Cancer Diagnosis in Children

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INTRODUCTION

Most people are unaware of the commonest fatal disease of childhood. Most physicians are unaware of the commonest killer of children. Yet the death certificates speak for themselves – Cancer! Cancer is the number one killer of children from infancy through early adulthood.

This has not always been the case. Forty years ago, when Fleming discovered penicillin, infectious diseases were rampant and took a striking toll. As they became conquered the overall death rates fell, but the death rate from cancer continued unabated until 20 years ago, when it rose above all other causes of death except for accidents. It continues second only to accidents as the leading killer of children. In 1955 nearly 4000 children aged 1 to 4 died of cancer, 12% of the childhood deaths that year. A dozen years later, the situation was unchanged: in 1967, 4000 children aged 1 to 14 still died of cancer. This persisting loss of children to cancer emphasizes the need to recognize the facts and to do something about them. One way to help is to make early diagnosis of children's cancer a high priority goal. This book is directed to the wide front with interest in children's cancer: the general physician, paramedical personnel, students, and anyone concerned with child health.

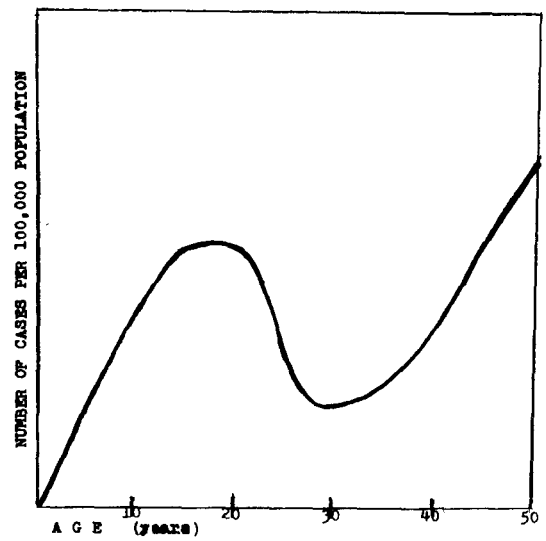
Cancer in children is different from adult cancer in type, location, natural history, and response to therapy (Table 1). Most adult cancer is carcinoma, of epithelial origin. Most pediatric cancer is sarcoma, of mesothelial origin. The most common adult cancers are in the lung, gastrointestinal tract, breast, and uterus. Pediatric cancer is rare at these sites but common in brain, kidney, blood, eye, and muscle. It is also relatively common in the adrenal gland or elsewhere along the embryological line of deposition of neural crest cells where remnants of neuroblastic cells may form the neuroblastoma. Only a few tumors appear in both children and adults; among these are Hodgkin's disease and bone sarcomas. But the pattern of distribution of bone tumors (see Figure 1), as well as their different histological patterns, suggest that pediatric bone tumors, most common in the teen ages, and adult bone tumors, most common after age 40, are 2 distinctly different entities.

The vast differences between pediatric and adult cancer suggest differences in etiology as well.

TABLE 1

Pediatric Malignant Tumors Seen at Children's Hospital

Leukemia	427
Brain Tumors	243
Neuroblastoma	107
Lymphomas, including Hodgkin's disease	99
Wilms' Tumor	84
Rhabdomyosarcoma, including undifferentiated soft-tissue sarcoma	58
Osteosarcoma and Ewing's tumor	43
Retinoblastoma	42
Hepatoma	25
Malignant gonadal tumors, thyroid carcinoma and misc.	71
Total	1200



INCIDENCE OF OSTEOSARCOMA BY AGE

FIGURE 1

Such is probably the case. The etiology of most cancers is unknown but there is increasing evidence as to causal factors in both adult and pediatric tumors, especially the former. The association between cigarette smoking and lung cancer now is well-documented. Since the incubation period for induction of lung cancer by cigarette smoking is relatively long, children would not have

this cancer until adulthood, even if they began smoking early in life. A similar situation probably prevails with skin cancer, where prolonged exposure to sunlight or certain poisonous chemicals is required for carcinogenesis.

Thus, most adult cancers probably arise out of contact with agents in the environment. The individual may inherit susceptibility to cancer induction but must be exposed to the proper agents for a sufficient time actually to develop a malignant tumor.

In contrast, most pediatric malignancies probably are present at birth, at least in an anlage state. Some, notably the nephroblastoma or Wilms' tumor, and the neuroblastoma, may be present as a full-grown tumor at birth.[1] Others may have their progression arrested until an apparent developmental stimulus initiates their rapid growth. Although many parents and some physicians may relate the onset of a child's cancer, especially those of the extremities, to an injury, there is usually good evidence against this as an etiological factor.

