Urogenital Tumors in Children

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INTRODUCTION

The urogenital tract is surpassed only by the central nervous system as the predominant site of origin of the solid neoplasms of infancy and childhood. Tumors of ovarian and testicular origin are discussed in other articles in this issue. Of greater incidence than either of these are two other neoplasms found in the urogenital tract: nephroblastoma (Wilms’s tumor) and the rhabdomyosarcomas of the pelvic viscera. These will be reviewed here in detail, as will rarer tumors of the urogenital tract, including (1) renal tumors (congenital mesoblastic nephromas and adenocarcinomas), (2) the “clear cell” adenocarcinomas and other tumors of the vagina and cervix, and (3) bladder wall tumors. Neuroblastomas will also be considered, as they are included in the differential diagnosis of the large retroperitoneal masses, which are the characteristic abdominal tumors of infancy and early childhood.

The Unique Features of Neoplasia in Pediatric Patients

The malignant solid tumors of infancy and childhood are, as a group, distinct from the neoplasms of adults, and this feature is nowhere more apparent than in the tumors of the genitourinary tract. So characteristic are these features that the neoplasms of different organs in children usually have greater similarity in respect to natural history, reaction to chemotherapeutic agents, etc., than do tumors of the same organ (even with similar general histology) occurring in the child and adult. Typical forms of pediatric...
genitourinary tract neoplasms — i.e., nephroblastomas and embryonal rhabdomyosarcomas — rarely occur in adults.\textsuperscript{1,2} Conversely, tumors of these organs with a high incidence in adults — i.e., renal adenocarcinomas and carcinomas of the cervix, uterus, and prostate — are rarely found in infancy or childhood.

In addition to nephroblastoma and embryonal rhabdomyosarcoma, other pediatric neoplasms — including neuroblastoma, hepatoblastoma, and retinoblastoma — display, to a degree, the same characteristics. These features may be summarized as follows: 1. The cause of these tumors is unclear, but a relationship to viruslike agents or genetic predisposition appears more significant than the influence of chemical or other environmental factors. Several of these tumors have a clear association with specific congenital anomalies. 2. These tumors are sarcomas or “mixed” tumors, with the carcinomas representing a minute proportion of the total group. 3. Pediatric neoplasms are characterized by more rapid growth than adult tumors, with many reaching a volume of 10 to 20 per cent of total body weight before clinical recognition. 4. Sensitivity to the effects of cancer chemotherapeutic agents is apparent in most pediatric neoplasms, to the extent that this factor may be regarded as the major influence on survival in patients with nephroblastoma and rhabdomyosarcoma.

Two prominent exceptions to these generalities concerning childhood tumors are the radiation-induced papillary thyroid carcinomas and the hormone-induced clear-cell vaginal carcinomas of the adolescent and young adult. These are clearly related to environmental factors, and they both assume the histology of and display the same natural history as similar tumors in adults.

**THE RENAL TUMORS**

**Wilms’s Tumor (Nephroblastoma)**

These tumors, representing 95 per cent of the renal malignancies of early life, have equal sex distribution. They are histologically “mixed” tumors with varying amounts of mesenchymal and epithelial elements. Striated muscle and even cartilage may occasionally be seen.

They may be enormous,\textsuperscript{1} often constituting as much as 20 per cent of the patient’s body weight. Despite tumor size, the capsule usually remains grossly intact, with invasion of other intra-abdominal viscera uncommon. Growth into the renal pelvis, producing hematuria and occasional demonstrable tumor cells, is found in 10 per cent of these patients. Gross hemorrhage into the tumor mass is common and accounts for the apparent rapid growth of some tumors under clinical observation. The renal veins may be invaded by gross tumor, and long outgrowths ascend the vena cava\textsuperscript{1} and even project into the right atrium.\textsuperscript{3}

**The Differential Diagnosis of the Retroperitoneal Tumors of Infancy and Early Childhood**

A significant group of tumors of infancy and early childhood are large, smooth, nonmobile masses, distinct from the liver and lying to one side of the abdominal midline. These may become immense without producing specific symptoms and are often discovered on routine examinations or examinations carried out for unrelated conditions or nonspecific symptoms.

Almost all such tumors will prove to be (1) nephroblastomas (Wilms’s tumors), (2) neuroblastomas, or (3) some form of benign renal disease, including hydronephrosis, diffuse in-

continued
trarenal infection, and unilateral multicystic kidney. A concept that such patients urgently require surgery has been widely held. Diagnostic studies may be performed within 48 hours of hospital admission, however, and these will ordinarily establish the correct preoperative diagnosis (Table 1); they should be satisfactorily completed before operation.

