# *Extracellular Matrix and Epithelial Differentiation of Wilms' Tumor*

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**Different histologic types of 82 Wilms' tumors were graded on the basis of the histologic pattern. Representative tumors of each group were analyzed by the immunoperoxidase method for evaluation of the histogenesis of Wilms' tumor and the value of antibodies against extracellular matrix (ECM) components (collagens I and III, laminin, fibronectin) in differential diagnosis of different types of Wilms' tumors. The tubules of classic Wilms' tumor expressed laminin, which could be seen also in and around some blastemal cells. Blastema and tubules were negative for interstitial collagens, but Type I and III collagen were prominent in the fibrovascular stroma. The monomorphous tubular, psammomatous and rosetting tumors expressed laminin, but no interstitial collagens. In sarcomas, only the blastemal variant of spindle-cell sarcomas was negative for interstitial collagens, which were abundantly seen in all other sarcomas. While spindle-cell sarcomas were devoid of laminin, the highly malignant rhabdoid and clear-cell sarcomas expressed laminin in a characteristic dotted fashion. Staining for fibronectin gave varying results and had therefore only a limited value in distinguishing different types of Wilms' tumors. However, the antibodies against interstitial collagens and against the basement membrane glycoprotein laminin turned out to be a useful adjunct in differential diagnosis and classification, especially of sarcomatoid Wilms' tumors. The basement membrane of normal nephrons is similar to that in tubules of triphasic Wilms' tumor, but the ECM of blastemas is different. This transformed phenotype might represent a maturation arrest of the blastemal cell when compared with the expression of proteins during normal nephrogenesis. (Am J Pathol 1985, 118:96–107)**

WILMS' TUMORS, or nephroblastomas, are malignant childhood cancers of the kidney. It is generally assumed that the tumor is formed from the metanephric blastema.[1,2] The apparent histologic similarities between some histologic subtypes of nephroblastomas and different developmental stages of embryonic kidneys has led to speculations that the tumor represents a malignant form of normal nephrogenesis.[3–6] These tumors are in many respects similar to teratocarcinomas, where the cells resemble different stages of normal early development.[7]

Normal nephrogenesis is known to be initiated by the ingrowth of the ureter bud into the metanephrogenic mesenchyme, which then condenses and forms tubules.[8,9] With specific antibodies against different matrix components, it has been shown that the developmental stages in murine kidney are characterized by a specific matrix composition. The early metanephric anlage initially expresses interstitial collagens (Types I and III) and fibronectin, which disappear when the mesenchyme condenses. The condensed cells start to express basement membrane collagen and glycoproteins and then form the epithelial basement membrane.[10–12]

In order to clarify the histogenesis of Wilms' tumor and its relation to normal nephrogenesis, we have classified Wilms' tumors histologically on the basis of epithelial differentiation and analyzed the matrix composition of different types of nephroblastomas by immunohistochemistry.

## Materials and Methods

Formalin-fixed, paraffin-embedded blocks of 103 kidney tumors of children (ages 0 to 10 years) were col-

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Table 1—Histologic Classification of 103 Kidney Tumors of Children (Ages 0 to 10 Years) Operated Upon at the Children's Hospital, University of Helsinki, During the Years 1948–1980

| Histologic diagnosis | Number of patients |
|---|---|
| "Classic" triphasic Wilms' tumors | 37 |
| Monomorphous epithelial Wilms' tumors | 8 |
| Rosetting tumors | 4 |
| Sarcomas | |
| Spindle-cell pattern | 15 |
| Clear-cell pattern | 10 |
| Rhabdoid pattern | 3 |
| Mixed pattern | 4 |
| Unclassified | 1 |
| Leiomyoma | 1 |
| Rhabdomyoma | 1 |
| Fetal hamartoma | 1 |
| Teratoma | 1 |
| Neuroblastoma | 1 |
| Not representative or necrotic samples | 16 |

lected from the files of the Pathology Service, Children's Hospital of the University of Helsinki, from 1948 to 1980. The blocks were resectioned, and sections stained with hematoxylin and eosin (H&E) were used for histologic classification of the tumors. Additional sections 5 $\mu$ in thickness were used for immunohistochemical staining.

In the histologic survey 82 of the 103 tumors were Wilms' tumors, including 33 pure sarcomas, and these constituted the material of the present study (Table 1). The grading of Wilms' tumors was based on the epithelial differentiation.[5] The tumors were divided into classic triphasic Wilms' tumors, monomorphous epithelial tumors, rosetting tumors, and sarcomas of clear-cell, rhabdoid, or spindle-cell pattern.

### Immunohistochemistry

Paraffin sections were deparaffinized in xylene and brought to phosphate-buffered saline (PBS) through decreasing concentrations of ethanol. They were incubated in 0.2 % pepsin solution for 2 hours. Previous studies have shown that matrix antigens can be reliably detected in routinely processed formalin-fixed samples after this treatment.[13] For immunoperoxidase staining, the biotin–avidin–peroxidase kit (Vector Laboratories, Burlingame, Calif) was used. The sections were incubated for 30 minutes in 0.3% $H_2O_2$ in methanol, washed with PBS for 10 minutes, incubated for 30 minutes with the primary antiserum, washed for 10 minutes in PBS, incubated for 30 minutes in PBS, incubated for 60 minutes with biotinylated horseradish peroxidase–avidin complex, washed for 10 minutes in PBS, reacted with 3,3'-diaminobenzidine-tetrahydrochloride and $H_2O_2$ for 5 minutes, washed for 5 minutes in tap water, and mounted.

Affinity-purified monospecific rabbit antibodies against laminin, Type I and III collagens, and fibronectin were those described previously.[14–17] The same antibodies have been used to characterize the stages of normal kidney development.[10–12]

## Results

### Classic, Triphasic Pattern

The classic Wilms' tumors with a triphasic histologic pattern, composed of tubules, homogenous blastema, and fibrovascular stroma (Figure 1a), expressed laminin in the basement membrane of tubular structures and vessels in a rather continuous fashion (Figure 1b). Only occasionally some laminin-positive areas were seen in the blastemal areas in a irregular network around the blastemal cells. Varying staining of fibronectin was seen in blastema, but it was prominent in fibrovascular stroma. Also, the tubules were positively stained (Figure 1c). The tubules and blastema were constantly negative for interstitial collagens. However, in fibrovascular stroma interstitial collagens were seen clearly in a reticular pattern (Figure 1d). The glomerular bodies seen in some triphasic Wilms' tumors were avascular. They were positive for fibronectin and laminin.