One of the most convincing pieces of evidence is the kinetics of growth of the tumor itself. By radioisotope labeling of growing cells, the time required for the cells to divide and double in number can be determined with some precision. Each type of tumor has a characteristic growth rate but most malignant tumors do not grow fast, not even as fast as some normal cells of the human body. For example, the osteosarcoma cell has a doubling time of about 30 days. This means that a month, on the average, is required for 1000 cells to grow to 2000 cells. Since about 1 billion cells are required to make 1 g of tissue, and since cancer can begin as just one aberrent cell, the number of doublings required to grow from unicellular to any given size can be estimated readily (see Figure 2).

In the case of osteosarcoma at least 30 doublings are needed to produce 1 g of tumor, and this requires 30 months' time at maximum growth rate. Most bone tumors are not diagnosed until they reach over 100 g in size, so over 3 years' rapid growth is needed before the diagnosis can be made. Yet at that rate of growth, if left unchecked the tumor would reach a lethal size of over 1 kg

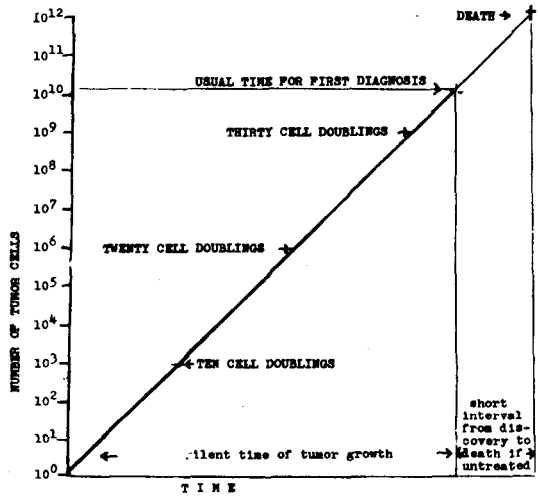


FIGURE 2

just four months later! The natural history of this tumor, if not diagnosed and treated, thus is like an iceberg: 90% of its life it remains hidden, and only 10% of its life is visible and apparent. The challenge to tumor diagnosis is to shorten the time of invisibility of tumors, for the earlier the tumor is found and treated, the more likely extended control and even cure can be accomplished (see Figure 2).

The one tumor of adults whose cure rate is the highest is carcinoma of the skin. One important reason for this is the early diagnosis, when the tumor is relatively small. This is true not only for the primary tumor but also for any subsequent recurrences. The only pediatric tumor with any similar fortune is that on the retina of the eye, the retinoblastoma. Because they produce visual loss early and can be seen readily through the lens of the eye, most retinoblastomas are diagnosed before they have extended beyond the globe of the eye.

For all other tumors, originating to deeper structures of the body, no such window is available for diagnostic inspection. In the following chapters of this book are a collection of the substitutes for the window of the eye, methods to permit the examiner to "see" the inside workings of the body and to ascertain the whether and the where of malignant tumors.

[1] For a comprehensive discussion of the possible life history and of the factors which may influence the growth of one such tumor, see The Biology of Neuroblastoma, proceedings of a conference Sept. 15-16, 1967 at Children's Orthopedic Hospital and Medical Center, Seattle, in *J. Pediat. Surg.*, 3, 101, 1968.

Chapter 1

HISTORY AND PHYSICAL EXAMINATION

Diagnosis of Children's Cancer – History and Epidemiology

Early diagnosis of cancer is a major goal in its treatment, for early detection more often allows definitive, curative primary therapy. Where the diagnosis hangs in doubt and is delayed, extension or metastatic spread too often prevents an eventual cure. In order for early diagnosis to be possible the patient must be seen by an alert physician as soon as the first manifestation of his disease is apparent. This requires heightened awareness in both parents and physicians.

The incidence of malignant neoplasms of childhood probably has not changed significantly over the past five decades. Case finding has improved with better diagnostic methods and greater awareness of cancer. Case reporting has been facilitated by collaborative treatment efforts which seek out cases of the disease and document their treatment.

Because children's neoplasms so often have been quickly fatal, the *prevalence* of pediatric cancer is very nearly the same as the incidence. This is because about as many old cases die each year as are diagnosed, and average survival is not over one year; hence, new cases, on the average, do not survive to be accumulated and counted in the prevalence another year.

