**Cellular Analysis of Renal Neoplasia: Induction of Renal Tumors in Dietary-conditioned Rats by Dimethylnitrosamine, with a Reappraisal of Morphological Characteristics**

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**SUMMARY**

The administration of a single i.p. injection of 60 mg/kg dimethylnitrosamine (DMN) to male rats that had been temporarily fed a protein-free diet induced renal mesenchymal tumors in all animals, as well as inducing some renal adenocarcinomas. The dose of 50 mg/kg in male rats temporarily fed either a protein-free diet or a sucrose only diet or subjected to starvation resulted in an incidence of from 86 to 89% of renal tumors. Of rats maintained on a protein-supplemented diet, receiving 60 or 30 mg/kg DMN, only 35 and 18%, respectively, developed renal tumors. The morphology of the mesenchymal tumor was reappraised in terms of those histological features which either were common to all tumors examined or were features of such frequency that they could be considered characteristic of tumor development. DMN-induced renal mesenchymal tumors were not considered to be nephroblastomas, and all epithelial components other than independently developed adenomas or adenocarcinomas were consistent with pathologically altered, preexisting renal parenchyma. Attention was drawn to the vascular nature of mesenchymal tumors. These results provided a working basis for a sequential study aimed at tracing the evolution of DMN-induced renal neoplasms.

**INTRODUCTION**

DMN\(^1\) is able to induce renal neoplasia, in addition to its known hepatocarcinogenic effect. Prolonged feeding of low levels of the compound to rats results in a high incidence of hepatocellular carcinoma with no kidney tumors, while higher doses for a short period produce the reverse effect (20, 21). A p.o. of 8 mg/kg for 6 consecutive days resulted in an 85 to 100% incidence of renal neoplasia, depending on the strain of rat (12). Magee and Barnes (20, 21) also reported that 1 p.o. dose of 30 mg/kg DMN, a 50% lethal dose at that time (9), induced renal tumors in 20% of surviving rats.

Recently, it has been shown that some rats given a protein-deficient diet prior to DMN treatment are protected from the lethal effects of a single i.p. dose of 60 mg/kg. All survivors developed renal neoplasia (31). In any attempt to trace the evolutionary development of a neoplastic process, the parameters of study with the most teleological significance must be those which can relate a 100% incidence of tumor formation to a single exposure of the animal to the carcinogen. Thus, the findings of Swann and McLean (31) provide an ideal model for the study of chemical carcinogenesis in the kidney. Furthermore, the use of DMN as the carcinogen in such a system is not without some relevance to the problem of human neoplasia, as nitrosamines have been implicated as potential environmental hazards (3, 18).

It is generally agreed that DMN-induced renal tumors in the rat may be either (a) epithelial lesions taking origin from the tubule parenchyma and, occasionally, the transitional epithelium lining the pelvis, or (b) anaplastic or undifferentiated cell tumors. The latter have been referred to variously as anaplastic tumor (21), nephroblastoma (6, 12, 28, 32), anaplastic epithelial tumor (36), Wilms' tumor (1), embryonal cell tumor and hemangiendothelioma (11), renal sarcoma (34), and, recently, stromal nephroma (29). These tumors have been considered to be the counterpart of Wilms' tumor of man. Identical renal tumors produced by the administration of cycad derivatives have been described by a similar diversity of terms (5, 15–17, 23). Thomas and Schmahl (33), in reviewing renal tumors induced by nitrosamines and nitrosamides, classified this diverse group collectively as mesenchymal tumors.

The present paper describes the induction of kidney tumors by a single dose of DMN with an incidence of up to 100%, with various dietary regimes. This study provides a basis for subsequent work aimed at tracing the light microscope and ultrastructural changes within the kidney leading to renal neoplasia and an analysis of the ultrastructure of the resulting tumors. The results of the accompanying study (7) demonstrate that this neoplasm arises from mesenchymal elements within the cortical intertubular spaces near glomeruli. Reappraisal of the essential morphology of the tumor was considered necessary to tabulate the consistent features and to stress their basically vascular nature. Until the

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\(^1\)The abbreviations used are: DMN, dimethylnitrosamine; HPS, hematoxylin-phloxine-saffron; PTAH, phosphotungstic acid hematoxylin; PAS, periodic acid-Schiff stain.

