Comparative Histopathology of the Development of Selected Neoplasms of the Liver, Pancreas, and Urinary Bladder in Rodents

by Dante G. Scarpelli*

The valid extrapolation of carcinogenesis data from one species to another depends, in part, on strong similarities of the metabolic and cellular mechanisms involved in the carcinogenic process and similarities in the nature and behavior of the various lesions that appear during the development of neoplasia between the species involved. Although there are many biological differences between the various rodent species used in carcinogenesis research, there are more similarities, in keeping with the surprising unity of basic cellular and tissue organization and function that is evident throughout biological systems at every level of evolutionary development. An understanding of intraspecies similarities and differences, especially as these modify the morphologic responses of the host to carcinogenic chemicals, is of central importance if carcinogenesis data from one species are to be used to predict carcinogenic risk in another. In this manuscript the histopathology of the various lesions that appear during chemically induced cancer of the liver, pancreas, and bladder in several rodent species has been selected to compare and contrast similarities and differences that exist among them and among the spontaneous premalignant lesions and carcinomas of these organs in humans.

Process of Chemical Carcinogenesis

Numerous studies have established that foreign compounds, including chemical carcinogens, are handled in a strikingly similar way by a wide variety of animal species, including lower vertebrates and certain invertebrates (1). The general pattern by which the organism protects itself from potentially noxious substances, many of which are lipophilic and enter cells, involves their metabolic conversion to more polar and more water-soluble metabolites, which are rapidly excreted. This property of cells, especially those at the portals of entry into the body, affords the organism an advantage for surviving in a hostile environment. This protective phenomenon is not foolproof, because during the biotransformation of certain chemicals, metabolites are formed that are highly reactive and toxic to the cell. In some cases, the host converts a chemical carcinogen that in its original form is nontoxic and noncarcinogenic to a form that is both toxic and carcinogenic.

Present dogma holds that DNA is the intracellular target molecule with which highly reactive metabolites of carcinogens react. This causes either serious physical distortion of the DNA double helix by intercalation of planar molecules, such as aromatic amines and polycyclic hydrocarbons, or base substitution throughalkylation by alkyl nitrosamines or nitrosamides. If these defects are not removed and repaired before the DNA is replicated, they are amplified and become fixed and persist through the replication process. This earliest recognized stage of carcinogenesis, designated as initiation, is considered to occur rapidly and to be heritable and irreversible. A significant property of initiated cells that has been identified in the past several years is that initiated cells acquire resistance to the cytotoxic and cytostatic effects of chemical carcinogens. This is due to a decrease in the intracellular levels of the enzymes responsible for the metabolic activation of carcinogens and a concomitant increase in the levels of those responsible for detoxification by conjugation and esterification (2). Thus, initiated cells have undergone adaptations that allow them to proliferate during continued exposure to a carcinogen while their adjacent, noninitiated counterparts are growth-inhibited, or, if sufficiently injured by toxic metabolites, these noninitiated cells ultimately die. The death of noninitiated, lethally damaged cells serves as a potent stimulus for compensatory growth, which leads to selective growth of the initiated cells, a phenomenon designated as clonal selection (3). The expansion of initiated cell populations

*Department of Pathology, Northwestern University Medical School, Chicago, IL 60611.  

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gives rise to islands, foci, and nodules of cells that show phenotypic differences as compared to noninitiated cells. While most of these early events in carcinogenesis were identified and documented from studies of experimental liver carcinogenesis in rats (3–5), preliminary evidence suggests that they probably also occur during carcinogenesis in other organs as well, although this remains to be established unequivocally.