This situation has changed in the past decade with advances in treatment, especially with the addition of extended courses of treatment with cytotoxic cancer chemotherapeutic drugs. These agents frequently prolong survival, even if they do not cure the cancer, so that survival for two or more years is not unusual, and extended survival now is being reported for the majority of children with at least one type of tumor, the nephroblastoma or Wilms' tumor.

The familial nature of cancer susceptibility commonly is suspected but it is not easily documented, since complex polygenic factors appear to be involved. For practical purposes a positive family history of cancer can serve best to alert both family and attending physicians to be on the lookout for evidence of the disease. Such watchfulness sometimes can be rewarded by an early diagnosis which may be lifesaving.

Unlike adult cancer, which probably arises from the interplay of environmental factors with inherited susceptibility factors, pediatric cancer seldom can be blamed on known environmental factors. Indeed, some pediatric cancers are clearly *congenital* since they may be found at birth when they may already be large. It can be argued that environment can play a role in pediatric tumors through prior influence on a parent, logically on the mother, whose germ cells are formed in the ovaries early in life and remain vulnerable to environmental assault throughout life until the time of ovulation.

Alterations in the bodily immunological competence clearly play a role in the incidence of malignant tumors. Studies on aborted fetuses have shown a higher incidence of malignant tumors than are present at full-term births, suggesting that there is immunological rejection of many of the tumors *in utero*. Follow-up studies of children who have received immunosuppressive therapy for organ transplants have shown a greatly-increased incidence of malignant tumors. And analysis of congenital syndromes associated with immunological incompetence has revealed an extremely high incidence of malignant tumors in these children.[1] All of these studies point to a mechanism present in the normal body for rejecting many foreign cells and thus eliminating clones of tumor cells before they become clinically evident. A major mistake of most parents and some physicians is that of linking the onset of children's cancer to an injury. Very often the known history of a tumor in an extremity begins with a bump which doesn't get better.

How parents will sift through their consciousness for any straw of experience on which the cancer can be blamed! From the facts of cell kinetics, the time between the insult of injury and the observation of a tumor is seldom enough to have allowed the growth of a tumor big enough to see even if it were on the skin, much less located deep within the body. The approximate age of a tumor mass can be calculated if the size of the average tumor cell and the cell doubling time are

[1] Gatti, R. A. and Good, R. A., Occurrence of malignancy in immunodeficiency diseases, *Cancer*, 28, 89, 1971.

known. The cell doubling time is the average time required for complete cell division so as to increase two times the number of cells. This may be a month or more for some tumors. Because tumor cells weigh less than one millimicrogram, over 1 billion are required to weigh 1 g and fill the space of 1 cm. If we assume that the cancer starts with 1 cell and has a cell doubling time of one month, 30 cell divisions or 30 months' time would be required to produce a 1 cm lump if all cells survived all that time. Thus, several months to years are required for growth of a cancer to a size which allows diagnosis.

The parent who is cancer-conscious may irritate the physician by too frequent visits because of his alarm with every lump or sore, but such awareness is to be encouraged. Parents may well be counseled to examine their children nightly or at least weekly for anything unusual in their appearance. Any physician who treats children's cancer can recall cases where an abdominal tumor has grown so large that the child bulges grotesquely, but the parents hadn't noticed anything wrong. The reasonable parent will know to look at the abdomen and feel it, perhaps daily at bath time. The observant parent will notice swollen inguinal or cervical lymph nodes, or the white eye of a retinoblastoma. "Awareness without fear" is an ideal feeling to be inculcated in parents. Such parents can give a more useful history of disease. However, with most children's cancer the history isn't as important in the long run as is prompt attention as soon as the abnormality is first seen or felt. This is where parental alertness counts most. Life saving comes from time saving between first observation and definitive treatment.

The actual symptoms of pediatric cancer may be no more than a limp or pain in an extremity, seen with bone sarcomas or with neurogenic tumors which produce pressure on spinal nerve roots. Easy fatigability is a common symptom of an internal cancer, although the tumor is too often advanced before this systemic complaint becomes evident. Pallor, easy bruising, or bleeding episodes are commonly the first symptoms of acute leukemia but they also may be seen with neuroblastoma.

Night sweats and fever are common leading symptoms of Hodgkin's disease and the physician should consider this, as well as tuberculosis, of which these are classic symptoms. As with adult cancer, weight loss is an ominous sign in children. It should be remembered that in a growing child, *failure* to *gain* weight can be the equivalent of weight *loss*.