The history of patients who have one of these three different tumor masses may include anemia, malaise, and fever. The tumors rarely interfere significantly with gastrointestinal function or obstruct the contralateral urinary tract, although they may distort it; thus, their effect on renal function is not necessarily apparent. The most common physical finding is a palpable mass. Neuroblastoma is frequently nodular; the other lesions rarely demonstrate nodularity. Associated hepatic enlargement suggests the diagnosis of neuroblastoma. Bilateral masses are more common in benign renal disease, and occasionally represent bilateral Wilms's tumors. Peripheral lymph node involvement, permitting biopsy, is not ordinarily found with either of these tumors.

TABLE 1

DIFFERENTIAL DIAGNOSIS OF UNILATERAL RETROPERITONEAL MASSES IN INFANCY AND EARLY CHILDHOOD

<table>
<thead>
<tr>
<th>STUDY</th>
<th>NEPHROBLASTOMA</th>
<th>NEUROBLASTOMA</th>
<th>BENIGN RENAL DISEASE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Intravenous urogram</td>
<td>Intrinsic distortion of renal pelvis</td>
<td>Extrinsic distortion of renal pelvis</td>
<td>Nonfunction (usual) or intrinsic distortion</td>
</tr>
<tr>
<td>2. Abdominal x-ray for calcification</td>
<td>Calcification rare</td>
<td>Calcification common and characteristic type</td>
<td>Calcification rare</td>
</tr>
<tr>
<td>3. Chest x-ray</td>
<td>Metastatic lesions frequently seen</td>
<td>Metastatic lesions rarely seen</td>
<td>Negative</td>
</tr>
<tr>
<td>4. Bone x-rays (survey)</td>
<td>Metastatic lesions rarely seen</td>
<td>Metastatic lesions frequently seen</td>
<td>Negative</td>
</tr>
<tr>
<td>5. Bone marrow aspiration for malignant cells</td>
<td>Rarely positive</td>
<td>Frequently positive</td>
<td>Negative</td>
</tr>
<tr>
<td>6. Urinary catecholamine excretion</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>7. Radiosotope scan (bone and liver)</td>
<td>Negative</td>
<td>Frequently positive</td>
<td>Negative</td>
</tr>
<tr>
<td>8. Analysis for hematuria</td>
<td>Infrequently positive</td>
<td>Negative</td>
<td>Infrequently positive</td>
</tr>
<tr>
<td>9. Demonstrable hypertension**</td>
<td>Infrequent</td>
<td>Infrequent</td>
<td>Infrequent</td>
</tr>
</tbody>
</table>

*Hydronephrosis, multiple intrarenal abscesses, or unilateral polycystic kidney.

**As determined by the conventional sphygmomanometer. More refined techniques may detect a higher incidence of hypertension, particularly in neuroblastoma.
Calcification in the mass, recognizable in plain abdominal x-rays, indicates a diagnosis of neuroblastoma but may also be found in both other lesions. Roentgenographic studies of the lung fields, including tomography of suggestive areas, and bone studies are of major significance. Multiple pulmonary metastatic lesions are seen in the lung fields of approximately 30 per cent of children with nephroblastoma at the time of their admission to the hospital. In contrast, metastatic neuroblastoma is rarely seen in the lungs but is classically found in flat bones (particularly skull) or the metaphysis of long bones. Conversely, roentgenographically visible metastases from early nephroblastoma to bone are uncommon.

Needle aspiration of the marrow cavity will frequently reveal neuroblastoma cells, even in the absence of roentgenographically demonstrated osseous lesions. In contrast, nephroblastoma cells are rarely recognized in marrow.

Neuroblastomas elaborate a group of specific biochemical compounds, the products of catecholamine metabolism, that are found in the serum and urine. At least 90 per cent of these tumors will excrete sufficient quantities of these compounds to produce abnormal urinary levels, but the excretion pattern for each tumor is unique. In some, only the vanillylmandelic acid, the homovanillic acid, or the total catecholamine excretion may be sufficiently elevated to be of diagnostic value.

The intravenous urogram has traditionally been the definitive technique for this differential diagnosis. The nephroblastoma produces a distortion of the renal pelvis that appears to be secondary to an "intrinsic" renal mass, while the neuroblastoma produces a pressure defect that appears to be "extrinsic." Neuroblastoma arising in the adrenal medulla, superior and medial to the kidney, displaces the renal pelvis inferiorly, laterally, and anteriorly. The hydronephrotic kidney usually has impaired function, and the pelvis is not visualized. Retrograde pyelography is indicated only in this instance — i.e., the failure to visualize the renal pelvis by intravenous contrast studies.