### Pleomorphic Renal Carcinoma

One tumor of this type was found. Originally it was identified as unclassified sarcoma. The tumor was highly cellular and composed of pleomorphic cells, which were surrounded by hyalinlike eosinophilic material and occasionally formed some primitive glandular structures. A clear tendency to a primitive or abnormal glomerulus formation was seen throughout the tumor. The glomeruli varied in size from approximately normal to giant conglomerates. Within these bodies the cells were pleomorphic, and no vascular elements were found. The tumor was surrounded by a fibrous capsule, but many vessels in the surrounding kidney parenchyme contained tumor cells indicating the aggressive behavior of this tumor (Figure 2a). Laminin was clearly positive throughout the tumor. It surrounded all the cells in a network type of pattern (Figure 2b). The expression of fibronectin was similar to laminin (Figure 2c) and the hyalinlike stroma was strongly positive for Type I and III collagens (Figure 2d). The histologic pattern is peculiar to an epithelial tumor, and therefore this type of tumor was referred to as pleomorphic renal carcinoma.

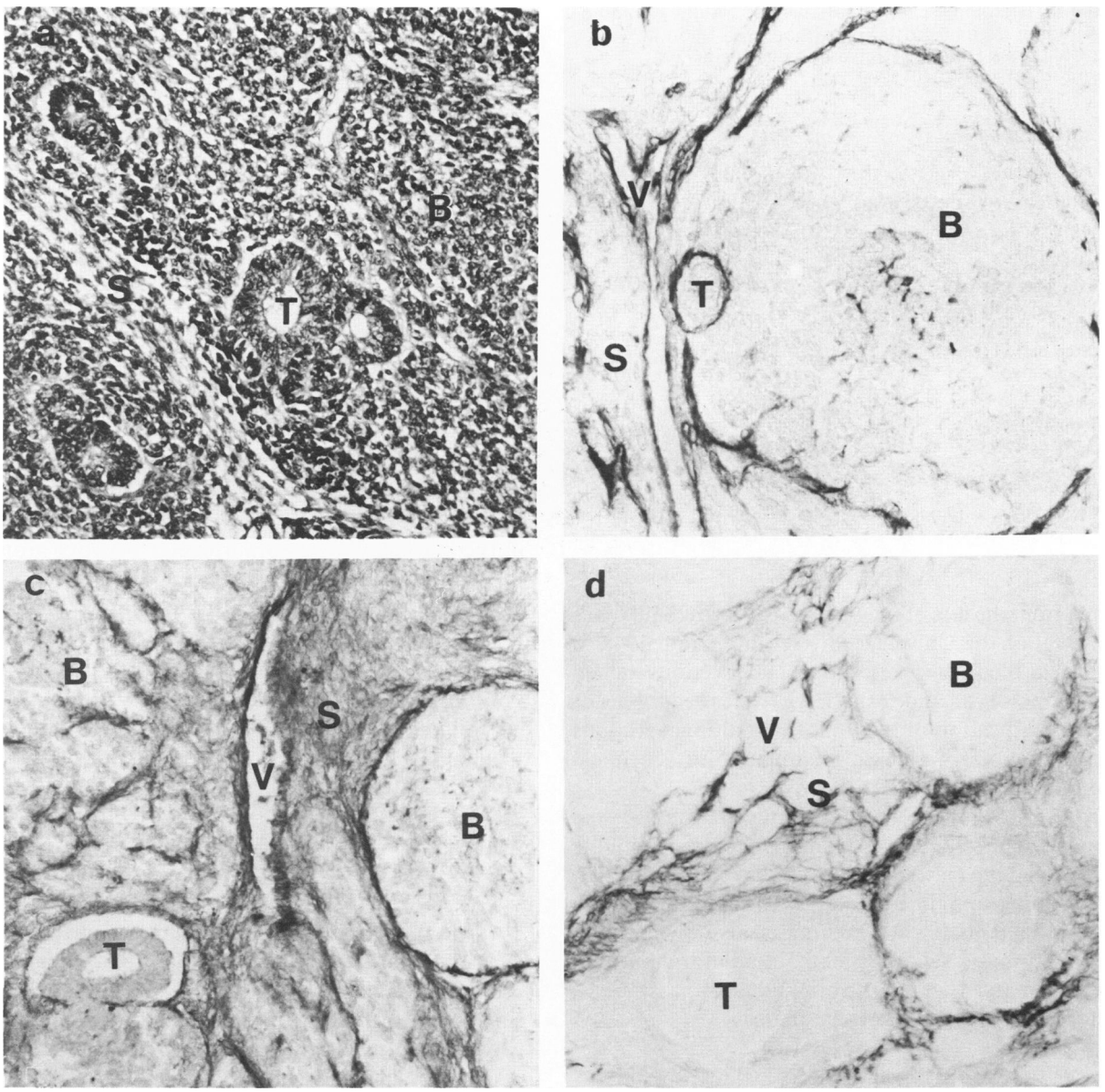


**Figure 1**—Histology (**a**) and matrix staining (**b–d**) of triphasic Wilms' tumor. **a**—The tumor is composed of varying amounts of tubules (*T*), homogenous blastema (*B*), and fibrovascular stroma (*S*). The tubules often locate beneath the stroma. **b**—The tubules are surrounded by a continuous laminin-positive basement membrane, but laminin is seen only in some blastemal cells. **c**—Fibronectin is seen in the tubular basement membrane as well as in some blastemal cells. **d**—Type III collagen is seen in the stromal areas and in the vessel walls. Note that laminin and fibronectin are positive in vascular basement membrane (*V*). (**a**, H&E, ×125; **b–d**, Biotin-avidin-peroxidase, ×125)

### Monomorphous Epithelial Pattern

The monomorphous epithelial tumors were composed of well-developed tubular or papillary structures. No blastemal areas were seen (Figure 3a). The epithelial structures were surrounded by a laminin- and fibronectin-positive basement membrane (Figures 3b and c). Type I and III collagen was seen in the fibrovascular stroma. Some positive areas also surrounded the epithelial structures, but the tubules were devoid of staining for interstitial collagens (Figure 3d).