Gastrointestinal bleeding is a common cancer danger signal in adults but gastrointestinal cancer is very rare in children, so this is not a common symptom. Blood in the urine, however, can be an early sign of one of the commonest of children's cancers, the nephroblastoma, or Wilms' tumor. Hypertension also can be a sign of Wilms' tumor.

Brain tumors are the commonest solid tumor of childhood. They can manifest themselves in various ways, with symptoms varying from persisting headache to seizures. There may be weakness of an arm or an extremity or disturbance of balance, leading to walking with a wide-based gait. However, the ability of most children to accommodate to a progressive disability sometimes allows rather severe neurological damage to go unnoticed until it is specifically looked for. Persistive vomiting, especially in the morning, is an important sign of a brain tumor, and should alert the parent to seek immediate medical aid.

A black eye can result from rough and tumble play, but whenever a child under five develops a black eye, especially if the eye appears prominent or protruding, the possibility of metastatic neuroblastoma should come to mind. This is one of the commonest causes of unilateral exophthalmos (protruding eye) in the young child. Similarly, bone pain from long bone metastases may be the first sign of this highly malignant tumor which metastasizes early.

With these few exceptions, most children's malignant tumors have a subtle onset which escapes the attention of even the most wary. Once a child is at the physician's office with real symptoms, therefore, it is imperative that no time be wasted with temporizing or extended observation: a definitive diagnostic work-up appropriate to the symptoms and signs of disease should be begun without delay. One of the saddest tasks in a cancer referral hospital is to hear the history of a child with a potentially curable cancer who has been treated with antibiotics for weeks and months because of tumor-filled lymph nodes, until a localized tumor has become disseminated, resulting in no hope of cure.

Physical Examination

Preparation

Examination of the young patient suspected of

having cancer may seem similar to the examination of an adult, but it may be very different indeed if the patient is an infant; every pediatrician should appreciate the need to adjust his examination procedure to the size of the patient. No matter what the age of the child, the examination should be performed in a well-lighted, comfortable area convenient to both physician and patient. Enough time should be budgeted to allow a thoughtful, thorough examination; haste may cause him to miss the small tumors for which there is higher hope of cure. A beginning medical student usually can detect the advanced, "hopeless" cancer, even in a child.

If the child's confidence and cooperation are won in advance, the subsequent examination procedure will be much more productive. The older child may be ill at ease, suspecting the presence of cancer. The young child may have anxiety because of the examination procedure or actually may be suffering real pain from the disease at the time he is first seen. Reassurance may be hard to give convincingly, but it should be attempted in every case. A few words can make the difference between an unsatisfactory examination and a satisfactory one.

The younger pediatric patient usually will have his mother and/or father present for the examination. Their presence may allow the child to relax, but if he wishes to be seen alone this should be permitted. The older pediatric patient, especially the teenager, usually will want to be seen alone and treated as an independent individual. This should be possible; treating the teen with the respect shown an adult can change initial truculence into complete cooperation. In any case, anything done to increase the patient's cooperation can only facilitate a better examination. Frequently a running commentary, either by way of history-taking or conversation, keeps the child interested and compliant during the examination procedure.

Where cooperation cannot be obtained, and especially if a thorough examination is needed for a possible neoplasm, as in the case of fundus examination for retinoblastoma or deep palpation for an abdominal tumor, examination under anesthesia may be justified and necessary. The risk of anesthesia (q.v.) is relatively minor if such a serious diagnosis as potentially curable cancer is possible.

Approach to the Examination

The examiner, whether he is parent or physician, must always remember:

> "Every solid or semisolid, semicystic mass in an infant or child should be regarded as a malignant tumor until its exact nature is determined by histological examination of the removed tumor."*

The approach used for the complete physical examination will depend in large measure on the person performing the examination and on his relationship to the patient. If he is the child's parent, the examination will be more cursory and superficial; if he is the family doctor, the examination should be more complete and thorough. The approach is different still for a consultant or house officer for a child hospitalized with suspected cancer. In the description which follows, approach to the physical examination of the patient by these different examiners will be considered.

Physical Examination – The Parent

Because the average parents are not trained in human anatomy, many physicians consider them inept at physical examinations. Such need not and should not be the case! The physician has experience with a variety of normal and abnormal children and the disease states which afflict them, but the parent has the advantage of continued, intensive experience with one or several children. The parent thus can appreciate the individual characteristics of a given child, characteristics which may vary from the average but which may nonetheless be that child's normal makeup. The typical parent is reluctant to palpate vigorously a newborn infant, but with experience he learns that most infants enjoy the patting and squeezing that accompany the palpation of the trunk and extremities.