Compression of the inferior vena cava by either nephroblastoma or neuroblastoma can be readily demonstrated by a contrast vena cavaogram; the urogram and inferior vena cavaogram can be performed simultaneously by pedal injection of the contrast media.

General or specific organ-scanning studies (gallium-67 citrate or technetium-99 diphosphonate) may show the dissemination of these tumors, primarily of neuroblastoma, to bone. Scanning of lung fields is not superior to tomography in identifying pulmonary metastatic nephroblastoma. The initial clinical decisions can ordinarily be made on the basis of (1) the intravenous urogram, (2) roentgenograms of the lung fields and a bone survey, (3) bone marrow aspiration, and (4) urinary catecholamine excretion studies. A definitive diagnosis of neuroblastoma may be made on the basis of a positive bone marrow aspiration and elevated catecholamine excretion, without histologic confirmation by biopsy of the primary tumor. In the absence of pulmonary dissemination, the diagnosis of nephroblastoma is, to a degree, one of the exclusion of the other two probable disease entities.

The management of these three clinical entities is quite different. The benign hydronephrotic and in-
fected kidneys, which clinically simulate malignant tumors, can be resected, or, in rare instances, reconstruction of their drainage pathway can be performed. Destruction of the parenchyma or the presence of multiple gross or microscopic renal abscesses usually indicates nephrectomy. Unilateral polycystic kidneys usually have little renal tissue or even a collecting system to preserve.

Nephroblastomas are highly sensitive to cancer chemotherapeutic agents\(^\text{15,16}\) and to irradiation.\(^\text{17,18}\) Initial treatment consists of nephrectomy without biopsy, and is carried out even in the presence of disseminated pulmonary disease. This is followed by irradiation to the tumor bed and a chemotherapy regimen extending for at least 15 months in all patients. Both dactinomycin and vincristine are effective,\(^\text{15,18,20}\) particularly in combination, and Adriamycin and cyclophosphamide are employed if there is tumor resistance to these agents. The survival rate in patients of all stages treated by these combined therapy programs is greater than 80 per cent.\(^\text{19,21}\) The first National Wilms’s Tumor Study indicated that irradiation to the site of a completely excised Wilms’s tumor (stage 1) is probably not required in infants who are to be treated by long-range two-agent chemotherapy regimens.

In comparison with Wilms’s tumor, the abdominal neuroblastoma is less sensitive to the effects of chemotherapy,\(^\text{22,23}\) and its response to radiotherapy is less predictable.\(^\text{24,25}\) The overall survival in patients with abdominal neuroblastomas, which are included in the differential diagnosis of the retroperitoneal masses of childhood, is less than 20 per cent, even when they are treated with multiple-agent chemotherapy programs. In contrast, for neuroblastomas originating in cervical, thoracic, and pelvic sites,\(^\text{9,26}\) the prognosis is excellent.

“Group” Studies of Nephroblastoma

Among the solid tumors of childhood, nephroblastoma has been the subject of the most extensive national and international “group” studies of the effects of different forms of therapy. The initial study of this type (1964-68), carried out in this country by the Children’s Cancer Study Group, demonstrated that a regimen of multiple-course dactinomycin would significantly reduce the incidence of pulmonary metastatic disease. It also showed the effectiveness of dactinomycin and other agents in “rescuing” patients who developed recurrent pulmonary nephroblastoma following short courses of dactinomycin therapy. The first National Wilms’s Tumor Study (1969-74) has shown that local tumor-bed radiotherapy is unnecessary in patients under two years of age with localized disease (stage 1) who are to receive long-range dactinomycin chemotherapy. It has also demonstrated a distinct superiority of the combination of dactinomycin and vincristine to either agent employed singly in advanced forms of this tumor. A study initiated by the Medical Research Council of Great Britain (1970-73) demonstrated the marked effectiveness of high-dose vincristine in controlling nephroblastoma in all stages. One could also conclude from the British study that the use of both agents, dactinomycin and vincristine, was preferable to the use of either as single-agent therapy. A study conducted by the Société Internationale d’Oncologie Pédiatrique (1971-74) clearly showed the effectiveness of preoperative radiotherapy in preventing tumor rupture, a problem more prevalent in Europe than in the United States. However, in series

continued
Indications Vernox (mebendazole) is indicated for the treatment of Trichuris trichiura (whipworm), Enterobius vermicularis (pinworm), Ascaris lumbricoides (roundworm), Necator americanus (common hookworm), and Ancylostoma duodenale (common hookworm) in single or mixed infections. Efficacy varies in function of such factors as pre-existing diarrhea and gastrointestinal transit time, degree of infection and helmith strains. Efficacy rates derived from various studies are shown in the table below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cure Rates</th>
<th>Egg Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (range)</td>
<td>Mean (range)</td>
</tr>
<tr>
<td></td>
<td>68% (61-75%)</td>
<td>53% (70-99%)</td>
</tr>
<tr>
<td></td>
<td>98% (91-100%)</td>
<td>99.7% (99.5-100%)</td>
</tr>
<tr>
<td></td>
<td>96% (91-100%)</td>
<td>99.8%</td>
</tr>
<tr>
<td></td>
<td>85% (90-100%)</td>
<td>—</td>
</tr>
</tbody>
</table>

