Factors

Environmental Factors
Congenital Malformations and Syndromes
Knudson's Hypothesis
Suppressor Genes
Oncogenes
Metastases of Maternal Neoplasms to Fetus

The causes of neoplasia in neonates and infants are probably related to the causes of cancer in general, which are not yet clearly defined. Various etiologic factors have been proposed, such as viral infections in utero, maternal use of drugs or exposure to irradiation, congenital malformations, and chromosomal abnormalities. In this chapter we examine environmental factors, congenital malformations and syndromes, gene defects, and metastases of maternal neoplasms to the fetus. These are general evaluations of the causes of neoplasia and do not examine the molecular and cellular biology involved (see references 2, 8, 17, 23, 27, 28, 31, 34, 38, 40, 41).

ENVIRONMENTAL FACTORS

Scant data are available to firmly establish that environmental factors play a signigicant role in the development of malignant tumors in the neonate and infant.[3, 35] Among some of the factors suggested are drugs and viral agents.

Reports of drugs associated with congenital malignancies have appeared only rarely in the literature (see references 3, 15, 33, 35, 37, 42). Hydantoin has been incriminated as a prenatal carcinogen; two offspring of epileptic mothers maintained on this drug were born with fetal hydantoin syndrome and subsequently developed neuroblastomas.[33,37] This malignancy also has been reported in babies with fetal alcohol syndrome.[35] Another drug, diethylstilbestrol (DES), results in vaginal clear cell adenocarcinoma in offspring, not at birth but later in life.[3, 15]

The role of viruses in the cause of congenital cancer has not been confirmed. Studies[4, 13] suggest, however, that an increased risk of developing malignant tumors follows in utero exposure to certain viral agents, such as varicella virus, influenza virus, rubella virus, and cytomegalovirus.

CONGENITAL MALFORMATIONS AND SYNDROMES

An important relationship exists between certain congenital malformations and the development of neoplasms (see references 5–7, 26, 34, 35, 41). The tumor occurs after birth or later in life in individuals with specific inherited diseases, congenital anomalies, or malformation syndromes (Table 2–1). For example, an increased incidence of neoplasms is associated with gonadal dysgenesis in patients having a Y chromosome where gonadoblastoma and germinoma arise in the dysgenetic gonads.[1, 7, 27, 41] Wilms' tumor, hepatoblastoma, and adrenocortical tumors develop in patients with hemihypertrophy and Beckwith-Wiedemann syndrome. Furthermore, aniridia and malformations of the genitourinary tract have been found in infants and children with Wilms' tumor (see references 5, 7, 30, 32, 36, 39, 41). The list of inherited syndromes and conditions associated with increased risk of developing tumors has grown considerably in recent years.[22, 24, 27, 34, 41]

Certain individuals who are at risk for leukemia have a definite chromosomal alteration, either congenital or acquired (see references 3, 7, 12, 25, 27, 35, 41; Table 2–2). Chromosomal anomalies are observed in patients with Down's syndrome, ataxia telangiectasia, and Bloom's and Fanconi's syndromes; they are also noted in older individuals after radiation treatment or exposure to certain chemicals, such as benzene.[3, 5, 7] Genetic conditions such as the neurocutaneous syndromes are also characterized by a high incidence of neoplasia. For example, tuberous sclerosis and

TABLE 2–1.

Some Examples of Syndromes and Congenital Malformations Associated With Childhood Tumors*

Malformation	Neoplasm
Beckwith-Wiedemann syndrome and hemihypertrophy	Wilms' tumor Adrenal cortical adenoma and carcinoma Hepatoblastoma
Aniridia	Wilms' tumor
Genitourinary system anomalies	Nephroblastomatosis Wilms' tumor
Hirschsprung's disease	Neuroblastoma
Poland's syndrome	Leukemia
Drash syndrome	Wilms' tumor

*Data from Bolande RP, in Rosenberg HS, Bolande RP (eds): *Perspectives in Pediatric Pathology*, vol 3. Chicago, Year Book, 1976, pp 145–183; Landing BH, in Miller JH, White L (eds): *Imaging in Pediatric Oncology*. Baltimore, Williams & Wilkins, 1985, pp 14–22; Mulvihill JJ, in Pizzo PA, Poplack DG (eds): *Principles and Practice of Pediatric Oncology*. Philadelphia, JB Lippincott, 1989, pp 19–37.

some forms of neurofibromatosis, which are autosomal dominant, predispose the individual to the development of astrocytoma, other gliomas, and neurofibrosarcoma.[3, 27] Among the pediatric neoplasms associated with recently recognized recessive chromosomal alterations are 11p13 deletion anomaly (observed with Wilms' tumor) and 13q14 deletion (in patients with retinoblastoma and osteosarcoma)[17, 28, 29] (see Table 2–2).