### Rosetting Pattern

The rosetting tumors consisted of homogeneous ovoid cells, cytologically similar to those seen in blastemal areas of triphasic Wilms' tumor. Through-

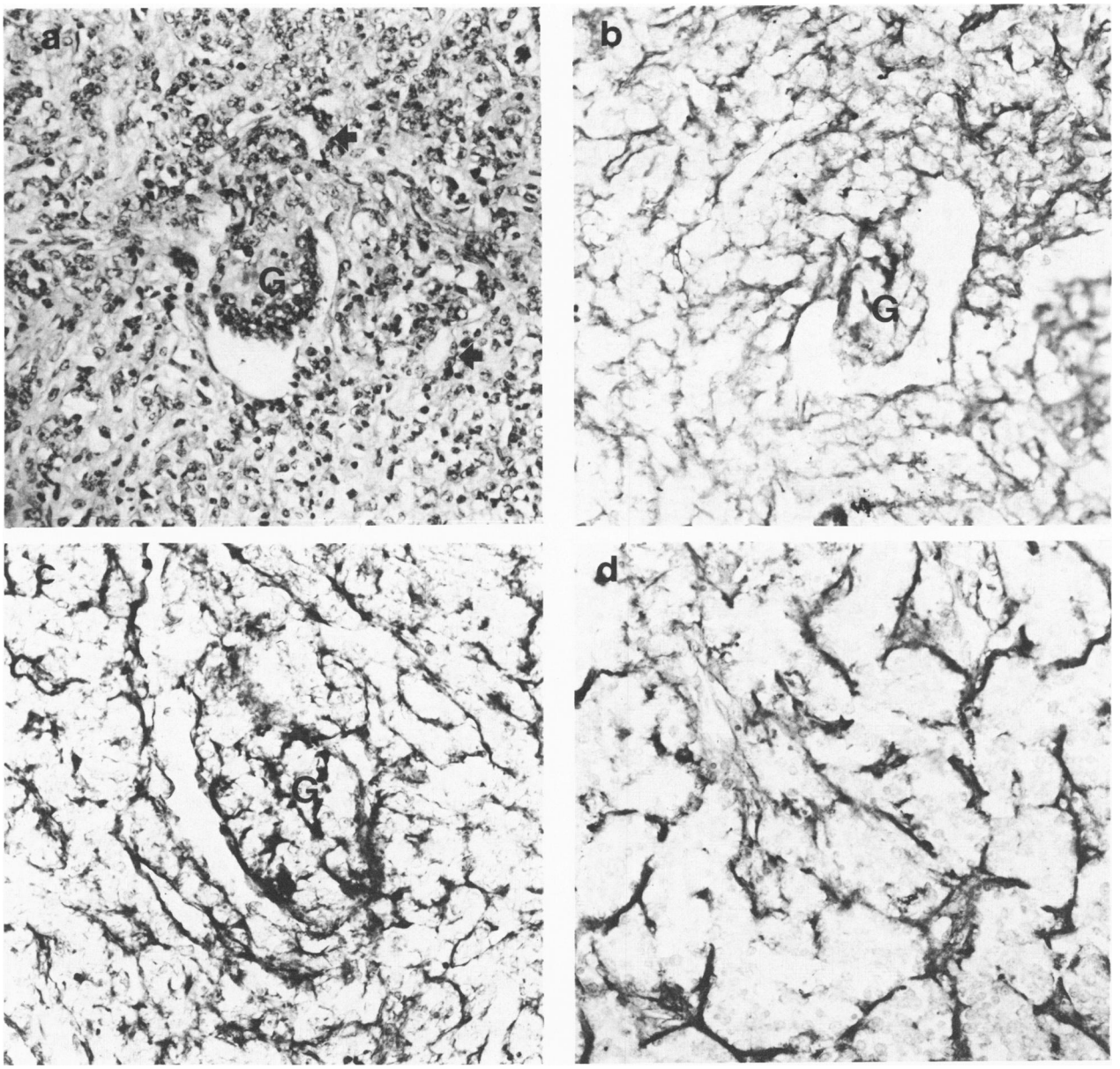


**Figure 2** — Histology (**a**) and matrix staining (**b–d**) of pleomorphic renal carcinoma. **a** — The tumor consists of large sheets of pleomorphic cells which occasionally form some primitive glandlike structures (*arrows*). However, it has a clear tendency to form primitive glomerulus-like bodies (*G*), which are clearly neoplastic; hence the cells are similar to those seen in other areas of the tumor. **b** — All cells are surrounded by a laminin-positive basement membrane. **c** — Fibronectin is stained with varying intensity and is similar in distribution to laminin. **d** — Type I collagen is seen in thick bundles throughout the tumor and surrounding many of the tumor cells. (**a**, H&E, × 150; **b–d**, Biotin-avidin-peroxidase, × 150)

out the tumor they showed the capacity to form tubulus-like cell condensates, also called rosettes (Figure 4a). Laminin was stained with varying intensity around the cells, but some areas were devoid of staining (Figure 4b). Fibronectin was deposited in an unusual dotted pattern, and some small areas were devoid of staining, especially near the stroma (Figure 4c). No Type I or III collagen could be detected among the tumor cells, but the vessel walls were brightly positive (Figure 4d).

### Rhabdoid Pattern

The rhabdoid sarcomas were composed of polygonal cells with an abundant cytoplasm, eosinophilic