Contraindications Vernox is contraindicated in pregnant women (see: Pregnancy Precautions) and in persons who have shown hypersensitivity to the drug.

Precautions Pregnancy: Vernox has shown embryotoxic and teratogenic activity in pregnant rats at single oral doses as low as 10 mg/kg. Since Vernox may have a risk of producing fetal damage if administered during pregnancy, it is contraindicated in pregnant women.

Pediatric Use: The drug has not been extensively studied in children under two years: therefore, in the treatment of children under two years the relative benefit/risk should be considered.

Adverse Reactions: Transient symptoms of abdominal pain and diarrhea have occurred in cases of massive infection and expulsion of worms.

Dosage and Administration: The same dosage schedule applies to children and adults. For control of trichuriasis, ascariasis, and hookworm infection, one tablet of Vernox is administered morning and evening on three consecutive days. For control of enterobiasis, a single tablet of Vernox is given. If the patient is not cured three weeks after treatment, a second course of treatment is advised. No special procedures, such as fasting or purging, are required. New supplied Vernox is available as tablets, each containing 100 mg of mebendazole, and is supplied in boxes of twelve tablets.

Because Vernox has not been extensively studied in children under two years of age, the relative benefit/risk should be considered before treating these children. Vernox is contraindicated in pregnant women (see: Pregnancy Precautions) and in persons who have shown hypersensitivity to the drug.

SEX-RELATED PROBLEMS II
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NOVEMBER 1975

599/19

Bilateral disease occurs in patients who are younger

Bilateral disease occurs in patients who are somewhat younger than those with unilateral disease, again suggesting the presence of a more active predisposing genetic factor. The most common clinical presentations continue...
are either bilateral masses or a unilateral mass, readily palpable, associated with a second lesion in the opposite kidney, which is detected by intravenous urogram or by examination at the time of surgery.

Surgically, bilateral nephroblastoma is preferably treated by bilateral partial nephrectomy, saving portions of both kidneys. If this is not possible, unilateral nephrectomy and partial nephrectomy on the less seriously affected side should be attempted, even if small elements of tumor tissue remain. Bilateral nephrectomy, anticipating renal transplantation, is the least desirable procedure. Most transplant patients have tumor recurrence during the period of immunotherapy associated with the transplantation regimen.

Radiotherapy is limited by the tolerance of renal tissue, and the deleterious effects of irradiation on kidney may be accentuated by dac-tinomycin. Because of this association, vincristine may be the initial chemotherapeutic agent of choice.

A recommended treatment regimen for bilateral Wilms's tumor is as follows: (1) initial laparotomy and bilateral biopsy; (2) intensive chemotherapy until a major reduction in tumor size is accomplished, employing vincristine preferentially, dac-tinomycin in addition if required, and even minimal radiotherapy if major tumor shrinkage is not apparent in four to five weeks; (3) bilateral renal "tumorectomy" or partial nephrectomy; and (4) long-range two-agent chemotherapy for at least 15 months. The second operative procedure is preceded by an arteriogram to aid in the renal dissection of the tumors.

Although some series of bilateral tumors treated before the advent of intensive chemotherapy regimens were without survivors, others had considerable success — in many instances employing only surgery and radiotherapy. When an intensive regimen — including long-range chemotherapy, radiotherapy, and surgery — is employed, approximately 50 per cent of these patients will survive (Figure 1).

**Congenital Mesoblastic Nephroma**

Because of the "mixed" and variable histologic pattern of nephroblastomas, attempts to subclassify these tumors on this basis have been made in the interests of more accurate
prognostic evaluation. The recognized success in this regard has been the separation of the "congenital mesoblastic nephroma of infancy" from the total group. This entity, also referred to as "fetal renal hamartoma," was brought to the attention of clinicians by Bolande, Brough, and Izant in 1967. Their description of this infantile renal tumor, composed predominantly of fibrous tissue, initiated a retrospective re-evaluation of the histologic slides of Wilms's tumor cases in large pediatric institutions. In many of these, at least 5 per cent of Wilms's tumor series could be recognized in retrospect as congenital mesoblastic nephromas. Thus, this entity was regarded in the past as a variant of Wilms's tumor, and it is still clinically, and at operation, indistinguishable from nephroblastoma.

