Solid Tumors in Children: Wilms’ Tumor, Neuroblastoma and Soft Tissue Sarcomas

Philip R. Exelby, M.D.

Once thought to be incurable, the outlook for the child with cancer has brightened over the last 10 years to one of cautious optimism. Markedly improved control rates and survival can be attributed to several factors: a multidisciplinary team approach in which surgeon, pediatric oncologist and radiotherapist design and apply treatment protocols cooperatively from diagnosis to completion of treatment; an increasing concentration of treatment in specialized centers, thus encouraging extensive clinical and laboratory research; earlier diagnosis and initiation of treatment; and finally, the formation of group studies, which have provided valuable data on the natural history and management of cancer in children.

However, cancer is still the most common cause of death from disease in children in the United States and Western Europe; only accidents claim more children’s lives. Thus, efforts must be directed to further improving cure rates in those tumors resistant to treatment and to improving the quality of survival for those children now cured of cancer.

**WILMS’ TUMOR**

Wilms’ tumor is the most common solid cancer found in children. It usually occurs in children between one and five years old, and occasionally in newborns and very young infants. Wilms’ tumor is extremely rare after the age of eight.

**Pathology**

Wilms’ tumor often appears as a large friable mass surrounded by a pseudocapsule with areas of necrosis and hemorrhage within the tumor. It arises in the renal parenchyma and distorts, but rarely invades, the calyceal system. Microscopically it is composed of three elements: primitive renal parenchymal cells known as blastema cells; mesenchymal stromal tissue, which resembles embryonal rhabdomyosarcoma; and epithelial cells in different stages of differentiation. Three congenital abnormalities are commonly associated with Wilms’ tumor: (1) congenital malformations of the urogenital system; (2) hemihypertrophy; and (3) congenital absence of the iris or aniridia.

**Clinical Presentation**

The presenting feature is typically an asymptomatic upper abdominal mass or abdominal distension. (Fig. 1.) Abdominal pain, fever or hematuria may occur but are quite rare. The tumor may grow to a very large size with remarkable absence of systemic symptoms. The children often present looking healthy and playing normally on the day that a huge tumor is discovered in the abdomen.
Fig. 1. Clinical presentation of a large abdominal and flank mass.

Fig. 2. IVP showing left-sided Wilms' tumor with distortion of calyces.

Diagnostic Evaluation

Intravenous pyelogram is the most useful diagnostic tool in the examination of all abdominal tumors in children. In Wilms' tumor, the intravenous pyelogram will usually demonstrate a parenchymal kidney lesion distorting the calyceal system. (Fig. 2.) The lateral view may show draping of the left colon over the tumor (Fig. 3), a finding often noted at surgery. A CT scan is useful to demonstrate the tumor in the presence of varying degrees of hydronephrosis or non-function on IVP. (Fig. 4.) Aortic arteriograms are helpful in evaluating the opposite kidney since the incidence of bilateral Wilms' tumor is between five and eight percent. The venous phase of the arteriogram may demonstrate tumor in the renal vein or vena cava. If a tumor is suspected in the renal vein or inferior vena cava, a vena-cavagram is carried out to determine the extent of involvement. Once a diagnosis of Wilms' tumor is suspected radiologically, X-rays of the chest and liver and a bone scan should be carried out as part of the metastatic evaluation. Since nephrectomy is indicated in all patients with Wilms' tumor, this should not be unduly delayed by a work-up for metastases. There is no longer the need to rush the patient to the operating room on the day of diagnosis as was done in the past, but a complete evaluation should still be done as rapidly as possible prior to surgery. If facilities are not available for rapid work-up, some studies may be performed during the postoperative period.

Course of Disease

Untreated Wilms' tumor will grow locally, eventually breaking through the capsule.
tumors that were spilled before or during surgery, those involving the intra-abdominal nodes other than the immediate peri-aortic nodes, and those infiltrating the wall of the vena cava that was not excised. Group IV tumors are associated with distant hematogenous spread to the lungs, liver and bone. Group V are bilateral Wilms' tumors.

Management

The treatment of Wilms' tumor historically mirrors the development of multidisciplinary treatment. First, radical nephrectomy alone was used; this was followed by irradiation of the renal bed after removal of the tumor to control small amounts of spilled or residual tumor cells. In the mid-1950s, actinomycin D was introduced as an effective chemotherapeutic agent. A second agent, vincristine, was also found to be effective for metastatic Wilms' tumor and was later combined with actinomycin D. The present management of Wilms' tumor has evolved out of a better understanding of the use of combined therapy and, at present, consists of radical nephrectomy, followed by irradiation of the renal bed, if the tumor has grown through the renal capsule, and irradiation of the entire abdomen, if the tumor has spilled or grown beyond the renal bed. All patients are then placed on a combination of daunomycin and vincristine, regardless of the stage of disease. Radical surgery remains an important part of initial treatment. The abdomen should be explored through a generous transverse incision allowing good exposure of the involved kidney and examination of the opposite kidney for possible bilateral tumors. As complete a resection should be carried out in all unilateral Wilms' tumors. This means a minimum of a radical nephrectomy and excision of surrounding involved tissues, such as the tail of the pancreas, the spleen, the diaphragm or psoas muscle. We also feel that isolated liver metastases should be excised, if accessible. The size of the tumor on diagnostic X-rays should not deter from laparotomy but rather suggest a more generous incision. The size of the tumor alone does not determine resectability and

of the kidney and extending into the perirenal connective tissue and beyond into neighboring structures. It may grow into the renal vein and then into the inferior vena cava. Metastasis is by lymphatics to regional lymph nodes and by the blood stream most commonly to the lungs, less frequently to the liver and rarely to the bones.