Knudson's Hypothesis

As the result of certain observations of neoplasms occurring in infants and children, specifically retinoblastoma, Wilms' tumor, and neuroblastoma, Knudson proposed an important hypothesis, the so-called *two-hit theory*. This proposes that two successive mutations are required in a cell for a tumor to develop.[18–21] The muta-

TABLE 2–2.

Some Examples of Chromosomal Abnormalities Associated With Childhood Tumors*

Chromosomal Defect	Childhood Tumor
11p13 deletion	Wilms' tumor
13q14 deletion	Retinoblastoma Osteosarcoma
p32p36 deletion	Neuroblastoma
Monosomy 7	Leukemia
Trisomy 18	Wilms' tumor
Trisomy 21 (Down's syndrome)	Leukemia
Gonadal dysgenesis	Gonadoblastoma Germinoma
Klinefelter syndrome	Teratoma

*Data from Israel MA, in Pizzo PA, Poplack DG (eds): *Principles and Practice of Pediatric Oncology*. Philadelphia, JB Lippincott, 1989, pp 39–64; Landing BH, in Miller JH, White L (eds): *Imaging in Pediatric Oncology*. Baltimore, Williams & Wilkins, 1985, pp 14–22; Mulvihill JJ, in Pizzo PA, Poplack DG (eds): *Principles and Practice of Pediatric Oncology*. Philadelphia, JB Lippincott, 1989, pp 19–37.

tions happen in two stages. If the first mutation or hit occurs in a germinal cell (germinal mutation), then conceivably all cells in the individual would be altered and made susceptible to the carcinogenic effect of a second mutation. Theoretically in this situation a neoplasm would develop bilaterally or in multiple sites and more likely would be found in a younger child, as compared with the sporadic tumors. Furthermore, the germinal mutation would be transmitted as an autosomal dominant trait. If the first mutation happens in a somatic (postzygotic) cell, then a local population of cells would result that would be susceptible to malignant change by a second hit. Conceivably the tumor produced would be unifocal, nonhereditary, and usually seen later in life. Examples include some of the adult malignant tumors such as carcinoma of the cervix or the lung.

Probably many childhood tumors, including sporadic retinoblastoma, result from two somatic mutations, if the theory is correct. In addition, Knudson proposes that if a first mutation produces a malformation and a second one a tumor, the association between teratogenesis and tumorigenesis could be explained. For example, the external manifestation of the first hit in infants and children with Wilms' tumor conceivably could be Beckwith-Wiedemann syndrome. The initial presentation in those individuals with retinoblastoma would be the 13q− syndrome. Subsequently the tumors develop after a second hit in these two situations.

Knudson's two-hit mutation theory of tumorigenesis has been shown to be plausible in several recent cytogenetic studies. Friend et al,[14] Murphree and Benedict[28, 29] and Yunis and Ramsay[45] have demonstrated a very important relationship between the integrity of the 13q14 retinoblastoma gene and the development of childhood cancer. The findings indicate that both copies of the 13q14 Rb gene must be altered in some way, for example, by loss, inactivation, mutation, or deletion, before a tumor can develop. An individual who acquires a defective 13q14 gene from either parent is heterozygous for the altered gene and, by definition, is a carrier for the gene. Before tumorigenesis can happen, however, a second event must occur, as originally proposed by Knudson; that is, both retinoblastoma genes must be altered. Furthermore, inheritance of a faulty copy of one allele at the 13q14 locus apparently makes the individual susceptible to cancer. When the second allele becomes altered or inactivated at the 13q14 locus, tumorigenesis occurs, with the development of retinoblastoma at an early age and then a second malignancy such as osteosarcoma later.[14, 28]

Suppressor Genes

Evidence to support the concept of recessive (suppressor) cancer genes comes from experiments with somatic cell hybrids such as fibroblast-fibrosarcoma hybrids.[28] If a fibroblast is fused with a fibrosarcoma cell, the ability of the hybrid to form a neoplasm in animals is lost. On repeated passages in tissue culture, however, suppressor genes are lost for some unknown reason, and the hybrid forms tumors when injected into a susceptible animal.

Certain evidence suggests that the second mutation, the one responsible for tumorigenesis, can occur any time from the moment of conception until the precursor cells in a developing organ have lost their ability to divide.[28] For example, terminal differentiation of the retinal precursor cells is usually completed by the fifth month of life. However, studies show that during embryogenesis and through the completion of organogenesis the development of a malignant tumor is actively inhibited.[28]