Its characteristics are as follows: 1. It occurs in early infancy. 2. To examination and by roentgenographic studies (intravenous urogram), its clinical presentation is identical to that of nephroblastoma. 3. Histologically, it presents a considerable spectrum of apparently malignant or nonmalignant characteristics that are superficially similar to those found in the spectrum of fibrosarcomas. Some tumors appear frankly malignant, histologically. 4. It may be that these tumors have a greater tendency to local invasion than nephroblastomas, or simply that these invasive tumor elements, if unresected, have not received the benefit of systemic chemotherapy. In any event, concern regarding the margins of the resected tumor is of importance, as local recurrences have been reported.

The actual sensitivity of this tumor to the cancer chemotherapeutic agents that are used for nephroblastomas is unknown, but there is some evidence that the tumor may be singularly susceptible to these agents. A substantial majority of these tumors seen since 1969 have been simply excised - i.e., treated without chemotherapy or radiotherapy. In general, the course of these patients has been benign. In view of the major problems produced by radiotherapy and chemotherapy in the infant, the elimination of both from the treatment of these patients seems justified.

**Adenocarcinoma of the Kidney in Children**

Approximately 60 children with this "adult" type of renal cancer have been reported, including one 22 months of age. Most tumors develop in late childhood, well beyond the usual age range for nephroblastoma. This tumor produces hematuria (45 per cent) more consistently than nephroblastoma and frequently a palpable abdominal mass. The hematuria is often gross and calls attention to the lesion.

The natural history of this tumor, and its reaction to therapy, appears to be unaltered by its occurrence in children. As in adults, survival is related to the extent of spread at the time of diagnosis. Excision is followed by survival in approximately 50 per cent of reported patients. It is apparent that if this tumor is recognized and distinguished from a nephroblastoma at the time of surgery or before, a more radical resection of adjacent tissue is indicated. It should be suspected in the older child with a renal mass, particularly with hematuria; and renal angiography, which may be diagnostic, should be performed.

**RHABDOMYSARCOMAS**

**General Aspects of the Current Treatment of Rhabdomyosarcoma**

Rhabdomyosarcomas of the vagina, bladder, and prostate have many characteristics common to...
tumors with the same histology in other body areas. Despite a deceptive "pseudocapsule," these tumors, irrespective of site, intensively infiltrate surrounding tissues, and local control may be difficult. Distant dissemination is rarely recognized early in the course. The primary tumors often become massive before they seriously interfere with adjacent organ function. Most important, all these rhabdomyosarcomas of diverse sites have a sensitivity to cancer chemotherapeutic agents — including dactinomycin, vincristine, cyclophosphamide, Adriamycin, and probably other agents — which is the paramount factor in treatment. It has been clearly demonstrated that regimens including these agents can increase survival for patients in whom there has apparently been complete excision of the tumor or in whom the tumor has been partly or even subtotally excised. It also appears that locally infiltrating lesions that are technically "unresectable" may be made "resectable" by employing chemotherapy regimens, either with or without radiotherapy.

The best results are obtained when the tumor is completely excised or only "microscopic" remnants remain. The latter may be defined as cases in which the tumor is completely resected from the point of view of the surgeon but tumor remnants are found in the margins of the specimen by the pathologist. Such cases constitute a sizable proportion of most series. All these features are clearly demonstrated by genitourinary rhabdomyosarcomas.

**Rhabdomyosarcoma of the Vagina**

This disease entity is usually recognized between six and 18 months of age, although occasional cases occur throughout childhood and adolescence. The most frequent site of origin is the proximal portion of the vagina, anteriorly. The tumor, however, may arise more distally in the vaginal wall, or even from the labia. In infants with malformations that include a persistent urogenital sinus, it appears in the proximal portion of this structure. This tumor may be primary in the region of the uterine cervix, occurring in somewhat older children; but the distinction between these sites of origin in large tumors is usually impossible.

The infantile form is the predominant one and will be discussed in detail. Almost without exception, these tumors are embryonal forms of rhabdomyosarcoma. They are usually of the botryoid type, which is the form (both gross and histologic) that the embryonal rhabdomyosarcoma ordinarily takes when it protrudes into a hollow structure, such as the nasopharynx, biliary tract, vagina, or bladder. Extension of tumor along the walls of the vagina and into the region of the bladder neck anteriorly is common, with posterior extension into the perirectal region less frequently seen. Early lymph node metastases are uncommon. The pelvic portion of this tumor may enlarge rapidly, forming a bulky solid tumor that may be felt as a suprapubic mass. The "botryoid" elements, which are actually the size of small currants rather than grapes, may protrude from the vaginal orifice, producing the visible classical clinical appearance of this tumor.