Grouping of Patients

The National Wilms' Tumor Study devised a grouping system that is now in general use. Group I tumors are limited to the kidney and completely excised. Group II tumors extend beyond the kidney, but are completely excised. These include lesions that have invaded the perirenal fat and involve regional lymph nodes. Group III tumors are incompletely excised, and without hematogenous metastases, such as

Fig. 3. Lateral IVP showing draping of descending colon over the tumor.
many very large tumors will be easily resected, whereas small tumors that have invaded surrounding tissue may be much more difficult to remove. During surgery an attempt should be made to isolate the renal artery and vein as early as possible, although there is some evidence from the National Wilms' Tumor Study that early ligation may not be as important as previously thought. In many cases, it may be difficult to ligate the vessels early, and certainly spillage of the tumor must be avoided at all costs. Good surgical technique involves gentle handling of the tumor during surgery, dissection of the regional node-bearing area, and ligation of the vessels as soon as they become safely accessible.

Bilateral Wilms' tumors often pose a dilemma for the surgeon; several operative approaches have been described and all appear equally successful. Even if a biopsy alone is performed on bilateral Wilms' tumors and no tumor resected, it seems that the children can be retrieved by irradiation and chemotherapy. Certainly, because of the high incidence of bilateral Wilms' tumors, the opposite kidney should be examined carefully during laparotomy. We usually make an incision in the peritoneum and Gerota's fascia and examine the kidney by inspection and palpation. If no suspicious nodules are found, the kidney is replaced and fascia and peritoneum resutured. If tumor is found, it is biopsied and submitted for frozen section. If there is one small tumor occupying the upper or lower pole of the kidney, which can be safely removed by less than heminephrectomy, this should be carried out. If there are multiple nodules or the tumor involves more than half the kidney, the kidney should be left in place. Postoperative irradiation is then given to the second kidney along with chemotherapy, and the kidney re-explored three months later with resection of any residual tumor if possible. It has been our policy to carry out radical nephrectomy on the major involved side in all patients. There are several patients in the National Wilms' Tumor Study, however, who survived following only partial resection of the tumor or, in some cases, no tumor resection. It would seem that the most desirable surgical approach is total nephrectomy on one

Fig. 4. CT scan of a large left-sided Wilms' tumor after IVP showed no function.
side and partial nephrectomy on the other, leaving the child free of tumor. If nephrectomy is performed on one side, then great care must be exercised in preserving the blood supply to at least half the opposite kidney. The varying approaches and almost uniformly good results with bilateral Wilms’ tumors in recent years have encouraged many centers to employ the most conservative surgery possible for these tumors.

Radiation Therapy

Postoperative radiation therapy was formerly given to all children with Wilms’ tumor. The National Wilms’ Tumor Study showed no benefit from irradiation of the renal bed in Group I tumors. It is the current policy in most centers to administer postoperative irradiation two or three days after nephrectomy in Group II and III patients. In Group II patients, irradiation is given to the renal bed with the portal extending beyond the midline to include the entire vertebral bodies. Group III patients receive total abdominal irradiation through anterior and posterior portals with shielding of the contralateral kidney after 1200 rads. The dosage of irradiation used in the National Wilms’ Tumor Study was age-related, with infants under 18 months receiving 1800 to 2400 rads, children 19 to 30 months, 2400 to 3000 rads, those 31 to 40 months, 3000 to 3500 rads and children older than 41 months, 3500 to 4000 rads. Evidence from a European study using 3000 rads as the maximum dose, suggests that favorable histological types of tumors may be treated safely with lower doses of irradiation. This is corroborated by many patients in the National Wilms’ Tumor Study who did not receive the full recommended dose. Further evaluation is necessary to confirm that a lower radiation dose does not jeopardize cure rates.

Chemotherapy

It was quite evident from the National Wilms’ Tumor Study that Groups II and III tumors had a much higher relapse-free survival rate with the two drugs, actinomycin and vincristine, than with either drug alone. Accordingly, it is our policy now to treat all children with Wilms’ tumor with actinomycin and vincristine for a period of approximately 15 months. The chemotherapy regimen was started formerly by giving actinomycin on the day of surgery. There is no evidence that a delay of two or three days is detrimental to the management of these patients, and it is now customary to wait two or three days before starting chemotherapy until the child’s general postoperative condition has improved. Actinomycin is therefore started on the same day as irradiation, if irradiation is to be used, and given daily for five doses to 15 mcg./kg. intravenously. Vincristine is administered on day seven in a dose of 1.5 mg./m.² intravenously and repeated weekly for eight doses. After the sixth dose of vincristine at six weeks postoperatively, a further course of five daily injections of actinomycin in the same dosage is given. After eight doses, vincristine is stopped and no treatment is given until the twelfth week, at which time vincristine is administered on day one followed by five days of actinomycin and a further dose of vincristine at the end of five days. This combined course of vincristine and actinomycin is repeated at three monthly intervals for 15 months. In Group IV patients where metastatic disease is present in the lungs at the time of diagnosis, nephrectomy is carried out as in other patients, and in addition to appropriate abdominal irradiation, 1400 rads is given to the total lung field. Chemotherapy is delivered in the same manner as in the other groups. If lung metastases develop during the course of treatment, 1400 rads of irradiation is administered to the entire lung field as soon as the lung metastases are detected. Even a solitary metastasis is evidence of systemic spread and the total lung should be irradiated, rather than just the area of the lesion seen on X-ray. If lung metastases re-appear after irradiation or are not resolved by irradiation while the patient is on chemotherapy, surgical resection of such pulmonary nodules can result in further retrieval of these patients. In Group V tumors, bilateral disease, all patients receive chemotherapy as outlined

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above. The irradiation will depend on what was accomplished at surgery. If all gross tumor is resected and both tumors are thought to be Group I, that is, confined to the renal capsule, no irradiation may be given. If the tumor is Group II with possible microscopic residual, then the side in which the kidney was resected receives full dosage and the side with partial resection, 1200 rads. If gross tumor is left behind in both kidneys, bilateral upper abdominal irradiation of 1200 rads is indicated prior to a repeat surgical exploration to see if residual disease can be resected. In practice, the treatment of Stage IV tumors must be individualized. As much tumor as possible should be resected leaving a safe amount of kidney. A recent report from the National Wilms' Tumor Study indicates that despite a wide variety of modalities of treatment, the cure rate of bilateral Wilms' tumor is surprisingly high. This may be due in part to the fact that these tumors tend to remain localized to the abdomen for a long period of time and appear to metastasize late to the lungs.