The transformation of initiated cells with the phenotypic and biological characteristics of neoplasia that occurs during a second, more protracted, stage of carcinogenesis is designated as promotion (3,6). This is much less well understood than initiation and remains a prime facet of contemporary research on carcinogenesis. Promotion is mediated by exposure of the host to a diverse group of substances, which include weak chemical carcinogens, low levels of potent carcinogens, growth factors, hormones, polyunsaturated fats in the diet, and certain noncarcinogenic compounds such as phenobarbital. The sequence of exposure to promoters is important, as they are effective only if encountered after initiation has occurred. While the mechanism(s) of promotion are complex and remain to be elucidated, several general effects common to many promoters have been identified, namely, the stimulation of cell growth or the modulation of differentiation, or for some promoters, both effects have been identified. Promotion, like initiation, has been documented to be operative during carcinogenesis in a variety of organs such as skin, lung, liver, pancreas, gastrointestinal tract, kidney, and urinary bladder. The general process of carcinogenesis is shown in Figure 1.

Some Interspecies Comparisons of Chemical Carcinogenesis

Hepatocarcinogenesis

Since the rodent liver, especially that of the mouse and rat, is susceptible to a variety of chemical carcinogens administered by diet or injected IP, it is important to compare and contrast the variety of proliferative, preneoplastic, and neoplastic lesions that develop in the two species. Although the mouse is widely used in chemical carcinogenesis research and testing, it has not been the species of choice for experimental liver carcinogenesis experiments. In part, this may be ex-

![Figure 2](image-url) An island of altered hepatocytes in rat liver following a single exposure to diethylnitrosamine (DEN). Note the absence of compression of adjacent normal liver cells. H & E, × 400.

![Figure 3](image-url) An early hepatic nodule in the rat showing marked cytologic abnormalities of liver cells and compression of adjacent normal liver indicating its proliferative capacity. H & E, × 355.
FIGURE 4. DEN-induced hepatocellular carcinoma in the rat characterized by a disorganized tissue architecture, cellular atypia, and numerous cells in mitosis. H & E, × 400.

FIGURE 5. Basophilic nodule in mouse liver following a single dose of DEN administered at 15 days of age. H & E, × 150.

Table 1. Histochemical properties of diethylnitrosamine-induced foci in mouse and rat liver.

| Histochemical marker                  | Mouse                  | Rat                  |
|--------------------------------------|------------------------|----------------------|
| Adenosine triphosphatase             | ↓ Cytoplasmic          | ↓ Membrane bound     |
|                                      | ↑ Membrane bound       |                      |
| Acid phosphatase                     | ↓                      | ↓                    |
| Glucose-6-phosphatase                | ↓                      | ↓                    |
| Glucose phosphate dehydrogenase     | ↑                      | ↑                    |
| γ-Glutamyl transpeptidase            | No change              | ↑ ↓ *                |
| Periodic acid Schiff reaction        | ↑                      | ↑                    |

*Appears to be related to the carcinogen employed.

Table 2. Lesions induced by carcinogens in mouse and rat liver.

| Lesion                          | Mouse | Rat |
|---------------------------------|-------|-----|
| Clear cell                      | Rare  | +   |
| Glycogen storage                | ?     | +   |
| Basophilic                      | +     | ±   |
| Basophilic nodule with vascular | +     | -   |
| invasion                        |       |     |
| Acidophilic                     | Rare  | -   |
| Megalocyte                      | Rare  | +   |
| Hyperplastic                    | +     | +   |
| Neoplastic                      | +     | +   |
| Carcinoma                       | +     | +   |

explained by the finding some years ago that inbred mice, especially the C3H and CBA strains, are prone to a high incidence of spontaneous hepatic tumors, including hepatocellular carcinoma (7). Strain C57BL mice, on the other hand, as well as crosses with C3H, have a low hepatic tumor incidence and are used in studies involving hepatocarcinogenesis. Grasso and Crampton (8) questioned the validity of the mouse as an animal model for carcinogenesis studies and the bioassay of chemicals on the grounds that its responses to carcinogens differ significantly from those of the rat and other mammals. This notion was later refuted in a carefully annotated survey of the literature reporting results from laboratories worldwide (9), which documented that the responses of mouse liver and other organs to hepatic microsomal enzyme inducers and chemical carcinogens are not unique. These responses include the development of tumors, and in many instances, are similar to those seen in other rodents such as the rat and hamster.