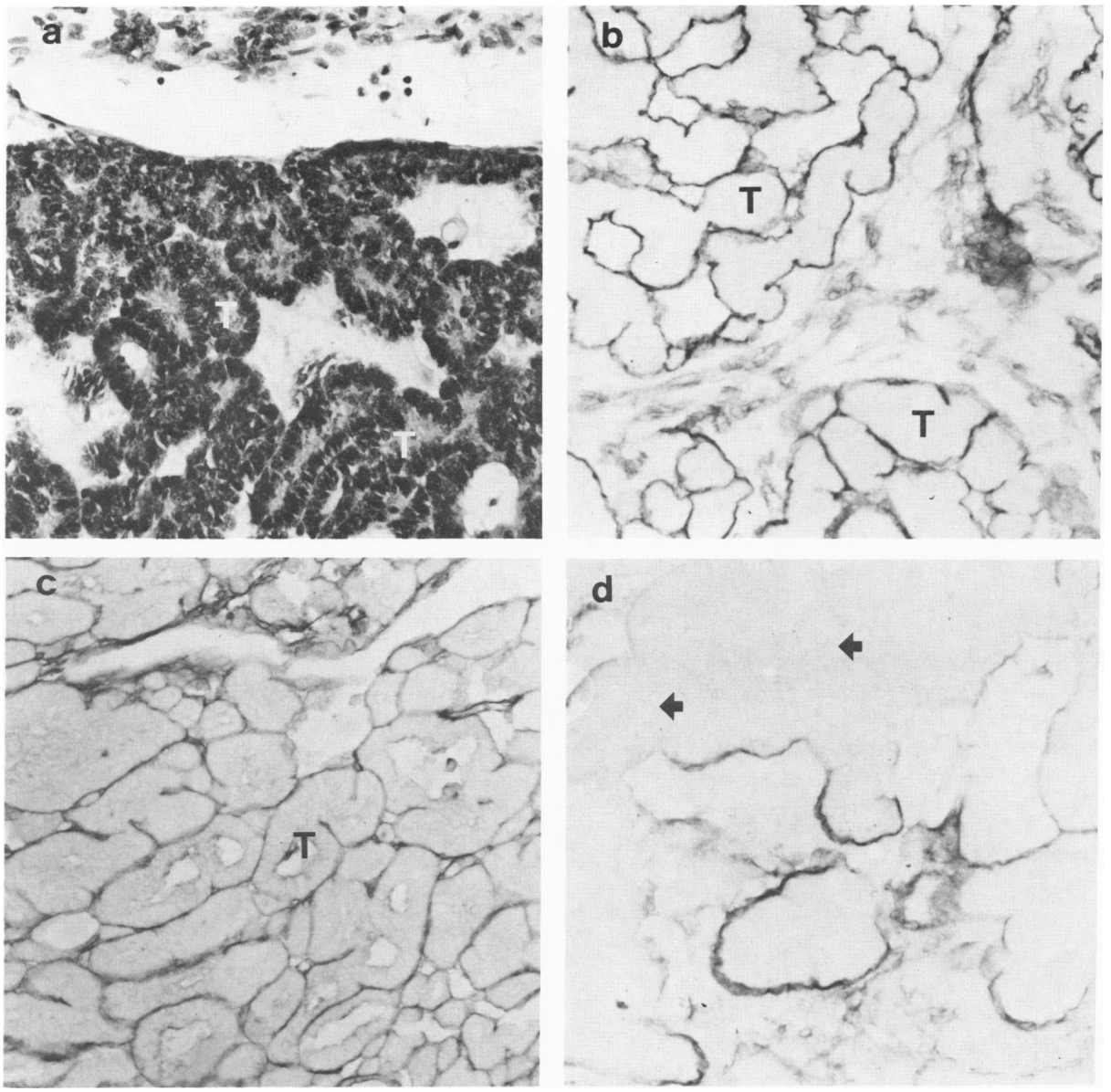


**Figure 3** — Histology (**a**) and matrix staining (**b–d**) of monomorphous epithelial tumor. **a** — The tumors are composed of tubular or papillary structures, and no blastemal areas are seen. **b** — All tubules (*T*) are surrounded by a continuous laminin-positive basement membrane. **c** — Fibronectin is seen in the tubular basement membrane as well as in stromal areas. **d** — Type III collagen often locates beneath the tubules, but the unstained tubular areas (*arrows*) show that the interstitial collagen is not deposited by tubules. A similar staining pattern is seen for Type I collagen. (**a**, H&E, ×150; **b–d**, biotin-avidin-peroxidase, ×150)

cytoplasmic inclusions, and hyperchromatic nuclei with a prominent nucleolus (Figure 5a). Laminin was found in a distinct dotted pattern. Some of the dots seemed to be located intracellularly, and some were clearly in the extracellular space. No laminin-negative areas were seen in this type of tumor (Figure 5b). Fibronectin, Type I and III collagens were expressed in a reticular network around tumor cells (Figure 4c and d).

### Clear-Cell Pattern

They were composed of rather homogeneous round or ovoid cells with a clear and abundant cytoplasm and vesicular nuclei. One of these tumors also contained tubules with a laminin- and fibronectin-positive basement membrane (Figure 6a). The dotted laminin deposits were similar to those seen in rhabdoid sarcomas

