Induction of Nephroblastomas in the Rat with Dimethylnitrosamine

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Summary. Highly anaplastic renal tumors (nephroblastoma type) have been induced regularly in rats fed dimethylnitrosamine. In the course of carcinogenesis, proliferative lesions — renal oval cell proliferation — have been commonly observed in the contralateral kidney. To elucidate the histogenesis of the nephroblastoma the histological structure of these tumors and the proliferative lesions are compared. It is assumed that the tumor develops from blastic reserve cell elements in the kidney which possess the potentialities of metanephrotic elements.

In 1959 Magee and Barnes and later Zak et al. (1960) found that adenomas and malignant anaplastic renal tumors occurred in rats fed dimethylnitrosamine (DMN). In systemic studies on the carcinogenic effects of different nitrosamines Deuckrey et al. induced renal tumors even after single application of the carcinogen. These renal tumors have been studied morphologically by Hamperl and by Thomas and Schmähl (1964). In two experiments initially planned for studying liver carcinogenesis with DMN a high incidence of nephroblastomas was observed. These observations as well as those of early stages in the formation of renal tumors are the subject of this report.

Materials and Methods

Male albino rats, local strain, weighing 120g, were used. Group 1: Ten animals were given 1 mg DMN per rat per day in the drinking water to a total dose of 185 mg. Group 2: Fifteen rats received 2 mg DMN per rat per day in the drinking water to a dose of 420 mg. Group 3: As controls, 150 male rats were observed and kept untreated. No spontaneous tumors were discovered in the control group. The renal tumors were studied histologically. Glucose-6-phosphatase activity after Wachstein and Meisel was examined on cryostat sections.

Results and Discussion

On the 240th day the animals from group 1 were sacrificed. Necropsy revealed large renal tumors in 4 rats, the remaining rats showed nodular and cystic lesions in the liver as well as one papilloma of the ureter. Necropsy performed on the rats of group 2 on the 270th day disclosed a high incidence of nephroblastomas (in
12 out of 15 animals). The contralateral kidney of a large number of rats fed the carcinogen contained grayish nodules of hyperplastic tissue (Fig. 1).

The renal tumors consisted of numerous oval and spindle cells with intensively stained nuclei and scarce cytoplasm. At places cellular elements gave the impression they formed smooth-muscle fibrils; in other regions they appeared very poorly differentiated. Single glandular formations with epithelial lining where a characteristic feature of these tumors. In a few of the tumors near the capsule glomerulus-like structures were seen which suggested an organoid differen
tiation in the tumor. Chondro-osteoid tissues, as described by Magee and Barnes (1959, 1962), were absent. Neither the sheets of tumor cells nor the epithelial lining of glandular structures gave a positive reaction for glucose-6-phosphatase (Fig. 2a, 2b).

The proliferation of grayish tissue which usually occurs in one of the poles of the cortex of the contralateral kidney is of particular interest. With the marked destruction of the tubular epithelium in these regions, we observed proliferation of young cells with oval nuclei and scanty cytoplasm. These cells which we call "oval cells" invade between damaged tubules, their proliferation begins under the capsule of the kidney where renal tubules are almost lacking. The proliferating cells form either small nests or grow diffusely. At places the formation of new tubules can be seen, although in these instances an ingrowth of the pre-existing tubules by oval cells can not be excluded. Near the preserved renal parenchyma the proliferating cells clearly surround preexisting renal tubules, arranging themselves concentrically around the basement membrane (Figs. 3, 4).

Since the histogenesis of the renal tumors referred to here as nephroblastomas remained nuclear, several intriguing questions arose. What is the cellular origin of these tumors? Anaplastic renal tumors may develop from the epithelium of the tubules, from the epithelium of the kidney papilla or from the interstitial cells. The first probability should be rejected because of the lack of any tendency of the tumors to form tubules. Single glandular formations in the tumors arose from the same markedly poorly differentiated cells as did the remaining tumor parenchyma. The possibility of malignant transformation of the renal stroma should also be rejected since the tumors show the formation of smooth muscle fibres, glandular structures and a tendency for glomerulus-like formations.

The histology of nephroblastomas induced with DMN in adult rats suggest the origin of the tumors from primitive poorly differentiated stem cells. It is probable that a regeneration of renal tissue starts from these cells during continuous parenchymal damage produced by the carcinogen; ultimately malignant transformation is brought about. The proliferating young oval cells observed in the contralateral kidney are quite similar to those in the tumors, a fact supporting such a