Results

With the treatment described, cure rates in excess of 90 percent can be achieved with Group I, II and III tumors. Even in Group IV tumors with distant spread usually to the lungs, a survival rate of over 60 percent has been reported.

Future Developments in Management

It has long been recognized that there is an anaplastic variety of Wilms' tumor that seems to behave worse than the classical Wilms'. It is clear from the National Wilms' Tumor Study that a large percentage of the failures are in an unfavorable histological group. Future study will determine whether more aggressive treatment in the form of more intensive chemotherapy and high-dose irradiation will be necessary for these unfavorable tumors. At the same time, it may be possible to give less aggressive treatment in the form of smaller doses for a shorter period of time and less irradiation to those children with more favorable histological patterns. It is important now with this highly curable tumor, to determine the reasons for failure in those few patients who die of their disease and to improve the quality of survival for those children who are apparently cured.

**NEUROBLASTOMA**

Neuroblastoma is the second most frequently diagnosed cancer in children after leukemia, lymphoma and central nervous system tumors. It arises from sympathetic ganglion tissue, and is composed of small, round primitive cells with hyperchromatic nuclei called neuroblasts. The tumor cells tend to congregate in a rosette formation with primitive nerve fibers emerging and intertwining in the center of the rosettes. (Fig. 5.) These primitive neuroblasts ma-

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**Fig. 5.** Histology of neuroblastoma with rosette formation.
ture into identifiable ganglion cells. Many neuroblastomas show areas of spontaneous maturation into ganglion cells, while others are highly undifferentiated with many mitoses. Neuroblastoma may be thought of as a tumor of embryonic neuroblasts, which duplicates the maturation to normal sympathetic cells during the embryonic period. Neuroblastoma seems to be an uncontrolled growth of these neuroblasts, metastasizing in widespread fashion throughout the body and killing the patient. Some tumors behave more like embryonal tissue multiplying, yet at the same time maturing, into ganglioneuroblastoma and then benign ganglioneuroma. These tumors vary from brownish red to grayish white depending on their histological make-up. They arise either in the adrenal medulla or in the paraspinal sympathetic nervous tissue anywhere from the neck to the pelvis. The great majority of tumors, however, will be found in the adrenal gland or in the lumbar sympathetic chain. Eighty percent will be intra-abdominal, 15 percent in the thorax in the dorsal sympathetic chain, and the remaining five percent either in the neck or pelvis.

**Age**

Neuroblastoma tends to occur in children at a younger age than Wilms' tumor. Fifty percent of the patients are under age two at diagnosis and 75 percent under age four. The tumor is rare in children over six years old, but it is occasionally seen in adolescence and adulthood. Interestingly, the age at diagnosis is very important in estimating the prognosis of this tumor. Patients who are diagnosed under age one, even those with metastases, have a much better prognosis than children over age two. Beckwith and Perin carefully examined the adrenal glands of neonates who died of other causes and found a surprisingly high incidence of neuroblastoma in situ—approximately 40 times the expected rate. It may be, therefore, that many infants have small foci of neuroblastoma, which are remnants of the multiplying neuroblasts of embryonic life, and that most of these mature into ganglionic tissue without becoming true metastasizing neuroblastomas. The metastatic pattern of neuroblastoma differs in different age groups, as well. In the infant, neuroblastoma tends to metastasize to bone marrow, liver and to form subcutaneous nodules. These tumors have a very good prognosis despite widespread metastases. In older children, metastases usually occur to bone, orbit and meninges with an extremely grave prognosis and very few documented survivals. Surprisingly, tumors with metastases to the meninges never invade the brain substance.

**Biochemistry**

Tumors of the sympathetic nervous system commonly excrete catecholamines, or their break-down products, in the urine. Neuroblastoma tissue very actively metabolizes norepinephrin and epinephrin, which are rapidly converted to break-down products and excreted in the urine as inactive vanillimendelic acid (VMA) or homovanillic acid (HVA). Many neuroblastomas also secrete catecholamines, and it was formerly thought that these tumors had a better prognosis than nonsecreting tumors. However, current evidence suggests that initial measurements of catecholamine excretion do not correlate with prognosis. Excretion of VMA and HVA is nevertheless useful in following the course of disease—the rise and fall of these products correlating well with the amount of tumor present in the body. If a tumor secretes VMA initially, it should fall to normal levels after successful treatment. Rising levels of VMA at any stage of treatment almost certainly herald the appearance of recurrence.