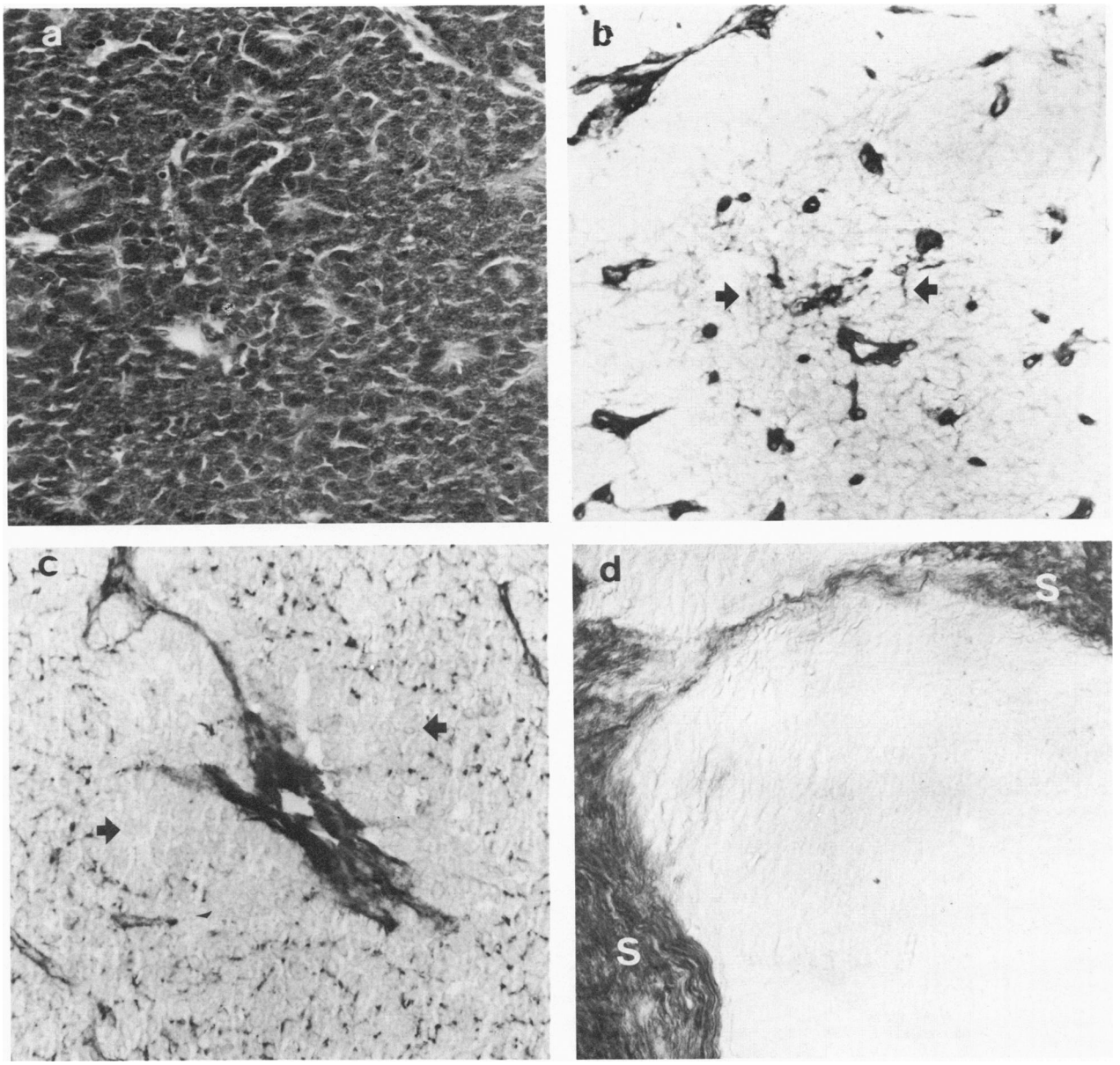


**Figure 4** — Histology (**a**) and matrix staining (**b–d**) of rosetting tumor. **a** — The rosetting tumors are formed by regularly orientated cell groups. Cytologically the rosetting cells resemble the blastemal cells. **b** — Laminin expression varies within the tumor. Most rosettes are devoid of laminin, but in some areas positive staining is seen between the cells (*arrows*). **c** — Fibronectin is expressed in a dotted polarized pattern, and the rosettes adjacent to the stroma are often devoid of fibronectin (*arrows*). **d** — No staining is seen in the rosettes by anti-Type III collagen antibodies, but a strong staining is seen in the stroma (*S*). (**a**, H&E, × 150; **b–d**, biotin-avidin-peroxidase, × 150)

(Figure 6b). Also, fibronectin and Types I and III collagen were found throughout the tumor (Figure 6c and d).

### Spindle-Cell Pattern

Two types of spindle-cell sarcomas were identified. The blastemal variant was composed of sheets of small or medium-sized spindle cells with a very dark staining nucleus and scattered cytoplasm (Figure 7a). The histologic pattern was clearly different from that seen in clear cell sarcomas or rhabdoid sarcomas and resembled somewhat that seen in blastemal areas of classic Wilms' tumors or oat cell carcinoma of lung. Laminin was seen only in vessel walls but not around tumor cells (Figure 7b). Fibronectin, Type I collagen, and Type III colla-

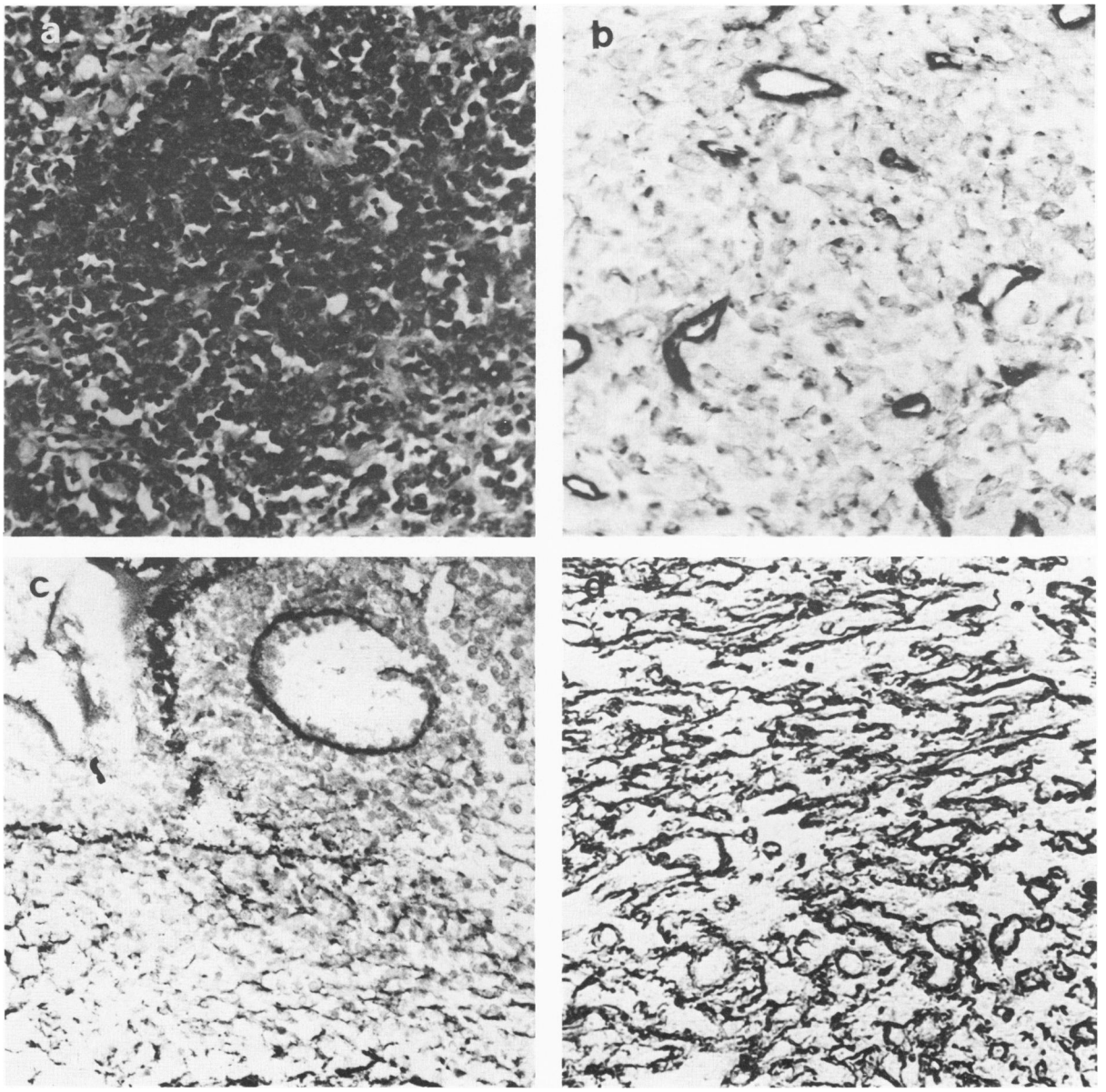


**Figure 5** – Histology (**a**) and matrix staining (**b–d**) of rhabdoid sarcoma. **a** – This rare sarcoma is composed of pleomorphic spindle-shaped cells with an abundant eosinophilic cytoplasm. **b** – Laminin is expressed in a distinct dotted pattern. **c** – Fibronectin is seen throughout the tumor. **d** – Type III collagen surrounds the cells. (**a**, H&E, × 150; **b**, Biotin-avidin-peroxidase, × 200; **c** and **d**, Biotin-avidin-peroxidase, × 150)

gen were clearly negative throughout the tumors (Figures 7c and d).

