Cancer of the Pancreas Induced in the Syrian Golden Hamster

Parviz Pour, MD, F. W. Krüger, D Chem, J. Althoff, MD, A. Cardesa, MD and U. Mohr, MD

A high incidence of pancreatic neoplasms was induced in Syrian golden hamsters following subcutaneous applications of diisopropanolnitrosamine (DIPN) once weekly for life. The tumor latency was as short as 15 weeks. In clinical and morphologic aspects the induced pancreatic tumors closely resembled those of humans (Am J Pathol 76:349–358, 1974).

Pancreatic cancer is an increasingly common and important neoplasm affecting man. Presently, it ranks fifth among neoplasms of all cancer sites and is the fourth leading cause of death from cancer in the United States. Despite thorough epidemiologic studies of this cancer in the population of the United States, no clues to its etiology have emerged. For the most part, attempts to induce pancreatic cancer experimentally in significant numbers have been unsuccessful and no practical experimental model for the induction and study of pancreatic neoplasms has been available. In the present communication, we report a high incidence of induced pancreatic neoplasms in the Syrian golden hamster following the administration of diisopropanolnitrosamine (DIPN, 2,2'-dihydroxy-di-N-propylnitrosamine).

Materials and Methods

One hundred and sixty randomly bred 8-week-old Syrian golden hamsters were used. They were kept under standardized conditions (room temperature, 21 ± 10°C; humidity, 50 ± 5%; ten air changes per hour) in plastic cages in groups of 5, according to sex. The animals received Wayne pellet diet and water ad libitum. DIPN in olive oil was administered subcutaneously to the hamsters in groups of 20 males and 20 females, at 3 dose levels (group 1, 500 mg/kg body weight; group 2, 250 mg/kg body weight and group 3, 125 mg/kg body weight) once weekly for life. A similar number of male and female controls received the...
vehicle only. Experimental animals were observed until death, at which time the controls were sacrificed. Routine autopsies were performed on all dead animals, and appropriate tissue sections selected for histopathologic examination. The tumor latency corresponded to survival following treatment.

**Results**

The average survival of the hamsters, tumor incidences and latencies are listed in Table 1. The frequency of pancreatic adenomas was as high as 100% in all treated groups, whereas the incidence of carcinomas was higher in males (100%) than in females (90%) of group 1 (highest dose level). However, in the low dose group (group 3) females showed a slight predominance (Table 1). The first tumors appeared as early as 15 weeks from the start of the experiment in a female and at 16 weeks in a male (Table 1). Many of the tumors were microscopic in size, but 51% could be observed grossly, measuring up to 20 mm in diameter. They frequently were multiple and often distributed in different anatomic parts of the pancreas in the same animal.

Histologically, the neoplasms were adenomas and adenocarcinomas of ductal origin. Adenomas were often multilocular (Figure 1), lined by flattened, cuboidal or cylindrical cells (Figure 2), sometimes showing cystic, papillary or cystic-papillary formations. Transitions of papillary adenomas to carcinomas were found frequently in step sections of some tumors (Figures 3 and 4). Carcinomas occurred simultaneously with adenomas in most hamsters (Figure 1). These were all adenocarcinomas showing various histologic patterns (Figures 5–12). Most of the adenocarcinomas were of ductal origin and only a few of acinar cell type (Table 1). Ductal adenocarcinomas were generally well differentiated, showing glandular patterns lined by columnar or cuboidal epithelia (Figures 5, 8–10). They sometimes formed papillary structures (Figures 8 and 9), frequently interspersed with goblet cells (Figure 8). Gelatinous or mucinous (Figure 5), tubular (Figures 6 and 7), scirrhous and signet ring cells and giant cell adenocarcinomas (Figure 11) occurred in different parts of the same neoplasms or in the different segments of the pancreas. Acinar-type carcinomas were found simultaneously with ductal-type carcinomas displaying widespread metastases. The acinar cell carcinomas developed in the body or tail (pars sinistra) of the pancreas and were composed of polygonal cells, which occasionally formed solid alveoli and manifested eosinophilic intracytoplasmic granules (Figure 12).

Invasions of the peritoneum, perineural lymphatics (Figure 13), blood vessels (Figure 14), regional lymph nodes (Figure 15), spleen
Table 1—Pancreatic Neoplasms in Syrian Golden Hamsters Treated with DIPN

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg body wt)</th>
<th>Number of hamsters</th>
<th>Average survival (wks)</th>
<th>Tumor latency (wks)</th>
<th>Adenocarcinomas</th>
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<td>3</td>
<td>125</td>
<td>20</td>
<td>20</td>
<td>35</td>
<td>32</td>
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<tr>
<td>Control</td>
<td>—</td>
<td>20</td>
<td>20</td>
<td>41*</td>
<td>38*</td>
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* Survivors were killed 44 weeks after beginning treatment.
(Figures 6 and 8) and stomach were seen in 18 (16%) hamsters and distant metastases in 10, while 7 showed metastases in the liver and 3 in the lungs (Figure 16). Weight loss occurred in all treated hamsters. Sixteen (14%) of the pancreatic tumor-bearing hamsters had hemorrhagic ascites. Focal fat necrosis, calcification and inflammation of the peritoneum were found in 2 animals with invading acinar cell carcinoma. Four hamsters showed vascular thrombosis occurring in the lungs, splenic vein (Figure 15) and renal arteries.

