ANIMAL MODEL OF HUMAN DISEASE

Carcinoma of the Pancreas in Azaserine-Treated Rats

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Biologic Features

PANCREATIC CARCINOMAS have been induced by azaserine in Wistar[1-4] and Lewis rats[5] fed standard laboratory chow or defined diets. There are significant differences in response to azaserine between species and rat strains. Lewis (LEW) rats are more sensitive and more uniformly responsive than are random-bred Wistar rats. F344 rats, CD-1 mice, strain 13 guinea pigs, and Syrian golden hamsters are clearly less sensitive with respect to induction of pancreatic lesions by azaserine.

The majority of invasive or metastasizing carcinomas have been observed in rats on which autopsies were performed 12 months or more after initial treatment with azaserine. Both solid and cystic carcinomas occur and have originated in the head, body, and tail of the pancreas. Some tumors arising in the head have caused obstruction of the common duct and jaundice. Metastases to regional lymph nodes, liver, and lung have been observed. Lipase, amylase, and trypsin activity have been demonstrated in tumor homogenates, although levels vary from tumor to tumor.

Focal abnormalities of acinar cell differentiation, which we have called atypical acinar cell nodules (AACN), seem to be the earliest sign of azaserine-induced growth abnormality in the pancreas. Ducts remain normal in appearance. AACN appear within 2 months after azaserine treatment and are recognized in increasing numbers over a several-month period, perhaps reflecting growth to a size which is more easily recognized. More than 100 AACN have been counted per pancreas. The phenotypic alterations that characterize the cells in AACN include 1) reduced cytoplasmic basophilia; 2) reduced zymogen content and increased cytoplasmic basophilia, and 3) nuclear abnormalities including enlargement and/or irregular shape.

Some AACN reach a diameter of several millimeters and have been classed as adenomas when they compress the surrounding pancreas and become encapsulated. A small percentage of AACN become increasingly anaplastic and indistinguishable cytologically from lesions that invade and/or metastasize. Such lesions are regarded as localized carcinomas or "carcinoma *in situ*" and have been found as early as 9 months after the first treatment. Carcinomas have been found only in pancreases with multiple AACN.

The pancreatic carcinomas have a wide spectrum of histologic types.[2,6] The majority are pure acinar cell adenocarcinomas with varying amounts of zymogen (Figure 1), while 5–10% are completely undifferentiated carcinomas without evidence of zymogen or acinar pattern (Figure 3). The remainder have a mixture of areas that show acinar cell differentiation and one or more of the following patterns: ductlike carcinoma with desmoplasia (Figure 2); cystic carcinoma with columnar lining epithelium; undifferentiated carcinoma; and microadenocarcinoma composed of very small glands without evidence of zymogen.

The carcinomas are induced by injecting 150–260 mg azaserine/kg (Calbiochem, LaJolla, Calif) dissolved in 0.9% NaCl intraperitoneally in 5–26 divided weekly doses.[2] We have recently induced carcinomas or localized carcinomas in 58% of male and 17% of female LEW rats on which autopsies were performed 15 months after they were given 15 weekly 10 mg/kg injections, beginning at 4 weeks of age. The responses of male rats are consistently greater than the responses of female rats. Our current pre-

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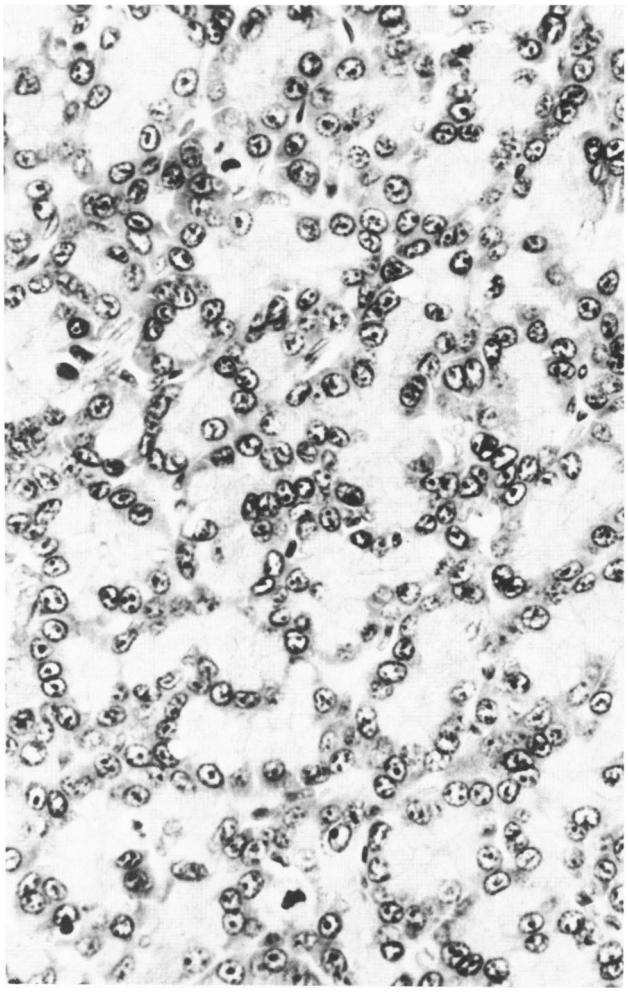