**Clinical recognition.** Vaginal discharge that is brown or hemorrhagic, occurring after the neonatal period, is ordinarily due to trauma, usually associated with a retained foreign body, or to vaginal rhabdomyosarcoma. Palpation of an abdominal mass, however, may be the initial sign leading to the recognition of this tumor. Dissemination is rarely the

continued
factor leading to the discovery of this tumor. Diagnosis is made by biopsy of the vaginal portion of the tumor, employing an endoscope if necessary.

The only other malignant vaginal tumor with a significant incidence in infancy is of the endodermal sinus (histologic) type. This may be grossly similar in appearance to rhabdomyosarcoma. The age range of children with the endodermal sinus tumor is slightly older, the youngest reported being seven months of age. This tumor is also seen through the remainder of infancy.65 The clear-cell carcinomas of the vagina are not included in this differential diagnosis, as they are not seen in preadolescent girls (Table 2).

Following the diagnosis of vaginal rhabdomyosarcoma by biopsy, preoperative studies should include contrast examinations of the bladder and rectum, intravenous urograms to identify the ureters, and cystoscopic examination of the bladder interior. Surveys for pulmonary and osseous dissemination are performed although, at the time of diagnosis, this tumor is rarely found in distal sites.

**Therapy.** Although this tumor was formerly regarded as rarely curable, survival rates among children have been tremendously improved by combination-therapy regimens. Anterior or total pelvic exenteration (including vaginectomy with lymphadenectomy), followed by radiotherapy and multiple-agent chemotherapy employed for 12 to 24 months, has provided high survival rates.66,67 When an intensive chemotherapy regimen is maintained for a prolonged period following surgery, the volume of radiotherapy can probably be reduced or irradiation can be eliminated altogether.

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**TABLE 2**

**VAGINAL MALIGNANCY IN CHILDREN**

<table>
<thead>
<tr>
<th>HISTOLOGIC TYPE</th>
<th>AGE RANGE</th>
<th>INCIDENCE</th>
<th>SIGNIFICANT HISTORY</th>
<th>AREA OF VAGINA INVOLVED</th>
<th>THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdomyosarcoma (largely botryoid, embryonal)</td>
<td>Peak incidence 6-18 months; may occur throughout infancy, childhood, and adolescence</td>
<td>Several hundred reported cases</td>
<td>Vaginal discharge or hemorrhage</td>
<td>Predominantly anterior wall</td>
<td>Combined therapy with surgery, radiotherapy, and chemotherapy</td>
</tr>
<tr>
<td>Endodermal sinus tumors</td>
<td>4-20 months; at times older, but preadolescent</td>
<td>Approximately 50 cases reported</td>
<td>Vaginal discharge or hemorrhage</td>
<td>Anterior or posterior wall</td>
<td>Probably as above (unknown)</td>
</tr>
<tr>
<td>Clear-cell carcinomas (adenocarcinomas)</td>
<td>12-25 years</td>
<td>Approximately 150 cases reported</td>
<td>Intermenstrual hemorrhage; maternal DES therapy in initial 5 months of pregnancy</td>
<td>Proximal, anterior vagina or cervix</td>
<td>Radical surgery and radiotherapy</td>
</tr>
</tbody>
</table>

*continued*
Approaches to this problem utilizing initial radical surgery, followed by radiotherapy and chemotherapy, have been successfully employed by Grosfeld, Smith, and Clatworthy, Jaffe et al., and Hilgers et al. Chemotherapeutic agents employed include vincristine and actinomycin D, or these agents plus cyclophosphamide (VAC therapy). Reduction of the scope of the exenteration to the anterior organs, sparing the rectum, is usually successful, and one ovary is ordinarily preserved. This undoubtedly represents the established method of therapy. The excised vagina may be reconstructed later during childhood and has not, per se, represented a major problem, although these patients, of course, are infertile and may have ovarian deficiency requiring therapy.

Undesirable features of this approach are principally those associated with the exenteration — i.e., the permanent abdominal stoma(s), including a cutaneous urinary diversion ("ileal loop") and, at times, a permanent colostomy. The effects of radiotherapy on osseous pelvic growth in infancy may be highly significant, with a contracted pelvis resulting from therapy.