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Identity of the cell of origin of these pleomorphic tumors is established, we will adopt the terminology proposed by Thomas and Schmahl (33), namely, renal mesenchymal tumor, since this best describes the histogenesis as presently understood.

MATERIALS AND METHODS

Chemicals. DMN obtained from Eastman Kodak Co., Rochester, N. Y., was purified by simple distillation, and its purity was assessed by polarography before use (8). The compound was administered by a single i.p. injection in doses of 30, 50, or 60 mg/kg body weight as 1.5 to 3.0% solutions in 0.9% NaCl solution.

Animals. Random-bred male, 5-week-old white rats, 90 to 100 g, of the Porton strain, bred in this laboratory, were used.

Dietary Regime. Group 1 and Group 2 rats (Table 1) were fed a protein-free powder diet for 2 weeks (22) and given a 60 or 50 mg/kg dose, respectively, 1 week after the commencement of the diet.

For 2 weeks, Group 3 rats were fed the same powdered formulation, in which a quantity of corn starch had been replaced by casein to provide 30% protein. Thirty mg/kg DMN were administered 1 week after the start of the diet. All rats in these groups were returned to pellet MRC Diet 41B, containing 16% crude protein, after 2 weeks of experimental feeding.

Group 4 rats were maintained entirely on pelleted MRC Diet 41B, and these received 60 mg/kg DMN.

Group 5 rats were maintained solely on sucrose granules for 3 days and then given injections of 50 mg/kg DMN and returned to MRC Diet 41B.

Group 6 rats were starved by withholding all food for 64 hr. After this period of starvation, they were dosed with 50 mg/kg DMN and returned to MRC Diet 41B.

Group 7 contained control rats fed on protein-free powder for 14 days and then maintained on MRC Diet 41B. These rats were not treated with DMN. All groups received water ad libitum.

Histology. The survivors of these various treatments were checked daily and weighed at weekly intervals throughout the experiment. If a significant fall in body weight occurred or if an abdominal mass could be palpated, the animal was killed and autopsied. The experiment was terminated at 12 months, when all surviving rats were killed. Apart from those rats which had been found dead, all but a few kidneys were first perfused with fixative via the abdominal aorta while the animal was under ether anesthesia. Samples were taken from major organs, except brain, and immersed in formal alcohol. Kidney and tumor sections were stained with Harris' hematoxylin and eosin, HPS, Van Gieson's collagen stain, Verhoeff's elastin stain, Masson's trichrome, Mallory's PTAH, Gomori's reticulin stain, and PAS-light green. A few selected sections were also stained with Green and Wood's Luxol brilliant green (4), Levanol fast cyanine 5RN (26), and modified Bowie's stain (2). Organs other than kidney and tumor metastases were stained only with hematoxylin and eosin.

RESULTS

Approximately 25% of rats maintained on a conventional pelleted diet survived the acute toxic action of 60 mg/kg DMN, while 44% of protein-depleted rats receiving 60 mg/kg and 58% receiving 50 mg/kg survived the acute injury. Of rats fed a casein-supplemented powder, 73% survived a dose of 30 mg/kg DMN. The incidence of macroscopic tumors in the kidney of these survivors is listed in Table 1, and the account that follows is based on a histological study of 75 tumor-bearing rats.