Chronic exposure of both the mouse and rat to hepatocarcinogens leads to the development of a spectrum of lesions ranging from foci of phenotypically altered hepatocytes with little or no evidence of augmented growth, to those forming nodules due to enhanced growth, and finally to hepatocellular carcinomas with all of the cytologic and biological attributes of malignancy (Figs. 2–5). In the rat, the development of chemically induced liver cancer has been studied in considerable detail (3,4). The early morphologic alterations of liver cells include increased eosinophilia or basophilia of the cytoplasm, and cytoplasmic accumulation of neutral
fat or glycogen that gives rise to clear cells. Early lesions consist of cells with minimal cytologic changes; as these progress, they show histochemical, biochemical, and cytologic features that differ significantly from those of normal liver cells.

More recently, these lesions have also been identified in the early stages of diethylnitrosamine (DEN)-induced hepatocellular carcinogenesis in B6C3F1 mice (10). The histochemical patterns of such foci in mouse liver are similar to those in the rat, with a few exceptions, such as ATPase and γ-glutamyltranspeptidase, for which the pathogenetic significance is not understood. These are compared and summarized in Table 1. As foci assume greater autonomy from host growth control factors, they grow into nodules that compress adjacent liver cells. More often than not, the liver cells in such nodules show cytologic changes associated with malignancy such as large hyperchromatic nuclei and nucleoli and increased numbers of cells in mitosis. Nodules are classified as hyperplastic or neoplastic, depending on the extent to which liver cell morphology and liver tissue organization differ from normal. These nodules are followed by the appearance of nodules with all the morphologic and biologic features of liver cell cancer. The various types of lesions induced by carcinogens in mouse and rat liver are compared in Table 2.

The salient difference between the two species is that lesions in the mouse tend, in general, to be more well-differentiated than those in the rat. This species difference may make the morphological distinction between nonneoplastic and neoplastic liver in the mouse difficult, and has caused much confusion and controversy, until it was established that some hepatocarcinomas that were almost indistinguishable from nonneoplastic hyperplastic lesions were indeed capable of metastases to distant sites such as the lung. Similar difficulties were encountered in a recent study that attempted to assess the potential of the various types of benign and malignant spontaneous hepatic nodules in B6C3F1 mice and those induced by a chlorinated hydrocarbon pesticide to grow following their transplantation into syngeneic hosts. It was concluded that morphology alone was not adequate for predicting the capacity of mouse liver nodules for autonomous growth (11).

An interesting property of basophilic nodules in the mouse that differs from similar lesions in the rat is their capacity to invade adjacent intrahepatic blood vessels (Fig. 6). This finding, which has been interpreted as evidence of malignant behavior (12), is curious because it is often encountered in small foci and nodules early in the carcinogenic process and is much less frequent, and often absent, in much larger nodules in the later stages of cancer development. This finding is counter to what one would expect if permeation of intrahepatic blood vessels in the mouse were indeed a reflection of malignancy. Its biological significance remains unclear.

The pathogenesis and histopathology of experimental liver cancer in rodents are strikingly similar to human hepatocellular carcinoma in many respects. In contrast to the rat and mouse, cirrhosis is a frequent precursor concomitant to hepatocellular carcinoma in man (13,14). Focal liver cell nodules showing phenotypic alterations and augmented growth have been identified as precursors to the development of liver cell cancer in humans, although it has not been possible to study these as thoroughly as those induced in experimental animals. For example, it has not yet been established that the histochemical spectrum of lesions documented in the rat and mouse also develops in humans. However, glycogen-rich liver cell lesions and carcinomas have been documented in humans, as well as proliferative nodules consisting of markedly atypical cells, so-called liver cell dysplasia. The status of liver cell adenomas in humans appeared unclear (13); some years ago, when such lesions appeared in patients on oral contraceptives and anabolic steroid medication, it was suggested that these adenomas might represent antecedent lesions for hepatocellular carcinoma. Our experience 10 years after the emergence of adenomas in some patients on oral contraceptives indicates that most of these do not progress to malignancy and, in fact, regress when such medication is discontinued. It appears that spontaneous hemorrhage is the predominant serious complication. On the other hand, anabolic steroids, which enjoy wide use among athletes, induce adenomas, some of which have been documented to evolve to hepatocellular carcinomas.