The sclerosing or stromal variant of spindle-cell sarcomas was characterized by an abundant hyalin-type extracellular matrix and very elongated spindle-shaped cells. These tumors resembled the stromal component of classic Wilms' tumor (Figure 8a). Laminin was negative, but fibronectin, Type I collagen, and Type III collagen were positive throughout the tumors (Figures 8b–d).

## Discussion

In Wilms' tumors, elements of tubular epithelium, mesenchymal blastema, and fibrovascular stroma are present in varying amounts. These differences provide a histologic basis for subclassification of this tumor, which is important because the tumors with epithelial differentiation have a better prognosis.[4,5] It is generally assumed that these morphologic differences reflect various stages in the differentiation pathways,[1–6] but the

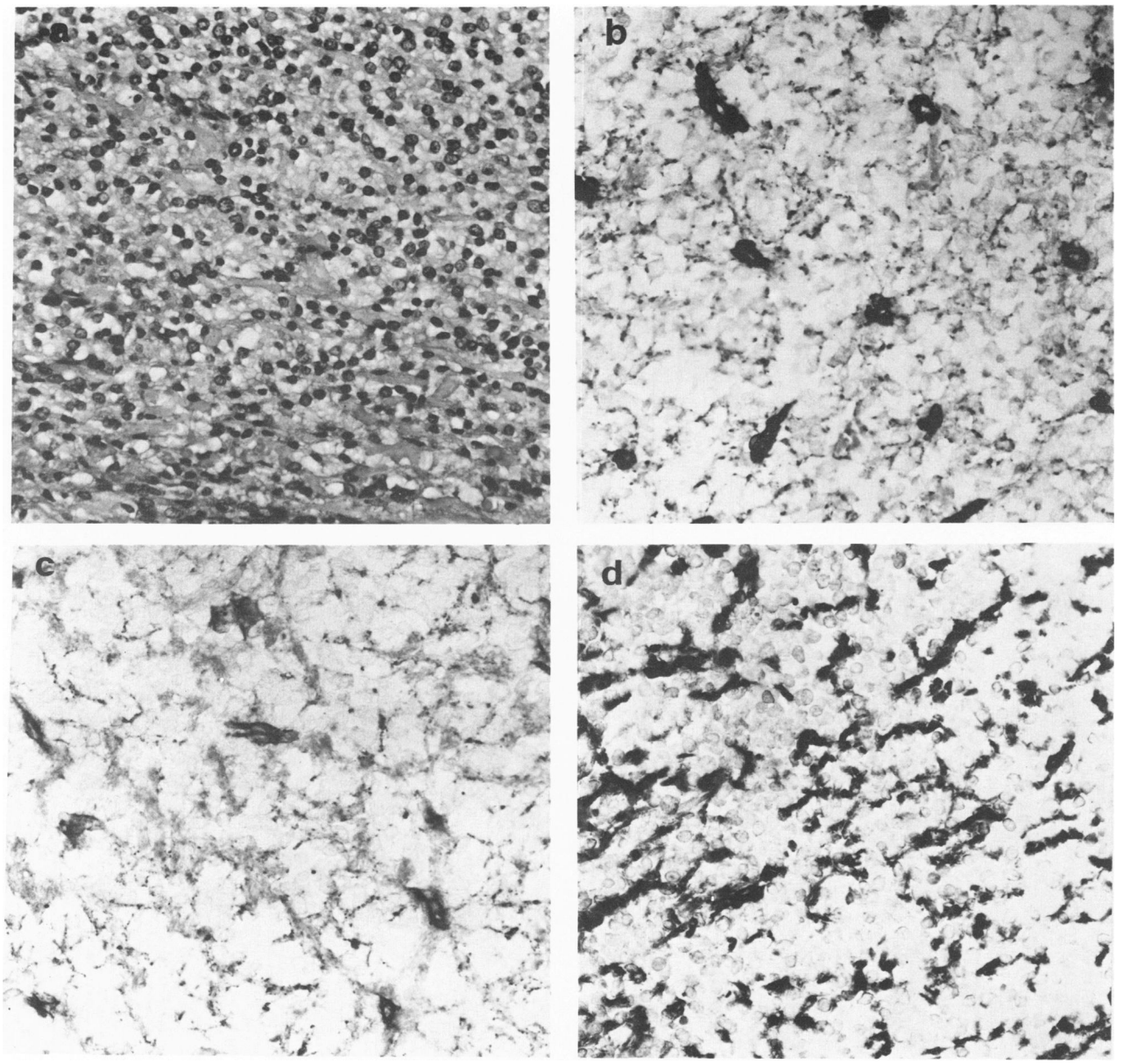


**Figure 6**—Histology (**a**) and matrix staining (**b–d**) of clear-cell sarcoma. **a**—It is composed of round or ovoid cells with regular shape and an abundant clear cytoplasm. Some areas show cystic degeneration of the tumor. **b**—Laminin is expressed in a dotted pattern similar to that seen in rhabdoid sarcoma. **c**—Fibronectin is seen among all the cells. **d**—Type I collagen is seen in bundles between cells. (**a**, H&E, ×50; **b–d**, biotin–avidin–peroxidase, ×150)

nature of different cell types in these tumors is poorly understood. Previous studies were mainly based on a morphologic and ultrastructural analysis of these cells,[18,19] and only limited data are available on the composition of the extracellular matrix (ECM).[20–22] Normal kidney morphogenesis is accompanied by an orderly appearance and disappearance of certain ECM proteins.[10–12] We found here that antibodies against interstitial collagens and laminin were also valuable in the characterization of the various types of Wilms' tumors, whereas the analysis of fibronectin was only of limited value.[23]

Our study reveals that the mesenchymal and epithelial areas of Wilms' tumors can be distinguished with antibodies against ECM components. In tubules of classic Wilms' tumor and of the monomorphous epithelial type laminin could be detected on the basal side of the tubular structures in a rather continuous fashion. Skin tumors of noninvasive or benign character such as solid basal cell carcinoma or cylindroma show a similar con-