Epithelial Tumors. These were frequent in protein-depleted rats given large doses of DMN. Macroscopically, they could be distinguished from the mesenchymal tumors in which they were sometimes sequestered by their regular, circumscribed outline and fleshy texture. Often these were multi-

Table 1

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Dietary regimen</th>
<th>Dose DMN, i.p. (mg/kg)</th>
<th>No. of rats with macroscopic tumors</th>
<th>Adenocarcinomas</th>
<th>Mesenchymal tumors</th>
<th>Tumor morbidity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Protein depletion</td>
<td>60</td>
<td>13/13</td>
<td>4</td>
<td>13</td>
<td>100</td>
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<td>50</td>
<td>27/31</td>
<td>6</td>
<td>25</td>
<td>87</td>
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<tr>
<td>3</td>
<td>Casein supplement</td>
<td>30</td>
<td>8/29</td>
<td>6</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>Conventional pellets</td>
<td>30</td>
<td>8/29</td>
<td>6</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>Sucrose only for 3 days</td>
<td>60</td>
<td>7/20</td>
<td>3</td>
<td>4</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>Starvation for 64 hr</td>
<td>50</td>
<td>8/9</td>
<td>4</td>
<td>8</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>Protein depletion</td>
<td>Nil</td>
<td>0/26</td>
<td>0</td>
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<td>0</td>
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</table>

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ple. Their histological forms have been adequately described (13, 21, 24, 33). In our series of tumors, contrary to some previous observations, clear cell variants were not uncommon, and mitoses were frequent in most epithelial neoplasms. In many tumors, evidence of local invasion into normal renal parenchyma was found (Fig. 1). The most anaplastic forms, which lacked a pseudocapsule, appeared to grow mainly by invasion rather than expansion (Fig. 2). All macroscopic epithelial tumors contained small to massive foci of necrosis and hemorrhage. Metastases were not found in this series.

Many of the macroscopically normal kidneys of treated rats at all dose levels contained multiple microscopic adenomatous foci. Thirty-five % of apparently normal casein-fed rats treated with 30 mg/kg DMN and 75% of pellet-fed rats receiving 60 mg/kg had tubule lesions of this nature. Forms included cysts lined by low papillary epithelium, multifocally papillary cysts, and small, solid nests of eosinophilic, basophilic, or clear cells. Their location was always cortical, but there was no predilection for any particular zone of the cortex. Mitoses were infrequent. Such lesions were never found in control rats.

Mesenchymal Tumors. The smallest macroscopic mesenchymal tumors up to 1 cm in diameter were cystic lesions often occupying the poles of the kidney. In some, the cortex was diffusely infiltrated, resulting in slight uniform increase in kidney size. The largest tumors were of irregular shape, frequently gelatinous in texture, and invariably possessed a small cap of normal renal tissue at the periphery. Some relation between high dose coupled with dietary conditioning and rapidity of proliferation was indicated, because tumors in Groups 3 and 4 were usually much smaller than those in the other treated groups and frequently did not deform the kidney outline. Despite the size or mode of growth of the tumors, certain histological aspects were common to all mesenchymal tumors. Other features were recorded in such a significant proportion of tumors that they could be regarded as equally characteristic of the tumors. These morphological characteristics are listed as follows.

The spindle cell was the predominant cell type. At the invading edge, this cell form was always present, infiltrating between renal tubules (Fig. 3). These cells formed fibrosarcomatous areas of moderate to dense cellularity in all tumors that were best developed in the larger growths. Their pattern of growth was frequently herringbone or storiform (Fig. 4). Sometimes sarcoma-like cells occurred in such densely crowded sheets that cell margins could not be delineated. These areas were strongly PAS positive. They merged without sharp demarcation into more typical areas of sarcoma or smooth muscle. Occasionally, sarcoma cells were condensed into nests and rosettes, which appeared to form pseudotubules (Fig. 5).

All tumors were characterized by a tendency for some sequestered tubule remnants to be closely encircled by several layers of tumor cells (Figs. 3, 6, and 10). Stellate cells with small, dense nuclei widely spaced on a network of reticulin and faintly PAS-positive material were found in some areas of all mesenchymal tumors. This arrangement strongly resembled primitive mesenchyme and frequently formed a loose pattern around sequestered tubules (Figs. 6 and 12).

