Report of a Workshop on Classification of Specific Hepatocellular Lesions in Rats

On December 11 to 13, 1974, The National Cancer Institute sponsored a workshop in Silver Spring, Md. on the classification of hepatocellular tumors and related lesions of rats. There were 20 participants with extensive and varied experience in pathology and experimental carcinogenesis.1 The results of studies in the Carcinogenesis Program of the National Cancer Institute and elsewhere have shown fundamental differences of opinion regarding the nature and significance of certain liver lesions in rats. There have also been problems that are semantic and have hampered communication among scientists and concerned laymen.

The Carcinogenesis Bioassay Program of the National Cancer Institute has broad responsibility for detecting environmental carcinogens and depends upon the evaluation of specific tumor diagnoses by the National Cancer Institute and collaborating scientists throughout the country. Of prime importance in many of the results is the interpretation of proliferative lesions of rodent livers. It is vital to the goals of the Program that these lesions are properly classified and a nomenclature agreed upon.

Research efforts in rat liver carcinogenesis have produced new information on the biological processes involved and have permitted a more objective basis for morphological interpretations. It was the purpose of the workshop to consider the experimental data together with specific diagnostic problems in an effort to determine the nature and significance of the lesions in question. At a minimum, a more uniform nomenclature was needed.

Slides of rat livers were selected from several sources to provide a representative spectrum of hepatocellular lesions frequently encountered. Duplicate sets were prepared from formalin-fixed tissues, stained with hematoxylin and eosin, and distributed to the participants in advance of the workshop. No information concerning animal history or test compounds, if any, was provided. Diagnoses and opinions regarding the neoplastic nature of the lesions were submitted anonymously and the results were tabulated and distributed at the workshop.

Recommended classification of specific hepatocellular lesions in rats

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<td>D. With glandular and/or papillary formation</td>
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| IV. Cholangiofibrosis       |

1The participants of the Rat Liver Tumor Workshop were Dr. P. Bannasch, Dr. Frederick F. Becker, Dr. William Busey, Dr. Emmanuel Farber, Dr. Harlan I. Firminger, Dr. F. M. Garner, Dr. W. Gössner, Dr. Gert L. Lauque, Dr. C. Alastair Moodie, Dr. Hans Popper, Dr. Melvin Reuber, Dr. Alfred Schauer, Dr. Katherine C. Smell, Dr. Robert A. Squire, Dr. Stephen Sternberg, Dr. Harold L. Stewart, Dr. John D. Strandberg, Dr. Richard W. Voelker, Dr. Donald A. Willigan, and Dr. C. Zurcher.

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Neoplastic Nodules (Figs. 4 to 10). This term was recommended to replace so-called “hyperplastic nodules,” which are thoroughly described in the literature. They are generally spherical lesions that usually occupy an area equivalent in size to that of several liver lobules, and the normal liver architecture is absent within the nodules. The hepatocytes within the nodules are similar to those in the foci or areas and may show mixtures of the cytoplasmic alterations. Mitoses and varying degrees of nuclear atypia including enlargement, hyperchromasia, doubling in number, and enlarged nucleoli are sometimes present. The cells may be arranged in solid or jumbled sheets or in irregular plates, one or more cells thick. Sinusoids may be compressed by enlarged hepatocytes or show varying degrees of dilation or ectasia. Portal areas are usually not present, although in rare cases they may be localized inside the nodules. An important feature is the architectural distortion and sharp demarcation of the nodule from surrounding liver around at least a portion of its periphery. The plates of nodule cells are usually not continuous with those of unaffected liver; rather they impinge perpendicularly or obliquely upon the tangentially arranged normal plates. The latter are often narrowed due to compression by the expanding nodule.

The decision to recommend the term neoplastic nodule was based upon the experimental and biological evidence available. Such nodules are proliferative lesions and are known to be induced by carcinogens and, at the least, they indicate an increased probability for the development of hepatocellular carcinoma. Although they may occur in control animals, the incidence is low, as is the incidence of naturally occurring hepatocellular carcinoma.

Stedman’s Medical Dictionary defines hyperplasia as “An increase in number of cells in a tissue or organ, excluding tumor formation, whereby the bulk of the part or organ is increased” (1). Thus the traditional term hyperplastic nodule was considered to be a misnomer by the majority of the participants, who felt these lesions to be neoplastic in nature.

Hepatocellular Carcinoma (Figs. 11 to 23). The diagnosis of hepatocellular carcinoma was based upon characteristic histological and cytological features that are well documented in the pathology literature. The following descriptions pertain to the specific slides discussed at the workshop and are not inclusive for all hepatocellular carcinomas in rats.