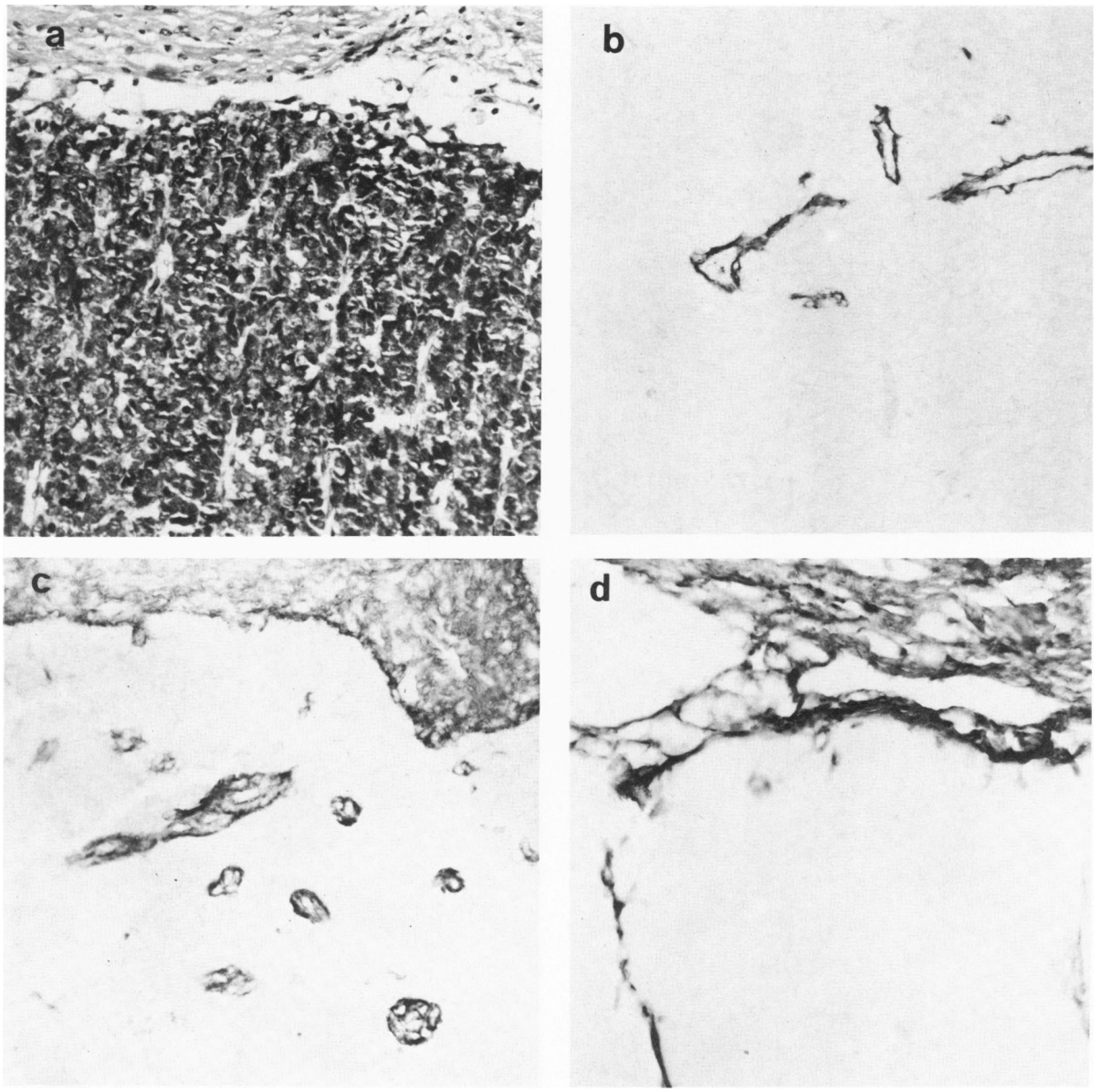


**Figure 7** — Histology (**a**) and matrix staining (**b–d**) of a blastemal variant of spindle-cell sarcoma. **a** — This type of spindle-cell sarcoma is composed of small or medium size pleomorphic fuciform cells with a scanty cytoplasm. **b** — No laminin is seen in the tumor cells. **c** — The cells are negative for fibronectin and (**d**) Type III collagen. (**a**, H&E, × 150; **b–d**, biotin-avidin-peroxidase, × 150)

tinuous basement membrane which can be strongly stained for laminin.[24,25] The presence of a continuous basement membrane is not typical for all malignancies. In fact, it seems evident that there are gross disturbances in basement membrane formation in most carcinomas, and the presence or absence of a continuous basement membrane can, therefore, be used to evaluate the degree of malignancy in adenocarcinomas and epidermoid carcinomas.[26–28]

In classic Wilms' tumors, we could detect tumors which showed some differentiation toward glomeruli, which contained some laminin and fibronectin. It is not possible to judge whether this basement membrane material is derived from the epithelial cells of glomeruli, because it cannot be excluded that endothelial cells are present within these glomeruli. Several reports have suggested an asynchronous development of epithelium and endothelium in Wilms' tumor.[1–6] We similarly could not detect any well-formed vessels in the glomeruli. Our recent studies on the angiogenesis process during normal kidney development have revealed that the blood vessels must be stimulated to grow into the kidney at