Cystic structures of varying size were always present, particularly near the sites of invasion into normal parenchyma. Their lining epithelium ranged from cuboidal to squamous. Very occasionally, a shrunken glomerulus was associated with the luminal periphery of a cyst, indicating that some cysts represented dilated Bowman’s capsules (Fig. 7). Sometimes, proliferating spindle or stellate cells indented the lining of a dilated tubule to form an inpouching of tumor cells within the tubule lumen (Fig. 8).

Coarse whorls or tufts of eosinophilic material with the staining characteristics of collagen were typical in some less cellular areas of all tumors (Fig. 9). Collagen-like material was present in lesser amounts throughout much of the tumor, but it was absent in the densest sarcoma cell aggregations. A dense network of reticulin was characteristic of all tumors, even in many highly cellular sarcomatous areas.

Sequestered, preexisting tubules and, usually, glomeruli could always be found in some part of mesenchymal tumors. Sometimes these epithelial elements were widely spaced and were found at some distance from the anticipated boundary of original renal tissue. Frequently, the epithelium of sequestered tubules was hyperplastic. Hyperplastic cells of preexisting epithelial elements sometimes appeared to merge rather imperceptibly with the surrounding aggregation of tumor cells (Fig. 10). Many tubules were small, shrunken remnants without lumen. These were frequently associated with a very dense encircling cluster of sarcoma-like cells (Fig. 11). Where proliferating mesenchymal tumor burst through the fornix into the renal pelvis, cords of transitional epithelium were carried and sequestered within the outgrowth (Fig. 12). Not infrequently, epithelial tumors were found within mesenchymal tumors, where they appeared to develop independently by collision. On these occasions, mesenchymal elements often swirled between and tended to separate their architectural units.

Throughout, most viable tumor tissue mitoses were frequent; they were particularly abundant in densely cellular areas and invading edges (Figs. 5 and 11).

Smooth muscle was identified in 60% of mesenchymal tumors. Usually, fibers were sparsely distributed, particularly around and in the vicinity of cysts. Sometimes bands of smooth muscle encircled islands of primitive mesenchyme which surrounded preexisting epithelial tissue (Fig. 12). In about 10% of tumors, smooth muscle was abundant; it occurred in sheets, sometimes with a slight swirling pattern. Striated muscle was present in 8% of tumors; it was usually in bundles separated by collagenous stroma (Fig. 13). Large cells with bizarre nuclei and abundant cytoplasm were also found. These had the appearance of rhabdomyoblasts (30) and, indeed, many stained positively with HPS and PTAH (Fig. 14). The mitotic activity of such cells was very high.

All mesenchymal tumors had a very rich supply of seemingly normal blood vessels, but one-third showed a conspicuous development of abnormal vascular structures which formed an integral part of differentiating malignant tissue.
Their various forms included capillary hemangioma, cavernous hemangioma (Fig. 15), and areas resembling hemangiopericytoma (30). The latter were dense sarcomatous sheets perforated by many sinusoidal clefts which frequently contained erythrocytes (Fig. 16). In many cellular areas there was also a marked tendency for individual neighboring cells to circumscribe spaces between their adjacent borders, resulting in a fenestrated appearance (Fig. 17). These minute spaces seemed in some instances to be in continuity with the vascular supply, as red cells were often present. Reticulin staining of these various areas was dense and accentuated the vascular channels.

Seventeen % of mesenchymal tumors infiltrated tissue beyond the kidney; this tissue was mainly perirenal fat and muscle. In one case, metastases of vascular sarcomatous tissue were found in the lung; in another, similar peritoneal seeding was widespread (Fig. 18). In a 3rd case, invasion of renal vein and vena cava had occurred. A solid white cord, 1 cm in diameter, of malignant tissue extended from the kidney to the heart. The cells were sarcoma-like, with occasional muscle fibers and large pleomorphic forms. Some of the latter cells were arranged into small tubular structures which sometimes contained red cells. A dense reticulin network and some collagen formation was present in all metastases.

In the larger mesenchymal tumors, thrombus formation and infarction, leading to extensive tracts of necrosis and hemorrhage, were common.