There are many similarities between the morphological aspects of chemically induced hepatocarcinogenesis of rodents and humans that suggest that they are probably valid models for carcinogenesis testing. How-
ever, difficulties in correlating the morphology of hepatic nodules in the mouse with their biological behavior, coupled with the apparent increased sensitivity of mouse liver to chemical carcinogens, somewhat limits the usefulness of hepatic nodules as models. The rat model, on the other hand, suffers from none of these problems and continues to be widely used for testing of chemicals for their potential as hepatocarcinogens.

Pancreatic Carcinogenesis

An alarming and sustained increase in the incidence of pancreatic carcinoma in many parts of the world has served as an impetus for the development of rodent animal models to study its causes and pathogenesis. At the present, Syrian golden hamsters and rats are widely used experimentally (15,16) and have added significantly to our understanding of pancreatic carcinogenesis. For reasons that are not immediately apparent, different cells of the pancreas appear to be susceptible targets to the chemicals that induce pancreatic cancer in the two species. In the rat, a variety of carcinogens [7,12-dimethylbenz[a]anthracene, 4-hydroxyaminoquinoline-1-oxide (4HAQO), azaserine, N,N\((N\text{-methyl-N-nitroso(carbamoyl)}\)\(\text{l-ornithine, and certain hypolipidemic drugs}\) induce carcinomas of acinar cells, which comprise about 84% of the cells of the pancreas. In humans, acinar cell carcinomas represent only 1% of all cases of pancreatic cancer. The major focus in this manuscript will be on the pathogenesis and histopathology of ductal adenocarcinoma in the hamster pancreas. In the hamster, \(\beta\)-oxidized derivatives of \(N\text{-nitrosodipropylamine induce adenocarcinomas of the ducts, a cell that constitutes less than 4% of the component cells of the pancreas. These neoplasms bear a close morphological and biological resemblance to the most common type (96% of all cases) of pancreatic cancer encountered in humans. This species difference in the histologic type of neoplasms induced by chemical carcinogenesis is of considerable interest because the acinar cell in both species is susceptible to carcinogens.}

Acinar cell lesions in the rat begin as localized groups of acini that undergo augmented growth and evolve from microscopic foci to millimeter-sized nodules (15,16), the larger of which are classified as adenomas. The majority of these lesions consist of large acinar cells packed with zymogen granules that are responsible for their intense acidophilic staining with the hematoxylin-eosin staining (Fig. 7). Large nodules and adenomas contain acinar cells with a greater degree of nuclear and nucleolar variability and are frequently not surrounded by a connective tissue capsule. Acinar cell carcinomas range from well-differentiated tumors comprised of zymogen-granule-rich tumor cells to those in which the neoplastic cells contain sparse granules (Fig. 8) or none at all. In the latter, in vitro studies have shown that these cells synthesize and secrete pancreatic enzymes, suggesting that the absence of cytoplasmic granules is probably due to a defect in the function of the Golgi complex. Depending on the level of differentiation, aci-
Pancreatic acinar cell carcinomas spread by local extension, invasion, and distant metastases.

Two other acinar cell lesions include basophilic foci and pseudoduct formation. Basophilic acinar cell foci consist of cells that are largely depleted of zymogen granules, have a low capacity for growth, and persist. They are seen many months following exposure to a carcinogen. Their biological significance remains unclear. An intriguing alteration of acini, which is often seen in rats exposed to pancreatic carcinogens, consists of their conversion to ductlike profiles referred to as pseudoductules (17). Pseudoductules are formed by a dilation of acini and shedding of the apical cytoplasm of the acinar cells so the ducts appear to be lined by acinar cells containing variable numbers of zymogen granules. This alteration is considered an example of cell modulation, as contrasted to true metaplasia where one cell type is converted to another.