These adverse factors, in addition to recognition of the major effect on these tumors of intensive chemotherapy regimens as demonstrated in "unresectable" tumors, have led to the consideration of alternative forms of therapy designed to preserve pelvic organs, the bladder as well as the rectum. Following biopsy, a major attempt at tumor mass reduction by an intensive chemotherapy regimen, with or without radiotherapy, has been employed before surgery. In some instances, the extirpation can then be confined to a hysterectomy and partial vaginectomy. Following surgery, such patients are treated with a prolonged multiple-agent chemotherapy regimen, possibly with the addition of radiotherapy if it has not been previously employed. Long-range survival has been reported for patients in whom this general approach has been followed.

**Rhabdomyosarcoma of the Bladder**

This tumor occurs in both males and females, although more commonly in the former. The site of origin is usually the bladder wall close to the trigone, although it may be found in other bladder sites, occasionally permitting excision without cystectomy. Such partial excisions, however, were rarely ultimately successful before the era of combined therapy, which includes multiplet-agent chemotherapy.

From its usual site, the base of the bladder, this tumor extends anteriorly into the urethra and perivesical tissue and, in females, posteriorly into the walls of the vagina and the uterine cervix. Although polypoid (often botryoid) within the bladder, it does not usually extend through the urethra to the exterior. This tumor frequently reaches a massive size before producing sufficient obstruction of the urethra or ureters to be clinically detected.

**Clinical recognition.** These children may have microscopic and at times gross hematuria, but mucosal ulceration is a late complication, and the urine may show no cells. As noted, urethral obstructive symptoms — i.e., abdominal pain and apparent dysuria — occur, particularly in males, but these are difficult to recognize in infants. Obstruction of the ureters with symptoms of infectious uropathy is uncommon. Frequently, during physical examinations for more nonspecific symptoms, these tumors are palpated as lower abdominal masses. The diagnosis can be continued
made by biopsy with an endoscope and the extent of the lesion assessed. The patient's preoperative evaluation includes those studies described above (vaginal, rhabdomyosarcoma). The final staging procedure is a laparotomy to determine the extent of intra-abdominal disease. The presence of metastatic tumor beyond the adjacent nodes is a contraindication to exenteration.

**Therapy.** The history of the surgical treatment of this tumor includes many reports of inadequate excisions, followed by local recurrence and ultimately death. It has occasionally been possible to remove tumors not originating in the trigone area by partial cystectomy. During the past decade a regimen has been developed that is usually successful for survival. This includes radical cystectomy, usually with hysterectomy and partial vaginectomy (in females), followed by pelvic radiotherapy and long-range multiple-agent chemotherapy. Success with this approach has been reported by several teams, including Ghavimi et al., Tefft and Jaffe, Grosfeld, Smith and Clatworthy, and Clatworthy, Braren, and Smith. Excisions that do not completely remove the tumor have been followed by long-range survival in patients on an intensive chemotherapy and radiotherapy regimen following surgery.

In some centers, attempts are being made to preserve the bladder by an initial intensive chemotherapy regimen. If the tumor decreases to a size that can no longer be palpated or visualized with an endoscope, total cystectomy may not be required for its control.

**Rhabdomyosarcoma of the Prostate**

Before the advent of combination therapy, this tumor had a clearly more unfavorable prognosis than rhabdomyosarcomas of the bladder or vagina. It was found to disseminate more rapidly and to be more difficult to eradicate locally. Chemotherapy regimens have made this difference less apparent. The general prognosis following surgery, radiotherapy, and chemotherapy may be similar to that for bladder lesions.

**Clinical recognition.** When located superiorly in the gland, these tumors may be difficult to differentiate from rhabdomyosarcomas of the bladder neck or trigone, at times producing hematuria and ultimately partial obstruction of the urethra and/or ureters. At the other extreme, they may be inferior in the gland and present as a mass, which may be readily biopsied through the perineal skin. It is difficult to understand why early clinical urethral obstruction does not occur, but large pelvic masses often develop before symptoms referable to the urinary tract are recognized. This may be explained by very rapid tumor growth. These lesions may be biopsied (1) through the bladder with an endoscope, (2) by open or needle biopsy through the perineum, or (3) occasionally at cystotomy or even laparotomy. Following diagnosis, the studies for dissemination outlined above are carried out. It is believed that intra-abdominal dissemination, including node metastases, is more common in this tumor than in the bladder or vaginal forms of rhabdomyosarcoma, but this is not apparent from routine preoperative studies. Here again, laparotomy is the final staging procedure. A thorough examination of the intra-abdominal contents should precede exenteration.

**Therapy.** Long-term survival of children with this lesion has been reported from a number of centers employing radical surgery (anterior or total exenteration), radiotherapy,
and long-range chemotherapy regimens. When a combination-therapy regimen is employed, even the presence of areas of "microscopic" residual tumor does not preclude long-term survival. Attempts to modify the therapeutic regimen either by eliminating radiotherapy in noninvasive lesions or by an intensive primary chemotherapy regimen have been described.