No elastin formation, cartilage, or osteoid was found in this series of neoplasms. Three rats in the study developed tumors unrelated to the kidney; these were a hepatocellular carcinoma, an epithelial carcinoma of nasal epithelium, and a pulmonary adenoma.

**DISCUSSION**

The results confirm the findings of Swann and McLean (31) that a single dose of 60 mg/kg DMN induces renal neoplasia in 100% of the surviving rats conditioned by a protein-free diet. Furthermore, all rats developed tumors of the mesenchymal type, providing a suitable model for a sequential study of the evolution of this histogenetically obscure malignant neoplasm. At the 50 mg/kg dose level, with an increase in survivors, tumor incidence was still high enough for correlative studies to be significant. An equally high incidence in starved rats or those fed sucrose provides the basis for an even simpler method of preparing tumor-prone rats.

The 50% lethal dose of DMN in protein-depleted rats rises from 45 to 79 mg/kg, and the extent of liver injury on a dosage basis is accordingly reduced (31). In normal rats, DMN is almost exclusively metabolized by the liver (19). Following protein depletion, it has been suggested that the enhanced incidence of kidney tumors is due to the diminished clearance of DMN by the liver and an increased metabolism of DMN by the kidney (31). Protein depletion markedly affects the rate of DMN metabolism in the liver, but the rate in the kidney is not affected. However, methylation of kidney DNA and RNA is 3 times greater in protein-depleted rats treated with 60 mg/kg DMN than in conventionally fed rats receiving 30 mg/kg (31). The basis of the high renal tumor incidence in sucrose-fed and starved animals is at present unknown.

All macroscopic renal epithelial tumors in this study showed areas of necrosis and hemorrhage. Surrounding renal tissue also was destroyed by the slow expansion of these tumors. Careful examination revealed focal invasion of normal parenchyma beyond the pseudocapsule. The cells and nuclei were frequently pleomorphic with many mitoses. No metastases were found, although the relatively short period of observation, together with the young age of rats at time of treatment, may have precluded this development. However, invasive properties of renal epithelial neoplasms induced by nitrosamines including DMN have been reported (24, 33, 36). These various characteristics lead us to concur with the classification of DMN-induced renal epithelial tumor as adenocarcinoma, rather than adenoma. The latter term applies to smaller lesions which consist of well-differentiated and organized cells lacking pleomorphism, mitoses, and evidence of local invasion.

The high incidence of microscopic tubular lesions in treated rats with macroscopically normal kidneys at 12 months is of interest. It has been suggested that similar lesions may develop into macroscopic epithelial neoplasms (21, 33). Indeed, a sequential study of the evolution of renal adenocarcinoma in DMN-treated rats confirms that such microscopic lesions may precede tumor development (G. C. Hard and W. H. Butler, in preparation). The failure of many lesions to progress to macroscopic size within the period of study is not understood.

A reappraisal of the histological character of DMN-induced mesenchymal tumor of the rat kidney was considered justified because earlier descriptions (1, 6, 11, 12, 21, 28, 29, 32-34, 36) failed to stress the fact that certain features are common to all of these tumors. Some have misinterpreted the significance of epithelial components. Features constantly found and characteristic of all tumors include differentiation into spindle cells which can organize into sarcoma-like tissue, differentiation into primitive mesenchyme-like tissue, a predilection for tumor cells to encircle closely or condense into aggregates around preexisting epithelial elements, deposition of a dense reticulin network throughout, formation of collagen-like material, and a rich vascular supply.

In addition to these features, the majority of mesenchymal tumors contain smooth muscle, the high incidence of which has not been emphasized previously. The incidence of smooth muscle in such tumors is likely to be much higher than the 60% reported here, as ultrastructural examination has demonstrated the presence of fibers in a number of tumors classified as muscle free by light microscopy (G. C. Hard and W. H. Butler, in preparation). The conspicuous differentiation into abnormal vascular structures of various forms, so commonly seen in these tumors, suggests that this was also an important feature of their structure.