Detailed studies of the lesions induced in pancreatic ductules and of the hamster ducts by various derivatives of β-oxidized-N-nitrosodipropylamine have documented that the earliest changes involve a proliferation of ductules and a peculiar, permanent transformation of acinar cells to ductulalike profiles indistinguishable from preexisting ones (15,16). This transformation is also accompanied by their augmented growth (Fig. 9). This alteration of ductules was not unexpected since acinar cells are part of the pancreatic duct system. However, the permanent transformation was surprising and is a very interesting facet of pancreatic carcinogenesis. The metaplastic transformation of one cell type to another is an early precedent lesion documented in the pathogenesis of squamous cell carcinoma of the bronchus, uterine cervix, and more rarely, the urinary bladder. Foci of proliferating true ductules and ductules arising from metaplastic acinar cells undergo dysplasia, malignant transformation to carcinoma in situ, and invasive adenocarcinoma. An alternate product of such foci involves the formation of dilated ductules and ducts lined by cuboidal epithelium. Since the epithelium often includes acinar cells that have retained their capacity for the synthesis of zymogen granules, it is believed these ducts arise from metaplastic acinar cells (Fig. 10). Such ducts remain benign lesions that grow slowly to form large complexes of cystic ducts, which are classified as cystadenomas and are often encountered in animals with invasive ductal adenocarcinoma. Larger ducts are also the focus of proliferative, dysplastic, preneoplastic, non-invasive (Fig. 11), and invasive (Fig. 12) malignant epithelial lesions, although epithelial lesions appear to develop later than lesions in ductules and metaplastic acinar cells, suggesting that the epithelium of the large ducts is somewhat less sensitive than that of ductules. Carcinogen-induced lesions of the exocrine pancreata of rat and hamster are compared in Table 3.

The metaplastic transformation of pancreatic acinar

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**Figure 9.** Pseudoductule formation from acinar cells in hamster pancreas following chronic exposure to N-nitroso-bis(2-oxopropyl)amine (BOP). A near normal acinus showing slight dilation of the lumen is shown at the lower right. The intense proliferative activity of acinar cells in this lesion is documented by their uptake of ³H-thymidine. H & E, ×395.

**Figure 10.** Dilated ductules in hamster pancreas in which several acinar cells (arrows) remain in the epithelial lining. These cells identify their origin from pancreatic acini. H & E, ×400.
Carcinogenesis of Urinary Bladder

The lower urinary tract of rodents extends from the kidney pelvis through the ureters to the urinary bladder. It is lined by transitional epithelium (urothelium) and is sensitive to a wide variety of chemical carcinogens. These carcinogens include 26 different amino and noninvasive intraductal adenocarcinoma in the pancreas of a hamster treated chronically with β-oxidized-N-nitrosodipropylamine. H & E, × 240.

Figure 12. An invasive pancreatic ductal adenocarcinoma in hamster pancreas induced by N-nitroso-2,6-dimethylmorpholine. H & E, × 155.

Table 3. A comparison of carcinogen-induced lesions in the exocrine pancreas of rat and hamster.

| Lesions                          | Rat  | Hamster        |
|----------------------------------|------|----------------|
| Acinar cell                      | +    | +              |
| Necrosis                         |      |                |
| Pseudoduct formation (metaplasia)| +    | +              |
| Proliferation                    | +    | +              |
| Ductal complexes                 | -    | +              |
| Ductal cystadenomas              | -    | +              |
| Basophilic foci                  | +    | -              |
| Acidophilic foci                 | +    | -              |
| Acidophilic nodules              | +    | -              |
| Adenomas                         | +    | -              |
| Carcinomas                       | +    | Very rare (mixed acinar-ductal) |
| Duct cell                        | -    | +              |
| Proliferation                    |      |                |
| Metaplasia                       | -    | +              |
| Papilloma                        | -    | +              |
| Carcinoma in situ                | -    | +              |
| Invasive adenocarcinoma          |      | +              |
| Islet cells                      |      |                |
| Intrainsular ductal metaplasia   | -    | +              |
| vs. proliferation                |      |                |
azo dyes, 6 nitrosamines, 6 nitroaryl compounds, and at least 13 miscellaneous compounds, including phenacetin, saccharin, and cyclamate that have achieved considerable notoriety. Since these compounds include important industrial chemicals, environmental pollutants, food additives, bacterial metabolites, and medications, the use of the rodent bladder as a model for the identification of chemicals posing a risk for humans assumes great significance. Thus, it is important to establish the extent to which the pathogenesis of carcinoma of the urinary bladder in the rat resembles the process in humans (20,21). As is true for other experimental carcinogenesis models, much is known about the earliest lesions that develop during bladder carcinogenesis in the rat, as contrasted to the situation in humans where there is a paucity of information about the very early lesions because patients are usually asymptomatic at this stage of their disease and are not biopsied.