The hepatocellular carcinomas are usually considerably larger and more irregular than neoplastic nodules, and they may involve major portions of liver lobes. At the periphery they compress or extend into the surrounding parenchyma. Trabecular carcinomas may be classified as well to poorly differentiated, depending upon their resemblance to normal liver. Tumor cells are in broad sheets or in plates 1 to several cells in thickness. The latter are haphazardly arranged in linear, papillary, or pseudocinar patterns. Tumor cells may also be individualized or in isolated nests and cords enveloped by lining cells. A histological variant of hepatocellular carcinoma is the carcinoma with a predominantly glandular, papillary pattern, resembling adenocarcinoma.

The tumor cells may resemble normal hepatocytes, or they may be enlarged or anaplastic in less well differentiated tumors. The cytoplasm may be clear, eosinophilic, or hyperbasophilic and nuclei are frequently enlarged and hyperchromatic. Multiple nuclei and mitotic figures may be present.

Detection of vascular invasion or metastases was not considered essential for the diagnosis of hepatocellular carcinoma.

It was concluded that benign hepatic cell tumors, i.e., without potential for malignant behavior, could not be recognized in rats. Therefore, terms such as “adenoma” were not recommended. It was also agreed that the term “hepatoma” was imprecise in its usage and was not recommended for any of the lesions under discussion at the workshop.

Cholangiofibrosis (Adenofibrosis) (Fig. 24). This lesion is characterized by foci or areas of hyperbasophilic, atypical ducts in a fibrous stroma. The nature of the lesion is controversial. In most cases, however, there later develops an excessive formation of collagen or of cystic glandular spaces.

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REFERENCES
Fig. 1. Clear cell focus. Note empty appearance of cytoplasm of altered cells. H & E, × 210.

Fig. 2. Eosinophilic, ground glass focus. Note characteristic appearance of cytoplasm of altered cells. H & E, × 150.

Fig. 3. Basophilic focus. Note diffusely basophilic cytoplasm of altered cells. H & E, × 140.

Fig. 4. Neoplastic nodule consisting primarily of eosinophilic ground glass cells. H & E, × 115.

Fig. 5. Edge of neoplastic nodule in Fig. 4. Note compression of surrounding liver plates. H & E, × 130.

Fig. 6. Neoplastic nodule consisting of eosinophilic and basophilic cells in a trabecular pattern. H & E, × 50.

Fig. 7. Edge of neoplastic nodule in Fig. 6. Note perpendicular arrangement of plates in nodule and compression of surrounding parenchyma. H & E, × 220.

Fig. 8. Large neoplastic nodule occupying major portion of liver lobe. There are areas of sinusoidal dilation within the nodule. Arrows, periphery of the nodule. H & E, × 7.

Fig. 9. Edge of neoplastic nodule in Fig. 8 showing compression of surrounding liver plates. H & E, × 80.

Fig. 10. Detail of neoplastic nodule in Fig. 8 showing sinusoidal dilation and distortion of plate arrangement. H & E, × 80.

Fig. 11. Hepatocellular carcinoma. Note thickened and haphazardly arranged plates and variations of patterns between adjacent areas. H & E, × 55.

Fig. 12. Hepatocellular carcinoma showing sinusoidal dilation and haphazardly arranged plates. H & E, × 140.

Fig. 13. Hepatocellular carcinoma. Note irregular blunted plates 2 or more cells thick. H & E, × 225.

Fig. 14. Hepatocellular carcinoma. Hepatocytes are isolated and in nests. Note 2 pseudoacinus formations. H & E, × 490.

Fig. 15. Hepatocellular carcinoma, poorly differentiated. Anaplastic tumor cells are in sheets and nests. Nuclei are large and vesiculate with prominent nucleoli. H & E, × 270.

Fig. 16. Hepatocellular carcinoma, poorly differentiated, showing bizarre tumor giant cells. H & E, × 270.

Fig. 17. Hepatocellular carcinoma, poorly differentiated. Note vascular invasion. H & E, × 225.

Fig. 18. Small hepatocellular carcinoma composed of diffusely basophilic cells. Arrows, edges of tumor and nodular aggregate in center. H & E, × 20.

Fig. 19. Edge of hepatocellular carcinoma shown in Fig. 18. Note individualized hyperbasophilic cells and compression of surrounding liver plates. H & E, × 225.

Fig. 20. Edge of nodular aggregate of cells in center of carcinoma shown in Fig. 18. The cells are enlarged and in jumbled sheets and cords. There is compression of the surrounding tumor mass. H & E, × 350.

Fig. 21. Same as Fig. 20 showing greater detail and mitotic figures. The presence of this proliferative nodular aggregate within the larger basophilic lesion resulted in a diagnosis of hepatocellular carcinoma. H & E, × 350.

Fig. 22. Hepatocellular carcinoma, glandular papillary pattern. H & E, × 125.

Fig. 23. Hepatocellular carcinoma, glandular papillary pattern. H & E, × 350.

Fig. 24. Cholangiofibrosis (adenofibrosis). Note hyperchromatic ducts within a fibrous stroma. H & E, × 140.
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