**Clinical Presentation**

Patients with neuroblastoma present with a great variety of clinical symptoms, and there is a marked difference in presentation between infants and children. In general, children with neuroblastoma present in a more advanced state than children with Wilms' tumor and often have much more marked systemic symptoms. Infants usually present with a markedly distended
abdomen due to either local tumor growth or massive enlargement of the liver with metastases. The infants may be jaundiced from liver involvement or have gross abdominal distension associated with ascites. The liver enlargement may reach gigantic proportions and fill the entire abdomen. The children may be tired and listless from replacement of the bone marrow by neoplastic cells. Subcutaneous nodules are a common presenting sign in association with the other signs of the neonatal variety. Presenting symptoms and signs in the older child vary widely but may often be the result of widespread metastases rather than the primary tumor. The children may present with an enlarging abdomen and a palpable abdominal mass in the adrenal area, upper or lower abdomen. More commonly, however, these children appear with proptosis and bruising of the orbit, or bone pain from metastatic disease. There may be swelling of the head due to intracranial metastases causing increasing intracranial pressure. Quite often these children show systemic signs of extreme lethargy, tiredness, anorexia, diarrhea and weight loss. In neck tumors, Horner’s syndrome may result from involvement of the stellate ganglion. Neuroblastoma arising in any part of the sympathetic chain, but particularly in the chest and neck, may form an hour-glass tumor with invasion of the spinal canal and extradural cord compression. (Figs. 6 and 7.) Symptoms of cord compression from mild sensory changes to complete paralysis may occur. The children may appear emaciated, anemic and irritable. Palpable lymph nodes in almost any part of the body may be the first evidence of metastases from an unrecognized primary. In all age groups, the amount of metastatic disease may appear to be out of all proportion to the size of the primary, which may occupy only a tiny portion of one adrenal gland. Usually, however, in those patients with metastases, the primary can be felt in the abdomen or detected by intravenous pyelogram or chest X-ray. In all age groups, two-thirds of the patients will present with the signs and symptoms of metastatic disease rather than the primary.

Fig. 6. Neuroblastoma in the left upper mediastinum on chest X-ray.

Fig. 7. Myelogram of the same patient showing cord block at level of T-2.
Diagnostic Evaluation

The diagnosis of neuroblastoma will often be fairly clear-cut from the constellation of signs and symptoms. If the patient presents with metastatic disease, biopsy of a lymph node or subcutaneous nodule often provides a rapid and reliable diagnosis. Bone marrow aspiration should be carried out in all children since many will have typical neuroblastoma cells in the bone marrow arranged in a rosette fashion. All children with suspected neuroblastoma should have X-rays of the abdomen, intravenous pyelogram and chest X-ray. An intrathoracic neuroblastoma almost always is large enough to be seen on a chest X-ray and the localization of the tumor in the posterior mediastinum is highly diagnostic. Tumors in the thorax may grow into the spinal canal and a myelogram should be performed even in asymptomatic patients. The most useful test for intra-abdominal neuroblastoma is the intravenous pyelogram, in which the classical drooping lily appearance of the suprarenal tumor may be seen. (Fig. 8.) Neuroblastomas often show speckled calcification within the tumor and the abdominal film may reveal a suprarenal or paravertebral mass containing calcific deposits. A calcified tumor in the upper abdomen in a young child is highly suspicious of neuroblastoma. When the primary cannot be located by these simpler measures, arteriography may be necessary to detect a small tumor. Recently, the introduction of CT scanning has provided very accurate information on the localization, extent and operability of neuroblastoma in the upper abdomen. When neuroblastoma is diagnosed, a skeletal survey and bone scan should be carried out to detect bony metastases, most commonly in the skull, orbit, pelvis and proximal femora. Biochemical determinations should be performed in all children suspected of neuroblastoma. VMA and HVA determinations in the urine are the most reliable, and are useful as a baseline in following the course of disease during treatment.

Management

Total surgical removal of the early localized neuroblastoma offers the best chance of cure. Ninety percent of children with a tumor completely localized to one or other adrenal gland can be expected to survive with surgery alone. Unfortunately, less than 25 percent fall into this category. Many patients with localized disease are found to be unresectable at laparotomy. There has been considerable discussion in the past as to whether a grossly inoperable tumor should have a lengthy procedure resulting in subtotal resection and often great risk to the patient. At the present time, the general consensus in this country is that an inoperable tumor should only be biopsied and the patient placed on irradiation and chemotherapy with a second-look procedure carried out at a later date in the hope that the tumor has shrunk sufficiently to be resectable. Neuroblastomas in the chest and abdomen, which have
hour-glass extensions into the spinal canal, will require a combined surgical approach with removal of the intravertebral part from the back. Often this can be accomplished in one stage. If extensive dissection is necessary, a two-stage procedure can be performed, removing the intravertebral component compressing the spinal cord first and then carrying out the thoracotomy or laparotomy excision later. These hour-glass neuroblastomas appear to have a good prognosis and justify a long, careful surgical resection. In the presence of metastatic disease, it is now customary to delay primary surgery (providing the diagnosis is established) and treat the patient with systemic chemotherapy and localized radiation to the primary. If control of metastases is achieved, a laparotomy or thoracotomy to extirpate the primary tumor is justified.

Radiation Therapy
Because surgical removal of these tumors can be accomplished in only a small percentage of patients, radiotherapy is used in an attempt to cure patients whose tumors could not be removed. It is also delivered to the local tumor bed when microscopic residual is suspected, or when tumor is found in the regional nodes. Radiation therapy may also be used for palliation of distant metastases and to attempt control of the primary tumor. When the tumor has been completely excised, but there is a possibility of residual microscopic disease, 2500-3000 rads to the tumor bed is usually recommended. When the tumor is incompletely removed, a similar dose of radiation is given to residual tumor along with chemotherapy. For extensive intra-abdominal tumors extending beyond the midline, which are usually non-resectable, radiotherapy in the same dosage range is used in an attempt to control the primary tumor. Stage IV tumors may be treated with small doses of radiation to palliate distant metastases, usually to bone, and a low dose to the primary tumor, if symptomatic. The special group of tumors in infants known as IV-S, with massive liver, bone marrow or subcutaneous nodules are often given small doses of irradiation to induce tumor regression; 500-1000 rads may be administered in a two-week period to the liver, often with dramatic results. Others believe that the large IV-S livers do not require radiation but can be watched carefully and perhaps given small doses of chemotherapy to induce maturation.