Simple hyperplasia is the earliest response of urothelium to exposure to carcinogens; this leads to cell replication with an increase of epithelial thickness consisting of four or more cell layers and no alteration of cell maturation. With continued exposure, these changes evolve to nodular and papillary hyperplasia, papilloma (Fig. 13), and noninvasive carcinoma. Some simple, nodular, and papillary hyperplasias regress and the urothelium tends to return to normal if the carcinogenic stimulus is removed. However, not all simple, nodular, and papillary hyperplasias regress, and when they persist, they progress to more advanced lesions. In the case of simple hyperplasia, two pathogenetic pathways culminating in invasive transitional cell carcinoma have been identified: (a) flat dysplasia with noninvasive carcinomas, and (b) nodular hyperplasia, polypoid inverted papilloma, dysplasia, and polypoid noninvasive carcinoma. In the case of papillary hyperplasia, the sequence involves papilloma, dysplasia, and papillary noninvasive carcinoma terminating in invasive carcinoma.

The pathogenesis of human bladder cancer has many parallels to the pattern in the rat and hamster. Although it is very likely that simple hyperplasia is a frequent early lesion, it has only rarely been encountered for the reasons cited earlier. However, the later lesions, which include papilloma, inverted papilloma, dysplasia, papillary and nonpapillary noninvasive transitional cell carcinoma, and invasive carcinoma, have all been established in man. Metaplasia of urothelium to squamous epithelium due to sustained exposure to carcinogens appears to be much more common in the rat (Fig. 14) and hamster than in humans (Fig. 15) in the Western World. In the Near East and other parts of the world, on the other hand, where infestation of the urinary bladder by schistosomal parasites is widespread, squamous metaplasia, squamous papilloma, and squamous carcinoma of the bladder are frequently encountered.

Another, though much rarer, metaplastic variant en-
Conclusions

The morphology and sequence of proliferative, preneoplastic, and neoplastic lesions seen during the experimental induction of hepatocellular carcinoma in the mouse and rat, ductal adenocarcinoma of the pancreas in the hamster, and transitional cell carcinoma of the urinary bladder in the rat and hamster bear a close resemblance to those encountered in humans. Although these qualitative features in some measure serve to validate rodent models for bioassays of carcinogenesis, other biological factors must be taken into account before carcinogenesis data gained from such studies can be extrapolated to the estimation of human risk (22). These other factors include the pharmacokinetics and metabolism of the particular carcinogen in question, which greatly affect the sensitivity of the host. While it would be ideal to know all the details of the absorption, organ and tissue distribution, and metabolic handling of carcinogens before testing them in animal bioassays in order to draw valid conclusions about their potential risk for humans, this is seldom the case. The situation is further complicated by the antagonistic dialogue that invariably ensues between federal regulatory agencies and industry, goaded by the news media and concerned citizens, when a chemical to which there is significant human exposure is identified to be a potential human carcinogen. These events often preclude the further detailed studies needed to allow meaningful extrapolation of animal bioassay data to humans. Until we learn how to cope with these problems, it is important that regulatory decisions be based on impeccable experiments and good science and are not a result of the pressures of society or industry.

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