For the parent, a good time to examine the infant or an older child is during and after the daily bath. The child is usually relaxed by the warm water and the entire abdomen can be palpated quite deeply, often enough to feel the pulse from the abdominal aorta without harm. Frequently, the liver edge and the tip of the spleen may be palpable, and their first perception may lead to an alarmed consultation with the family doctor. Once reassured as to the normality of these organs in the abdomen during infancy, the parent may note the normal course of their

*Wolback, S. B., quoted by Farber, S., in *Neoplasia in Childhood*, Yearbook Publishing Co., Chicago, 1969, 323.

disappearance as the child grows. The presence of formed stool in the colon can deceive even the experienced physician. Parents should be advised to recheck the child after a few hours to see whether a lump on the left side of the abdomen, especially the left lower quadrant, does not change shape or position with time or after a bowel movement. If it does, the mass was most likely feces. If it does not, the family physician should be consulted for a diagnostic evaluation.

Any significant lump on an extremity should be detectable if the extremities are cleansed with a soft wash cloth during bathing, or stroked gently with the fingers during or after drying. The first known survivor, in the writer's experience, of the very malignant muscle tumor rhabdomyosarcoma was treated early because his father noticed a small lump on his calf.

The most common cause of a palpable lump in an extremity is a bruise, either subcutaneous, intramuscular, or subperiosteal hematoma, or a localized collection of fluid due to local tissue injury. This usually can be recognized by signs of injury in the overlying skin, by having witnessed the accident, or by obtaining a history of the injury. Where there is any question in the parent's mind of whether there has been an injury to account for the lump, the physician should be consulted. An ordinary bruise should be smaller after 24 hours, but a hematoma may persist for weeks or even months. Characteristic blue-green discoloration of the overlying skin is usually a sign of a resolving hematoma. A malignant tumor is more likely painless, but if bruised it can have all the characterisitics of a simple bruise.

A focal infection also can produce a local mass in the extremities. Such an infection may be secondary to a prick by a pin or thorn, or it may have no known etiological factor. If superficial, the necrotic center will point and drain spontaneously and be recognized by most parents as a "pimple." If an abscess is deep, however, it may not be recognized as such by the parent. In this case the family physician should be consulted, for systemic antibiotic treatment usually is needed and incision and drainage may be required. Often the only sign of infection noticed by the parent will be enlarged lymph nodes. The groin or inguinal nodes are especially prominent in most children of preschool and primary age. They may be enlarged because of an inconspicuous infection around a toenail or on the sole of a foot, a frequent spot for injury to barefoot toddlers. In any event, the parent should know how much his child's lymph nodes are usually palpable so that he can detect changes and know better when to consult his physician. Axillary nodes are less frequently detectable by parents, probably due to both their relative inaccessibility and the tendency of most children to be ticklish and thus to resist axillary examination.

Cervical nodes are easily palpable when enlarged and sometimes even may be seen on inspection when they are grossly enlarged. Normal cervical nodes should not be palpable except for the tonsillar nodes at the angles of the mandible. In many children these will remain palpable in the absence of significant tonsillar infection. The parent should know that the neck can be safely palpated without fear of choking the child. A few moments spent by the family physician explaining the locations of the chains of cervical nodes may save needless house calls and office visits later.

Direct examination of the brain of course is not possible, and the average parent is not expected to perform a standard pediatric neurological examination. However, the day-to-day observation of alertness, responsiveness, movement of eyes, arms, feet, and body, watching for coordination and the progressive improvement of muscular control provides an excellent measurement of neurological status. Whenever the child is well-rested, yet shows a decrease in alertness or performance compared with his previous performance (not with *another* child's performance), the family physician should be consulted.

The movement of the eyes is a sensitive indicator of dysfunction of cranial nerves, often an early sign of a brain tumor. A congenital strabismus or squint must be distinguished from the eye which has been normal but which begins to lose coordination with the other eye. One good test for this by a parent is to observe the child watching a mobile or to snap his fingers at the child from several positions around the head so as to coax the child to turn his eyes in each direction.

A small flashlight can be flashed at a child's eyes without harm. The normally dark pupils will appear red with the reflection of the light. Any child whose pupil appears light-colored or white on reflection should be seen immediately by an opthalmologist: this is a leading sign of retinoblastoma, a tumor which is curable if detected early while it remains contained inside the eye.