Chemotherapy
Many of the tumors in infants under one year of age appear to do very well with surgery and/or irradiation, and it is questionable whether adding chemotherapy improves survival. The incidence of spontaneous regression and differentiation is so high in these tumors that evaluation of chemotherapeutic agents is difficult. The effectiveness of chemotherapy is also hard to evaluate in those older children who have had their tumors totally resected or who had irradiation for microscopic residuals. In Stage IV tumors with widespread disseminated disease, the effects of chemotherapy are easier to study because surgery and radiation therapy are not used. It is in this group, however, that chemotherapy has been especially disappointing, and it is questionable whether any of the currently tried multiple drug regimens has improved survival. Various combinations of agents have shown temporary responses and increase in length of survival, but almost always the children finally succumb to their disease. Cyclophosphamide and vincristine in various dosages and combinations have produced the most encouraging prolonged remissions. Many studies are in progress in the hope of finding a combination that will produce significant cures for children with metastatic neuroblastoma, but as yet no successful combination has surfaced.

Results
In a period when other solid tumors have responded well to treatment, the cure rates of neuroblastoma have shown little change. The age of the patient at diagnosis and the extent of disease seem to influence prognosis far more than any of our therapeutic efforts. Children under 12 months of age have an excellent prognosis
whatever the stage of disease. When the tumor is completely resected, the chance of cure is almost 100 percent in these children. Even when disease is more advanced and particularly in the IV-S tumors, which have spread to bone marrow, liver or subcutaneous tissue, survival is 80 percent. In the child over two, however, unless there is a small, completely resectable tumor, the prognosis appears as hopeless today as it was when chemotherapeutic agents were first used.

Future Prospects
There are several interesting approaches to the management of neuroblastoma based on the natural history and increasing understanding of its immunological aspects. Efforts are underway to develop protocols that may mimic the natural maturation of these tumors to more benign ganglioneuroblastoma and ganglioneuroma. Maturation does appear to occur more frequently where metastatic disease can be controlled for longer periods of time by chemotherapy. We have seen primary tumors mature and become operable after chemotherapy alone, without the added effects of irradiation. Neuroblastoma seems to be an immunologically active tumor with surface antigens, which is susceptible to destruction in tissue culture by activated lymphocytes. There also appears to be a blocking factor in the child’s serum that prevents the cytotoxic activity of the mother’s lymphocytes against the tumor. Although these studies have been well known in the laboratory for several years, as yet they have not been applied successfully in the management of the patient.

SOFT TISSUE SARCOMAS
Soft tissue sarcomas form the third most common group of solid cancers in childhood, and among them, the most common by far is rhabdomyosarcoma, occurring almost always as the embryonal variety in children. Less frequent are fibrosarcoma and synovial sarcoma and, extremely rare, liposarcoma, neurosarcoma and angiosarcoma.

A. EMBRYONAL RHABDOMYOSARCOMA
Two varieties of embryonal rhabdomyosarcoma are seen in children: the solid variety and the grape-like lesions, so-called, sarcoma botryoides. (Fig. 9.) These are really variants of the same tumor; the difference in gross appearance is accounted for by the site of origin. Solid embryonal rhabdomyosarcomas occur in the extremities, trunk, head and neck region. Sarcoma botryoides arises in hollow viscera, such as the bladder, vagina and common bile duct. The solid tumor is an irregular lobulated mass with a soft or rubbery consistency. It is often red or purple but the color varies as a result of hemorrhage and necrosis. The botryoid variety, as its descriptive title suggests,
appears like a bunch of grapes growing into the hollow viscus. These grape-like polyps are soft and shiny and arranged in clusters. They may reach an enormous size due to unrestricted growth in the hollow cavity. The surface lining of the polyps is often the normal mucosa of the organ involved, which becomes thinned out, ulcerates and may bleed. In some locations a mixed solid and sarcoma botryoides tumor is seen, as in prostate and bladder lesions. Here the solid variety occurs in the prostate where the tumor is compressed by the prostatic capsule; as it invades the bladder it becomes polypoid growing profusely into the hollow cavity of this organ. The microscopic appearance of solid embryonal rhabdomyosarcoma and sarcoma botryoides is essentially the same, the difference being the amount of myxoid ground substance that is markedly increased in the grape-like lesions. The basic cell is a rhabdomyoblast. This may vary in size and maturation, often being small and rounded with or without acidophilic cytoplasm. Sometimes the larger cells form cross striations or peripherally arranged vacuoles, called the spider web cell. The cells may be elongated with acidophilic cytoplasm and have two or more nuclei. There are often areas of myxoid tissue with stellate cells predominating and only rare differentiated cells. The botryoid tumors generally have a layer of the less differentiated small rounded rhabdomyoblasts between two and four cell layers thick under the mucosa. (Fig. 10.) Beneath the layer of rhabdomyoblasts is an abundance of myxoid tissue with a varying number of stellate cells. The remainder of the tumor in its deeper layers may resemble the solid variety with embryonal rhabdomyoblasts in different degrees of maturation and with different amounts of mitotic activity.

**Fig. 10. Histological section of a sarcoma botryoides.**

Paratesticular rhabdomyosarcoma occurs most often in adolescents and older children. Tumors arising in the head and neck, extremities and intra-abdominally are seen at all ages. Sex incidence is equal between boys and girls.