Seventy-two to 100% of hamsters with pancreatic neoplasms simultaneously had tumors of other sites. These were located primarily in the respiratory tract, particularly in the nasal cavity (mostly adenocarcinomas), liver (hemangioendotheliomas, angiosarcomas, cholangiomas and cholangiocarcinomas) and kidneys (adenomas and adenocarcinomas). The detailed results of these experiments will be presented in a later report.

Discussion

Previously, a practicable experimental model for studying pancreatic cancer was not available. Past attempts to experimentally induce pancreatic cancer were hampered by either the difficulties in technical manipulation of the potential carcinogens, low rates of cancer production, too long latency periods or by combinations of these factors. In addition, the pancreatic neoplasms reproduced in experimental animals differed in their morphologic and biologic characteristics to the extent that they were unsuitable for comparative purposes with the pancreatic neoplasms of man. Significant incidences of pancreatic cancer were, however, induced after a very short latent period in the present study, following the administration of DIPN to Syrian golden hamsters. Furthermore, the present experimental model resulted in the induction of pancreatic neoplasms which, in morphologic appearance and biologic behavior, closely resembled those of humans. As in humans, most of the induced neoplasms were of ductal origin and only a few of an acinar cell type. Ductal adenomas with transition to carcinoma seen in the present study have been repeatedly reported in man. Ductal adenocarcinomas showed patterns similar morphologically to those occurring in humans. Also, the tumor metastases and their elected sites were in accordance with observations of the disease in man. Another notable point of resemblance to human pancreatic cancer was the weight loss, focal fat necrosis of the peritoneum and the vascular thrombosis. However, further studies are
needed to clarify whether or not the described symptoms in the hamsters which had simultaneous multiple tumors in other organs were due to the pancreatic cancer alone.

References
8. Vesselinovitch SD, Rao KVN, Milhailovitch N: Enhanced delivery of chemical carcinogens to the pancreas.7 p 34
Acknowledgments

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Fig 1—Multilocular ductal adenoma (top) and ductal adenocarcinoma in the body of the pancreas of a male hamster at 32nd week (H&E, x 100).  
Fig 2—Higher magnification of a ductal adenoma composed of cuboidal or flattened cells. Pancreatic acinar cells are seen in the lower right corner (H&E, x 400).  
Fig 3—Cystic papillary adenoma in the body of the pancreas of a female at 37th week. Focal invasions of the capsule are seen in the right portion of the photomicrograph (H&E, x 40).  
Fig 4—A step section of the same tumor shown in Figure 3, demonstrating invasion (H&E, x 100).
Fig 5—Large ductal adenocarcinoma of the pancreas occupying the body and tail (see Figure 6) of the organ. Note the glandular structure with partial mucus production and moderate inflammatory reactions in the margin of the carcinoma. Distension of the pancreatic ducts is seen in the upper portion. Male hamster, 27th week (H&E, x 40).

Fig 6—The same adenocarcinoma shown in Figure 5 invading the spleen (top) (H&E, x 100).

Fig 7—A less-differentiated area of the same carcinoma demonstrated in Figure 6 (H&E, x 400).

Fig 8—Ductal adenocarcinoma (in the tail of the pancreas) invading the peritoneum. Part of the spleen is seen in the upper portion of the photo. Glandular-like spaces are lined with columnar cells, interspersed with goblet cells. This carcinoma had metastasized to a regional lymph node (Figure 15). Female hamster, 32nd week (H&E, x 250).
Fig 9—Adenocarcinoma in the head of the pancreas, showing glandular and papillary formations. Male hamster, 23rd week (H&E, x 70).

Fig 10—Ductal adenocarcinoma in the body of the pancreas in a male hamster at 18th week. The tumor cells are columnar or cuboidal. At least three mitotic figures are seen (lower left corner) (H&E, x 400).

Fig 11—Giant cell adenocarcinoma in the head of the pancreas in a female hamster at 24th week. This tumor had metastasized to the lungs (see Figure 16) (H&E, x 100).

Fig 12—Adenocarcinoma of acinar cell type in the body of the pancreas in a female hamster at 23rd week. Alveolar formation of the fine granulated cells is seen in the lower and right middle parts (H&E, x 400).
Fig 13—Invasion of a ductal adenocarcinoma into the perineural lymphatics (H&E, × 250).

Fig 14—Invasion of a less-differentiated adenocarcinoma into the splenic vein with thrombosis. The original tumor is illustrated in Figure 6 (H&E, × 400).

Fig 15—Lymph node metastases of the ductal adenocarcinoma pictured in Figure 8 (H&E, × 120).

Fig 16—Lung metastases of a giant cell adenocarcinoma shown in Figure 11. No liver metastases of the tumor were found (H&E, × 120).