CARCINOMAS AND OTHER UNCOMMON TUMORS

**Carcinomas of the Vagina and Uterine Cervix**

Carcinoma of the vagina is ordinarily regarded as a disease of women over 50 years of age. Squamous cell carcinoma of the cervix, occurring in the female adult (30 to 65 years), is one of the most common human neoplasms. Adenocarcinomas of the cervix occur in somewhat younger women.

Cases of carcinoma of the vagina in infants and children were sporadically reported before 1968. These were clearly not squamous cell carcinomas and were described as embryonal carcinomas, "mesonephric remnant" carcinomas, or mesonephric adenocarcinomas. The age range was much younger than for the hormone-induced tumors, which are described subsequently, and included infants and preadolescent girls.

In 1970, Herbst and Scully reported the rather "epidemic" occurrence of seven cases of adenocarcinomas of the vagina in females 15 to 22 years of age, occurring in two institutions during a four-year period (1966-69). One year later, additional study of these cases (and one additional case) revealed that seven of the eight mothers of these young women had received diethylstilbestrol for the control of bleeding during the first trimester of pregnancy. The span of the birth of these patients (1946-51) coincides with the prevalence of the use of synthetic estrogens in complicated pregnancies, particularly in some areas of the United States. Additional cases with similar histories were soon reported from many other institutions, and a "Registry of Clear Cell Adenocarcinoma of the Genital Tract in Young Females" was established. A total of 91 patients were included in this study by 1972. One-third of the tumors apparently arose from the cervix rather than the vagina. By 1974, 154 such cases had been registered, and in 82 per cent of these a history of treatment of a high-risk pregnancy by diethylstilbestrol was established. The highly malignant nature of this tumor was apparent, as 37 patients had persistent or recurrent disease following therapy. Twenty-four deaths were noted, with a mortality of 77 per cent for those patients with recurrence.

The current status of this problem may be summarized as follows: 1. Histologically, these represent a group of distinct tumors, described as "clear cell" adenocarcinomas. They occur in both the vagina and cervix, the former being the more frequent site. 2. Maternal hormone therapy was not restricted to diethylstilbestrol in these cases. Progesterone administration during early gestation may also be a factor, although demonstration of induction of this tumor by maternal progesterone ingestion alone has not been seen. Even very low doses or intermittent therapy with diethylstilbestrol may be active in inducing a susceptible state in the female fetus. 3. There appears to be a geographic factor in the distribution of these tumors, but this may be entirely accounted for by the selective use of continued
INDICATIONS
Based on a review of this drug by the National Academy of Sciences — National Research Council and/or other information, FDA has classified the indications as follows:
“Probably" effective: For symptomatic relief of upper respiratory infection, rhinitis, acute sinusitis, asthma, hay fever, nasal congestion, pharyngitis, bronchitis, and otitis.

CONTRAINDICATIONS: Hypersensitivity to antihistamines. Not recommended for use during pregnancy.

PRECAUTIONS: Administer with care to patients with cardiac or peripheral vascular diseases or hypertension. Until the patient's response has been determined, he should be cautioned against engaging in operations which require alertness.

SIDE EFFECTS: Hypersensitivity reactions including skin rashes, urticaria, hypotension and thrombocytopenia have been reported on rare occasions. Drowsiness, lassitude, nausea, giddiness, dryness of the mouth, mydriasis, increased irritability or excitement may be encountered.

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diethylstilbestrol during the 1940s. 4. "Premalignant" vaginal changes, including "adenosis" and dysplasia, have been reported in young females in the group at risk. The size of this group is unknown, but in one estimate 10,000 to 16,000 fetuses were exposed per year between 1960 and 1970. 5. This lesion — i.e., "clear cell" carcinoma — is best treated by radical surgery, including vaginectomy and hysterectomy, probably supplemented by local radiotherapy. Recurring cases have been successfully treated by re-excision and radiotherapy. Chemotherapy has not been effective.

Unusual Bladder Tumors
Malignant bladder tumors other than rhabdomyosarcomas in children include fibrosarcomas and lymphomas. The adult type of squamous cell carcinoma has been described. Pheochromocytomas are found in the bladder wall, as well as in the adrenal medulla and other retroperitoneal areas. These are seen only in older children and may be associated with systemic symptoms secondary to tumor secretion. Most bladder tumors, as in adults, produce gross hematuria, which is usually more obvious than in the case of bladder rhabdomyosarcomas.

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