**Site of Tumors**
The most common site of origin of embryonal rhabdomyosarcoma is the head and neck region, particularly the orbit but also the nasopharynx, parotid and neck. Between 35 and 50 percent of tumors originate in this location. Approximately 30 percent arise in the extremities and trunk, which is surprising since the largest proportion of striated muscle is located here. Also surprising is the high percentage of rhabdomyosarcomas in the genitourinary tract of both girls and boys — 20 to 30 percent. Common locations include the bladder, vagina, prostate, as well as distal cord lesions known as paratesticular rhabdomyosarcomas.

**Age and Sex**
The median age of occurrence of rhabdomyosarcoma is five years. Age incidence varies in different locations. Sarcoma botryoides in the bladder, prostate and vagina has a peak incidence in infants.
Clinical Presentation

The presenting signs and symptoms of rhabdomyosarcoma vary with the location of the tumor. In the head and neck region, the tumor may present as a mass in the orbit, parotid or neck. In the nasopharynx, they are accompanied by nasal obstruction, nose bleeds or chronic upper respiratory infections. Trunk and extremity lesions commonly present as a palpable tumor mass usually deep-seated but occasionally involving the skin. The tumors also vary in consistency from soft to firm, and are relatively fixed to underlying musculature. They are not usually painful and, in fact, rarely produce any other symptoms but the mass. Tumors in the extremities may spread to local lymph nodes, particularly upper extremity lesions, which frequently metastasize to the axilla. Sarcoma botryoides of the vagina, bladder and prostate tends to occur in infancy. The vaginal lesions present most commonly with bleeding or tissue passed from the vagina or a polypoid mass protruding from the introitus. Tumors in this area usually spread by direct extension to other pelvic structures such as the bladder, rectum and pelvic wall, and also to pelvic and para-aortic lymph nodes. Pain is remarkably absent until the tumor is far advanced locally. Obstruction of ureters or bladder outlet is seen in advanced disease.

Bladder and prostate lesions are generally located low down on the posterior wall of the bladder or in the prostate, and cause urinary retention as an early symptom. In many patients, both the bladder and prostate are involved and the exact site of origin cannot be determined. Some children present with hematuria or passage of tissue in the urine. In those with paratesticular rhabdomyosarcomas there is an expanding non-tender mass in the scrotum usually lying above and separate from the testis. Tumor in this location tends to spread to pelvic and retroperitoneal lymph nodes, and may be associated with a pelvic or abdominal mass. A secondary hydrocele occurs in about 25 percent of patients; rarely, bilateral lesions are seen.

Diagnostic Evaluation

Rhabdomyosarcoma spreads by lymphatic and hematogenous routes. In all locations, it is important to evaluate regional lymph node drainage areas. This can be done clinically in the head and neck, upper extremity and trunk, and may be aided by lymphangiogram for lower extremity and genitourinary tumors. Chest X-rays should be taken on all patients, with chest tomography for suspicious lesions. Tomograms of the facial bones, skull and pharynx are useful to delineate the extent of tumor in these areas. Intravenous pyelogram is the most valuable study for genitourinary lesions and should be carried out in all bladder, prostate, vaginal and paratesticular tumors. Deep-seated abdominal or pelvic lesions may require angiography to determine the extent of tumor. Liver and bone scans complete the radiological work-up. The CT scan gives exact information on the extent of disease in head and neck lesions, particularly when invasion of the cranium is suspected. It also provides accurate information on deep-seated abdominal lesions. Bone marrow aspiration should be carried out in all patients, although spread to the bone marrow is relatively rare in the absence of pulmonary metastases.

Staging

There have been many staging systems proposed, reflecting the difficulty in forming a uniform system for a tumor arising in so many different sites. That adopted by the Intergroup Rhabdomyosarcoma Study, which divides patients into groups, is most widely used at this time. Group 1 is localized disease, completely resected. Group 1A is confined to muscle or organ of origin; 1B is contiguous involvement with infiltration outside the muscle or organ of origin, with microscopic confirmation of complete resection and no lymph node involvement. Group 2A is localized disease grossly resected but with residual microscopic disease and no lymph node involvement; 2B is regional disease, i.e., extension of tumor into an adjacent
organ or regional lymph nodes or both, completely resected without residual microscopic disease; 2C is regional disease with lymph node involvement grossly resected but with residual microscopic disease. Group 3 is local or regional disease with biopsy or incomplete resection and gross residual tumor. Group 4 is distant metastatic disease present at onset in the lungs, liver, bones, bone marrow, brain or distant lymph nodes.

Management

The aims of treatment are: (1) to completely remove the local tumor and any local extension, and at the same time preserve maximum possible function of organs in the region involved; (2) to control metastatic disease or prevent the appearance of metastases in localized tumors using combination chemotherapy.