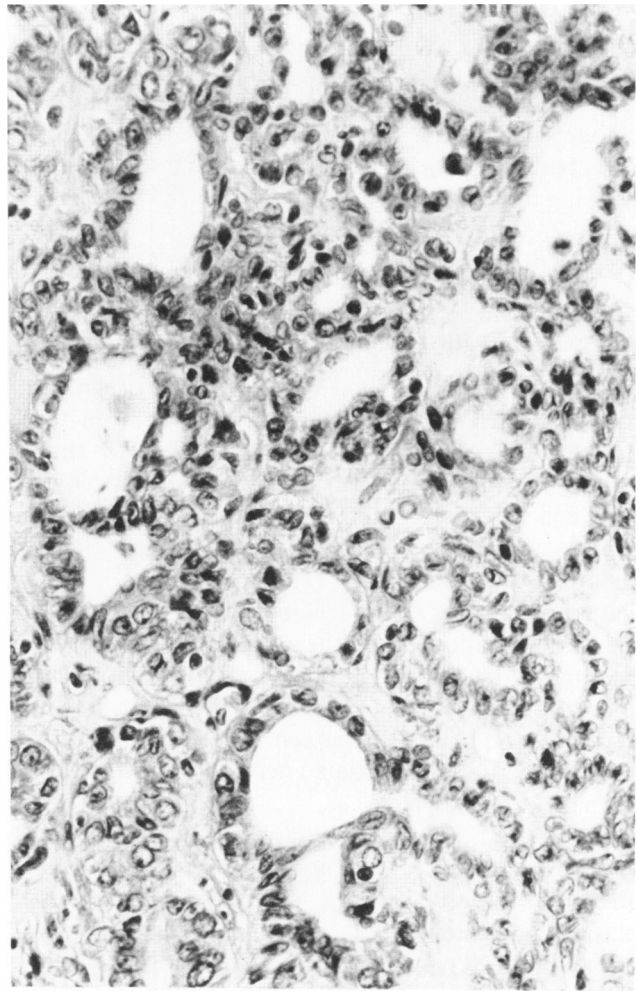

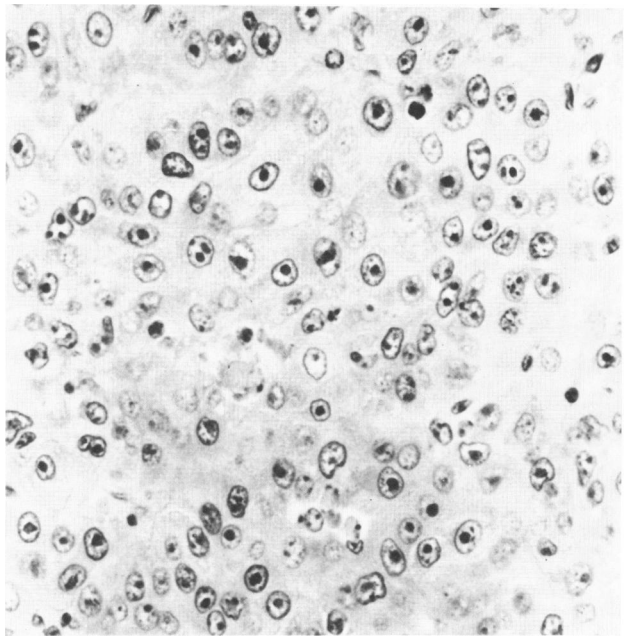

Figure 1—Acinar cell carcinoma from the pancreas of an azaserine-treated rat. (H&E, × 200) **Figure 2**—Ductlike area from an azaserine-induced pancreatic carcinoma. (H&E, × 200) **Figure 3**—Undifferentiated pancreatic carcinoma from an azaserine-treated rat. (H&E, × 200) **Figure 4**—Carcinoma of the head of the pancreas in a rat killed 7 weeks after intrapancreatic transplantation of an azaserine-induced acinar cell carcinoma of the pancreas. The stomach (*top*), duodenum (*left*), and spleen (*right*) are included. The body and tail of the pancreas extend from the neoplasm to the spleen.

ferred regimen in LEW rats is to give 5 weekly injections of 30 mg/kg. Azaserine-induced pancreatic carcinomas have been serially transplanted.[7] Injection of a few 1-cu-mm or smaller fragments of rapidly growing tumor into the head of the pancreas has produced 2–3-cm carcinomas in 3 weeks. Thus a "rapid" version of the model is available (Figure 4).

Comparison with Human Disease

Carcinoma of the pancreas in humans arises in the head of the pancreas more commonly than in the body and tail (ratio 3:1), and in men more often than in women (ratio 1.7:1). The most common histologic type is a moderately differentiated, ductlike adenocarcinoma, which typically incites a desmoplastic reaction. Twelve histologic types of pancreatic carcinoma are suggested by Cubilla an Fitzgerald in their classification,[8] and the types are grouped according to the presumed cell of origin. Seven types, constituting 89% of their series, are classed as ductal in origin, two types (1%) as acinar cell in origin, and three types as undifferentiated neoplasms (9%) of uncertain histogenesis.

Ductal epithelial changes that have been associated with the presence of carcinoma of the human pancreas have been designated "marked atypical hyperplasia" and "carcinoma *in situ*."[9] These are the most widely accepted precursor lesions for tumors of ductal origin in humans. Foci of dysplastic acinar cells have been described in the human pancreas.[10–12] Some of these are histologically similar to azaserine-induced lesions in rats, but their significance in humans is unknown. It seems likely that some of the more cytologically atypical of these lesions could represent precursor lesions for neoplasms of acinar-cell origin in humans.

The spectrum of histologic types of pancreatic cancers arising in azaserine-induced rats overlaps that described in humans and provides a basis for asking whether some types of human pancreatic carcinoma other than acinar cell tumors might result from transformation of acinar cells. The histogenesis of human pancreatic cancer requires further scrutiny, as does the relevance to the human of the azaserine-induced model in rats.

Availability

A limited number of LEW rats bearing transplanted tumors are available from the author. LEW rats are available from Charles River Breeding Laboratories, Wilmington, Mass or Microbiological Associates, Bethesda, Md.

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