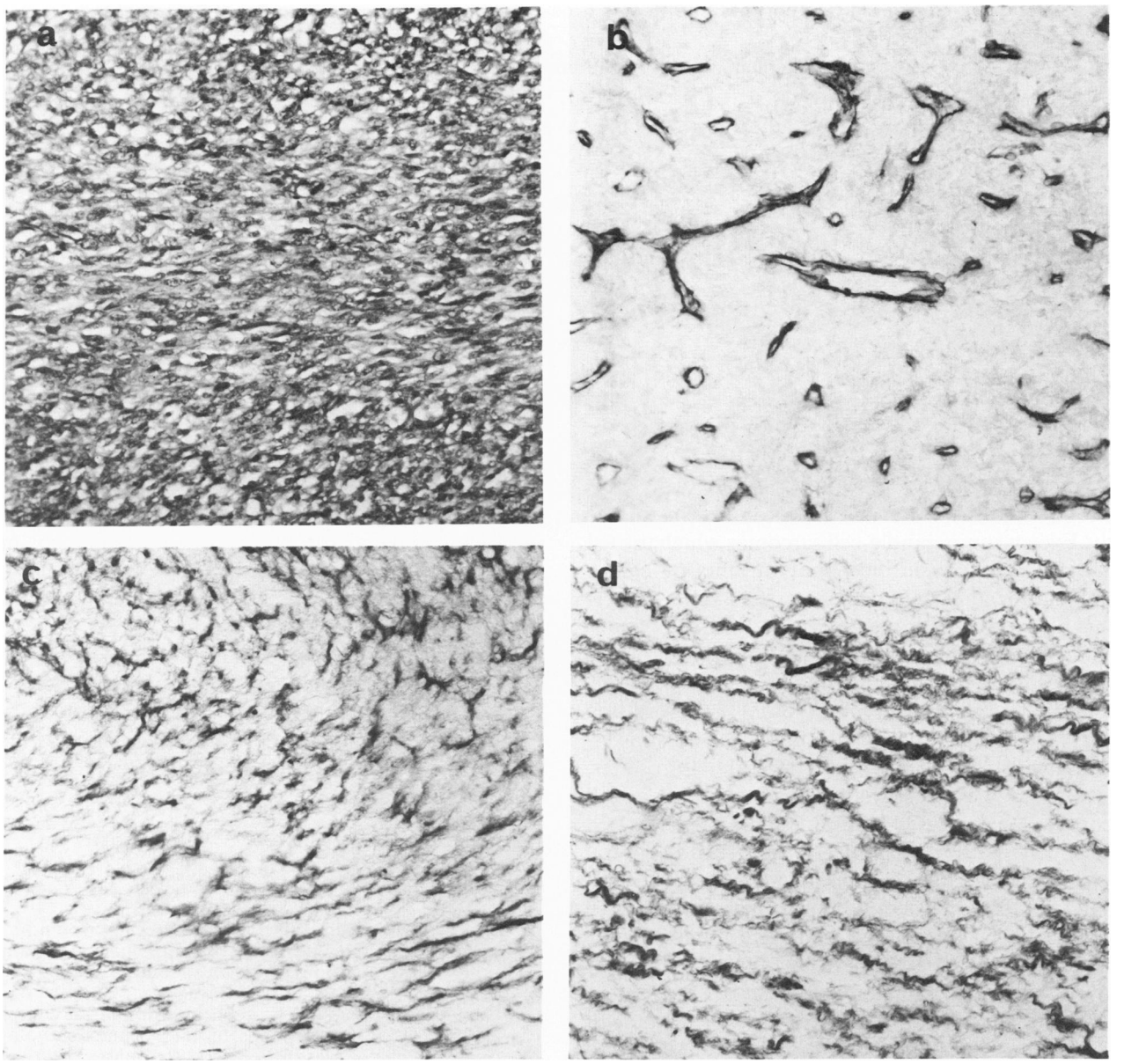


**Figure 8** — Histology (**a**) and matrix staining (**b-d**) of a stromal variant of spindle-cell sarcoma, also called sclerosing sarcoma. **a** — The tumors are characterized by an abundant hyalin-type matrix and spindle-shaped cells. **b** — They are negative for laminin. **c** — They contain abundant fibronectin. **d** — They contain Type III collagen. (**a**, H&E, × 125; **b-d**, biotin-avidin-peroxidase, × 125)

a certain period. If these temporal correlations are confused, the end result is an avascular glomerulus,[29,30] which might have occurred during formation of Wilms' tumor.

In the blastemal areas of classic triphasic Wilms' tumors, no interstitial collagens were found, but the cells and the extracellular space were in large areas also negative for laminin. It is possible that the blastemal cells represent metanephrogenic cells with some maturation arrest. They may have lost their mesenchymal phenotype but apparently did not acquire the capacity to continue differentiation by turning on the expression of basement membrane components. The presence of fibronectin in the blastema could possibly have some role in this process. During normal kidney differentiation, there is a coordinated loss of fibronectin and interstitial collagens at the condensed blastema stage.[10-12]

Recent studies have emphasized that the sarcomatoid variants are tumors different from classic Wilms' tumor. Their identification is important, because the sarcomas have a very poor prognosis and metastasize rapidly.[31-36] However, it has proven difficult to distin-

Table 2—Composition of ECM Components in Different Types of Wilms' Tumor Including Renal Sarcomas*

| | Laminin | Fibronectin | Interstitial Type I and III collagens | Number of tumors analyzed |
|---|---|---|---|---|
| Monomorphous epithelial | + | + | – | 2 |
| Classic triphasic pattern | | | | |
| Tubules | + | + | – | 6 |
| Blastema | –† | V | – | |
| Rosetting pattern | V | D | – | 2 |
| Sarcomatoid pattern | | | | |
| Spindle-cell | | | | |
| Blastemal type | – | – | – | 2 |
| Stromal type | – | + | + | 3 |
| Clear-cell | D | + | + | 5 |
| Rhabdoid | D | + | + | 2 |

* Staining of vessels not included.
† Occasional positivity.
D, dotted expression; V, varying expression.

guish the aggressive variants by ordinary histologic study. Except some spindle-cell sarcomas which turned out to be monophasic blastemal variants of classic Wilms' tumor, the sarcomas expressed Type I and III collagen as well as fibronectin around the cells abundantly. The expression of interstitial collagens provides a reliable tool to differentiate the sarcomas from poorly differentiated classic Wilms' tumor and rosetting tumors, where interstitial collagens are seen only in vessel walls and stromal areas, but not in tubules, rosettes, or blastema. Unexpectedly, the rhabdoid and clear-cell sarcomas also expressed laminin in an unusual dotted pattern. The pattern is similar to that seen in several developing tissues during embryogenesis.[10,37] This pattern distinguishes these sarcomas from the spindle cell sarcomas, which are negative for laminin. It is possible that the presence of laminin in this fashion offers the cells a selective advantage for growth. Several studies have suggested that laminin and other basement membrane proteins play important roles in cell adhesion and growth both in normal morphogenesis[10,38-40] and in cancer invasion.[41-43]

Our data demonstrate that the pure epithelial, classic, and rosetting Wilms' tumors can be distinguished from sarcomas by the ECM composition, although no epithelial differentiation is seen in histologic study (Table 2). Thus, it is likely that both clear-cell and rhabdoid sarcomas are distinct tumors, not monophasic variants of classic Wilms' tumor, which seems to originate from an abnormal nephrogenic mesenchyme. The only sarcomas likely to be monophasic variants of Wilms' tumors are the spindle-cell sarcomas. The histogenesis of rhabdoid and clear-cell sarcomas is somewhat difficult to judge, because they concomitantly express both interstitial and basement membrane type ECM. However, these findings are in accordance with the recent work by Vogel et al, who described both epithelial and mesenchymal specific intermediate filament proteins in rhabdoid tumors.[44] It might be that laminin and keratin expressions represent an incipient epithelial differentiation of these sarcomas.

In conclusion, our study shows that the antibodies against various defined ECM components provide a useful adjunct in the histopathologic evaluation of these tumors, offering a new approach for differential diagnosis and classification, especially of sarcomatoid Wilms' tumors.

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