Control of the primary lesion is usually attained by surgery or irradiation or a combination of both. Selection of treatment of the primary lesion depends on the tumor and the stage of disease. Some centers have treated the primary with irradiation and chemotherapy prior to any major surgery with the hope of shrinking the lesion, thus making it resectable without radical surgery. It seems that, at the present time, treatment must be individualized so that the modality used gives the best chance of cure while preserving maximum function. Trunk and extremity lesions are usually amenable to surgical resection by wide excision. Because of the high incidence of metastatic regional nodes, we advise groin dissection in most lower extremity tumors and axillary dissection in upper extremity lesions. Amputation of extremities is rarely recommended for rhabdomyosarcoma in a child, except when other treatment modalities have failed. However, resection of the lesion should be as complete as possible, and all gross tumor should be removed. Microscopic residual can be handled by irradiation and chemotherapy but it appears that gross residual disease may not respond as well to non-surgical treatment. When residual microscopic disease is left behind after surgery, radiation therapy is given to the operative field and any other area of risk to a dose of 4000-5000 rads in four to five weeks. Following wide excision of the tumor and, coinciding with the beginning of radiation therapy, multiple-drug chemotherapy is commenced. Various combinations of chemotherapeutic agents have been used, usually a combination of dactinomycin, vincristine and cyclophosphamide. At our institution we have used a four-drug protocol starting with five doses of dactinomycin (450 gamma/m.\textsuperscript{2}) daily for the first five days of irradiation, a rest period, and then three doses of adriamycin (20 mg./m.\textsuperscript{2}) beginning at day 20, and a further three doses beginning at day 40. After recovery from adriamycin, approximately two weeks later, vincristine is started (1.5 to 2 mg./m.\textsuperscript{2}) in four weekly doses. Cyclophosphamide (1200 mg./m.\textsuperscript{2}) is administered with the first and third vincristine dosages. After recovery from vincristine and cyclophosphamide, the cycle is restarted with dactinomycin. This protocol is continued for two years, which appears to be the period of risk for developing metastatic disease. Head and neck lesions are treated by either irradiation or surgery, depending on location. Orbit and nasopharyngeal lesions are best treated by irradiation, since good control can be achieved without mutilating surgery. A dosage of 5000 to 6000 rads is usually required. If the tumor is accessible to surgical excision, such as in the cheek or neck, a wide resection of the primary tumor is carried out. If margins of resection are clear of tumor, then no irradiation therapy is given, but patients are placed on multiple-drug chemotherapy. If margins of the specimen show microscopic disease, irradiation therapy up to 3500 rads is given to the area at risk, as well as chemotherapy.

Sarcoma botryoides of the vagina, bladder and prostate are the most controversial group of tumors in respect to primary treatment. In the past, the only treatment achieving cures consisted of radical resection, usually pelvic exenteration of some type. Such radical resection is destructive to a large amount of normal tissue and leaves the patient with various
forms of urinary diversion and/or colostomy. It is obviously preferable to do less radical surgery, if the patient can still be cured. Over the past few years there has been increasing evidence that preoperative treatment with irradiation and chemotherapy could perhaps shrink the size of the primary, making a local resection possible. Certainly, in vaginal lesions, there is increasing evidence that local control may be achieved with as little as 3000 rads and multiple-drug chemotherapy. Tumors in the bladder and prostate do not appear to respond as well to preoperative irradiation and chemotherapy, even though bulky lesions may be shrunk in size. We have tried all types of approaches to primary tumors in the bladder, prostate and vagina and believe, at this time, that each case must be individualized. A typical example is that of a six month-old child who had a small perineal lesion in the prostate, which was easily excised locally by separating the tumor from the urethra below the pelvic diaphragm. It was quite obvious that microscopic residual disease was left in this patient and he was treated by 3500 rads of radiation and multiple-drug chemotherapy. Not only was complete control of the tumor achieved, but the baby was toilet trained while on multiple-drug chemotherapy after completion of irradiation. Another child with a moderate-sized bladder lesion was treated by preoperative irradiation of 2000 rads and multiple-drug chemotherapy. (Fig. 11.) Despite this treatment, the tumor continued to grow and he developed severe urinary tract obstruction with hydrourerter and hydronephrosis. (Fig. 12.) Surgery then had to be performed in less than ideal circumstances with the skin showing irradiation changes, infected urine and an obstructed GU tract. In this child, a radical cystectomy and prostatectomy, pelvic node dissection and urinary diversion had to be carried out. Examination of the specimen after surgery showed that the tumor had continued to grow and was completely viable, despite irradiation and chemotherapy.

Why some tumors respond so well to irradiation and chemotherapy and others continue to grow is not clearly understood. It does, however, further emphasize the need to individualize treatment. The aim, as in all other locations, is successful control of the primary tumor with preservation of bladder and rectal function, when possible. If preoperative irradiation and chemotherapy fail, there is the danger that even more radical surgery may be necessary than at the time of diagnosis. Morbidity of surgery carried out after failure of other treatment may be considerable and may, in fact, delay the resumption of effective chemotherapy to prevent distant metastases. A reasonable approach now seems to be excision of small lesions that can be taken out by partial cystectomy, partial vaginectomy or perineal excision, without destroying bladder or rectal function. If gross excision of the tumor cannot be performed without sacrificing the bladder or rectum,
then pretreatment with irradiation and chemotherapy should be tried with the hope of carrying out less radical surgery at a later date. If this course is undertaken, the patient must be very carefully evaluated by all members of the multidisciplinary team, and if control is not being achieved, then surgical intervention may be necessary at an earlier time than originally planned.

Paratesticular rhabdomyosarcomas are best treated by radical orchietomy combined with a pelvic and retroperitoneal node dissection. It has been our experience that two-thirds of these patients will have involvement of pelvic or retroperitoneal nodes at the time of diagnosis. If there has been a prior trans-scrotal biopsy, then hemiscrotectomy is indicated in addition to orchietomy. If the tumor is completely resected and pelvic and retroperitoneal nodes are negative, no irradiation need be given. If, however, there is microscopic disease in the lymph nodes, the hemipelvis and retroperitoneal node area should be irradiated to 3500 rads. If there has been contamination of the scrotum, tumor spillage or evidence of spread beyond the cord structures, the operative site and the scrotum should receive irradiation as for residual microscopic disease. All these children are then placed on four-drug chemotherapy, as described above.

**Results**

Patients with localized disease completely resected and placed on four-drug chemotherapy now have close to 100 percent survival. Those children who have residual microscopic disease following surgery that is treated by 3500 rads and multiple-drug chemotherapy have a survival rate of over 80 percent. Head and neck lesions treated by high-dose irradiation and chemotherapy and/or surgery also have a high survival rate. At the present time it appears that treatment failures are concentrated in those patients where gross residual tumor is left behind after inadequate surgery or in those children where metastatic disease is present at the time of diagnosis. Future treatment will be aimed at achieving more effective multiple-drug protocols in the management of metastatic disease and further refining current protocols to improve the quality of survival for these children.