No epithelial structures were seen which necessarily indicated the formation of primitive nephrons. The epithelial
components conformed to the variation expected of preexisting nephric elements subjected to sequestration and compression by malignant interstitial tissue. Epithelial structures represented adult tubules or Bowman’s capsules dilated into cysts, sequestered tubules in which the lining epithelium often displayed hyperplasia, shrunken tubule remnants without lumens, or nests of transitional epithelium isolated by rapidly growing tumor tissue from the lining of the pelvis. Some of these remnants could be intimately surrounded by discrete layers or more haphazard aggregations of tumor cells, leading to an appearance which has been interpreted by some as nephroblastoma (Figs. 10 and 11). The palisade-like and rosette patterns occasionally adopted by fibrosarcomatous cells in the center of very dense aggregations also could be confused with primitive nephron formation (Fig. 5). The focal proliferation of dense nests of tumor cells indenting the lumen of dilated tubules sometimes mimicked primitive glomeruli (Fig. 8).

It is concluded that DMN-induced renal mesenchymal tumors are not nephroblastomas or embryonal nephromas. In this we oppose the views of Taper (32) and Hadjioilov (6), who believe that some epithelial components represent true nephroblastic differentiation; we concur with the recently altered opinion of Jasmin and Riopelle (12, 14, 28, 29). Subdivision of renal mesenchymal tumors into groups based on their predominant tissue form or pattern of growth seems unnecessary at this stage. Thus, the divided classification of stromal nephroma suggested by Riopelle and Jasmin (29), or the splitting of cycad-induced tumors into histological types, adds little to the comprehension of their histogenesis. In our series, with the classification of Riopelle and Jasmin (29), 83% of the protein-depleted rats receiving 60 mg/kg DMN (Group 1) possessed tumors which conformed to the “large-cell” variant of the stromal nephroma. In contrast, only 27% of tumors in treated rats fed a protein-supplemented diet (Groups 3 and 4) were of this type, since most conformed to the “small-cell fibrosing” variant, which is also histologically consistent with the cycad-induced form termed “interstitial tumor” (5, 17). This suggests that the rapidity and mode of proliferation and degree of differentiation is dose dependent and may be related to the amount of carcinogen reaching the susceptible kidney cells. In addition, an accompanying paper (7) provides evidence to indicate that all mesenchymal tumor cell variants take origin from identical interstitial lesions which persist from an acute interstitial reaction induced by DMN. It is likely that similar changes are produced by cycad derivatives. Recently, Hiro no, et al. (10), following transplantation studies, speculated that cycad-induced renal tumors classified as sarcoma, interstitial tumor, and nephroblastoma may have a single cell of origin.

An analysis of the features listed above as characteristic of renal mesenchymal tumors suggests that these tumors tend to differentiate into the various components of vascular tissue, e.g., spindle-shaped, fibroblast-like cells, smooth muscle, and vascular channels. The spectrum of differentiation witnessed in these tumors is within the capability of the vascular pericyte, a cell which is considered to be one of the few within the adult body sufficiently unspecialized to retain the capacity to serve as a precursor for other cell types (27).

The tendency of mesenchymal tumor cells to ‘swirl around’ preexisting epithelial elements in several closely investing layers can also be a characteristic of the malignant pericyte (30, 35). Although Riopelle and Jasmin (29) consider that the vascular elements are not neoplastic components of mesenchymal tumors, their tumor transplantation results support our suggestion of vascular origin. They have shown that with successive passage this neoplasm evolves towards a mesenchymal differentiation of muscular type (14). These views are consistent with studies which indicate that the embryological derivation of the vascular system of the renal cortex has an entirely different source from that of the epithelial cells of the nephron. Mesenchymal cells constantly accompany the ingrowing capillaries, and some of these differentiate into the mesangial cells of the glomerulus and smooth muscle cells of the arterioles (25, 37). Thus, it is unlikely that tumors derived from the mesenchymal cells of the renal cortex would be capable of bipotential differentiation into epithelial as well as mesenchymal elements, as is held by proponents of the nephroblastoma classification. It is likely, however, that tumors so derived should be capable of differentiation into vascular components. Ultrastructural examination of DMN-induced mesenchymal tumors has confirmed their vascular basis (G. C. Hard and W. H. Butler, in preparation).