**B. FIBROSARCOMA**

Fibrosarcoma is the second most frequent soft tissue sarcoma in children, although it is extremely rare and there is only limited experience at any single institution. In our experience, fibrosarcoma is usually low-grade, so-called, extra-abdominal desmoid, which is well-differentiated and invades locally but does not normally metastasize to the regional nodes or distant organs. Metastasizing high-grade fibrosarcomas in children have been described, but are not common in our ex-
perience. The low-grade type is unique among soft tissue sarcomas in that it is treated exclusively by surgery; it is very radioresistant and does not respond to chemotherapy. Fibrosarcoma is seen largely in children over eight years of age and is more common in boys at a ratio of two to one. The tumor may occur in the trunk, head and neck or on the extremities. The lesions grow as painless, slow-growing lumps and may cause secondary symptoms by extension and pressure on surrounding structures, particularly the nerves. In the head and neck they may produce pressure on structures, such as the trachea or esophagus and major vessels. They are extremely difficult to eradicate because of a great tendency to local recurrence. In our series, the average number of recurrences was three, and a third of the tumors recurred as many as five times. This was particularly a problem in the lower extremity, where 90 per cent of the children ultimately required amputation after failure of repeated local excisions. Treatment consists of wide local excision with repeated excision when recurrence occurs. Unfortunately, in our experience, almost 50 per cent of the lesions in the extremities ultimately require amputation for control. We feel that early wide excision of these tumors should be carried out with very careful postoperative follow-up. Recurrent lesions should be excised early before they reach a large size. This is a surgically curable lesion, in which the cure rate should approach 100 per cent.

C. SYNOVIAL SARCOMA

Synovial sarcoma is seen with the same frequency as fibrosarcoma. It is highly malignant and arises in the vicinity of joints, bursa and tendon sheaths. The tumor is firm to hard in consistency with smooth, rounded surfaces. Microscopic examination shows cords of tightly packed cylindrical cells, referred to as the synovial elastic elements. The spaces between the cords are filled with spindle cells and reticulum fibers resembling fibrosarcoma. The tumor is largely found in young adults and most patients are adolescents. Two-thirds of the lesions will occur in the lower extremities, and the remaining in the upper extremities or trunk.

Course of Disease

The tumor presents as a firm, painless lump. It is clinically indistinguishable from other soft tissue sarcomas, particularly fibrosarcoma. Synovial sarcoma may grow slowly and metastasize late to regional nodes, lungs and distal organs. Some tumors will show very aggressive behavior, metastasize early and quickly lead to death. The average time from diagnosis to development of lung metastases in children is about 12 months. The majority of children with this disease have the aggressive form with a rapid course, particularly when treatment was late or inadequate. A small proportion of children, however, run a chronic course and survive many years despite the presence of metastases.

Current Management

In the past, treatment consisted largely of amputation of the involved extremity. Currently, however, it is felt that these tumors can be treated like rhabdomyosarcomas. Primary treatment should be a wide local excision removing all gross tumor. If microscopic residual is suspected, radiation therapy is given postoperatively; all patients are placed on chemotherapy. There is evidence that the type of protocol used for osteogenic sarcoma, that is high-dose methotrexate, is most effective for this tumor. The current plan is to perform wide local excision followed by 12 months of treatment with high-dose methotrexate and citrovorum rescue. We have too few cases to evaluate, but in the patients that have been treated in this fashion, approximately 80 per cent are surviving more than two years. Other soft tissue sarcomas such as liposarcoma, neurosarcoma and angiosarcoma are treated in exactly the same way as rhabdomyosarcoma. These tumors are so rare in children that it is
difficult to analyze the results in any meaningful way. It does appear that liposarcoma is a highly curable disease in children, whereas neurosarcoma and angiosarcoma are much more difficult to treat.

SUMMARY

The management of solid cancers in children has been revolutionized by the development of multidisciplinary treatment, which has not only increased survival but has turned the once hopeless outlook into one of cautious optimism. In the past, the diseases were poorly understood because so few children survived, and only scattered small series were reported in the literature. With increased survival, more of these young patients are now available for study, resulting in a better understanding of the natural history of these diseases. Extensive cooperative projects, in which randomized trials have been carried out, have further improved the management of the childhood cancers. Studies of the immunological and pathological features of these tumors are just beginning to give meaningful information. The long-term effects of treatment, both physical and psychosocial, must still be evaluated. Thus, despite a decade of remarkable progress, a great deal of work remains to be done in improving protocols and achieving a better quality of survival for these children.

MEDICAL TERMS—PAST AND PRESENT

Some pathological terms that are purely descriptive are as useful today as ever. Abscessus = a withdrawal or separation aptly characterizes a soft-tissue infection that is "walled off" from surrounding structures. In this sense it appears in the medical works of the Roman encyclopedist Celsus, who wrote during the lifetime of Christ. Celsus also uses the Latin cancer = crab to indicate an eroding and ulcerating lesion. This word has an interesting progeny in the language of modern medicine. We employ it unchanged as an English term for malignancies in general, though with the advance of microscopic pathology it has become more of a lay term than a technical one . . .

In German, Krebs = crab is the usual term employed by laity and physicians alike in speaking of malignant disease. The expression Krebsmilch, meaning a white secretion from the nipple in patients with carcinoma of the breast, thus has the somewhat fanciful alternate meaning crab milk. Carcinoma is derived from the Greek word for crab, karkinos.

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