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REFERENCES

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Fig. 1. Adenocarcinoma 4 months after DMN treatment. Small nests of adenocarcinoma (arrows) invade the normal parenchyma beyond the periphery of the parent tumor (left). H & E, X 110.

Fig. 2. A highly anaplastic adenocarcinoma which appears to be growing by invasion, 12 months after treatment. A preexisting tubule (7) has been engulfed and sequestered within the mass. Arrow, mitosis. H & E, X 260.

Fig. 3. Mesenchymal tumor 12 months after treatment. The predominant cell form is spindle shaped. Characteristically, the tumor cells are aligned in many layers around a preexisting renal tubule. H & E, X 260.

Fig. 4. Mesenchymal tumor 8 months after treatment. The cells are arranged in a herringbone pattern characteristic of fibrosarcoma. H & E, X 260.

Fig. 5. A densely cellular fibrosarcomatous area of a mesenchymal tumor 10 months after treatment. Some cells appear to be arranged in palisades or rosettes. The latter arrangement has led to pseudotubule formation. Mitoses are abundant in such areas. HPS, X 260.

Fig. 6. Mesenchymal tumor 11 months after treatment. Stellate cells supported by a fine stromal network resemble primitive mesenchymal and encircle preexisting tubules. H & E, X 125.

Fig. 7. Highly cystic area of a mesenchymal tumor 7 months after treatment. One cystic structure is associated with a preexisting glomerulus (arrow). H & E, X 50.

Fig. 8. Mesenchymal tumor 12 months after treatment. Proliferation of tumor cells has formed indentations into the lumens of preexisting renal tubules (arrow), mimicking primitive glomerulus formation. The tubule epithelium, in addition, exhibits a degree of hyperplasia. H & E, X 120.

Fig. 9. Area of mesenchymal tumor 11 months after treatment, in which densely staining bands and whorls of collagen-like material are prevalent. Arrow, preexisting sequestered renal tubule. Verhoeff-Van Gieson, X 110.

Fig. 10. Mesenchymal tumor 12 months after treatment. A preexisting renal tubule sequestered within a mesenchymal tumor exhibits hyperplasia of the lining epithelium. HPS, X 260.

Fig. 11. Fibrosarcomatous area of a mesenchymal tumor 11 months after treatment, in which spindle cells are condensed into highly cellular aggregates around collapsed preexisting renal tubules (arrows). Mitoses are numerous. H & E, X 260.

Fig. 12. Mesenchymal tumor 8 months after treatment. Bands of smooth muscle encircle areas of primitive mesenchyme, within which are located nests of transitional epithelium (arrows). HPS, X 110.

Fig. 13. Fibers of striated muscle separated by collagenous matrix within a mesenchymal tumor at 8 months after treatment. PTAH, X 410.

Fig. 14. Large cells with bizarre nuclei in a mesenchymal tumor 12 months after treatment. Many of these cells have the tintorial properties of muscle and the appearance of rhabdomyoblasts. HPS, X 260.

Fig. 15. Area of mesenchymal tumor with the appearance of cavernous hemangioma, 12 months after treatment. H & E, X 110.

Fig. 16. Highly cellular area of mesenchymal tumor which contains numerous vascular clefts characteristic of hemangiopericytoma 10 months after treatment. H & E, X 110.

Fig. 17. Very cellular area of mesenchymal tumor 10 months after treatment, in which the constituent cells appear to circumscribe numerous small spaces that may contain erythrocytes. H & E, X 260.

Fig. 18. Metastasis of renal mesenchymal tumor 9 months after treatment. A nodule on the surface of the liver has arisen by peritoneal seeding. H & E, X 110.
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