Extrahepatic Biliary Carcinomas in Asiatic Bears [1, 2, 3, 4]

Richard J. Montali, *D.V.M.,* [5] **P. Jack Hoopes,** *D.V.M.,* [5, 6] *and* **Mitchell Bush,** *D.V.M.* [7, 8]

ABSTRACT—Extrahepatic biliary carcinomas occurred in 2 Asiatic bears at the National Zoological Park in Washington, D.C. The tumors were associated with ascites in both cases and jaundice in 1 and metastasized widely. Neither bear had gallstones. Microscopically, the tumors were infiltrative, scirrhous adenocarcinomas that produced varying amounts of mucin. A genetic predisposition and change from the natural diet were factors proposed to contribute to the development of this neoplasm.—JNCI 1981; 66:603-608.

In humans important tumors of the biliary tract include carcinomas of the gallbladder and extrahepatic bile ducts. Gallbladder carcinomas are more prevalent in women and are often associated with gallstones. Carcinomas of the extrahepatic ducts are uncommon and predominate in men. The cause of these biliary tumors in humans is not known, but it appears to be associated with lithogenesis and perhaps carcinogenic substances in the bile (*1*).

Tumors of the extrahepatic biliary apparatus in domestic and laboratory animals are considered rare. Experimentally, adenocarcinomas of the gallbladder and associated ducts have been induced in irradiated guinea pigs (*2*), in dogs given the insecticide aramite (*3*), and in dogs (*4*) and cats (*5*) treated with 3-methylcholanthrene. The highest natural incidence of these biliary tumors in animals thus far appears to be in Asiatic bears. The purpose of this report is to describe 2 such cases occurring at the NZP in Washington, D.C., and to review similar cases reported elsewhere.

CASE REPORTS

The first case, a male sloth bear (*Melursus ursinus*) (fig. 1), was born and exhibited at the NZP for 10 years until it became lethargic and refused to eat 1 day and died. At autopsy, the bear was jaundiced and had marked peritoneal effusions. A large mass extended from the hilus of the liver, involved the gallbladder, and obstructed the cystic duct (fig. 2). The hepatic ducts and proximal segment of the common duct were obliterated by the tumor; the distal common duct was unaffected. There were tumor nodules in the gallbladder fossa of the liver and regional lymph nodes. Tumor plaques involved all peritoneal surfaces, and a few were found in the lungs.

Microscopically, the tumor appeared as irregular glandular structures composed of cuboidal or flattened cells within a very dense stroma (figs. 3A, 3B). Lumina of the neoplastic glands in some areas contained periodic acid-Schiff and Alcian blue material indicative of mucin.

The second case, a 20-year-old female Malayan sun bear (*Helarctos malayanus*) (fig. 4), was wild born but lived in captivity most of its 28 years. In March of 1979, the bear developed darkened stools, became anorectic, and showed weight loss. Hematologic and serum chemistry tests indicated moderate anemia and elevations of serum alkaline phosphatase, serum glutamic-oxaloacetic transaminase, and lactate dehydrogenase values. Because the bear had liver tumors at laparoscopy, it underwent euthanasia and was completely necropsied.

There were peritoneal effusions but no icterus. The gallbladder had an increased diameter and a thickened wall and contained thick, mucoid material (white bile). The cystic duct was obstructed by a large mass, but most hepatic ducts and the entire common duct were unaffected. Multiple nodules were either firm or cystic within some of the liver lobes. Tumor nodules were also evident in the diaphragm and uterus.

Microscopically, the tumor was more cystic (fig. 5) and less scirrhous than that described for the sloth bear. Besides metastases to the diaphragm and uterus, the adrenal glands, pancreas, portal and mesenteric lymph nodes, and omentum were involved.

DISCUSSION

Because of the advanced stage of the disease in both bears, it was uncertain as to whether the primary tumors arose from the gallbladder or the extrahepatic ducts or whether they were multicentric. The cause of these ursine biliary tumors was not evident, and although they may morphologically resemble the infiltrative types of gallbladder tumors of humans, no gallstones were present in either bear. Most naturally occurring bile duct tumors of animals are of the

ABBREVIATION USED: NZP = National Zoological Park.

[1] Received August 11, 1980; accepted November 14, 1980.

[2] Supported in part by the Smithsonian Institution Fluid Research Fund.

[3] Presented at the 69th Annual Meeting of the International Academy of Pathology, New Orleans, February, 1980.

[4] Animals were maintained under the guidelines set forth by the National Zoological Park.

[5] Department of Pathology, National Zoological Park (NZP), Smithsonian Institution, Washington, D.C. 20008.

[6] *Present address:* Department of Pathology, College of Veterinary Medicine, Colorado State University, Ft. Collins, Colo. 80523.

[7] Department of Animal Health, NZP.

[8] We acknowledge the assistance of Ms. Francine Schroeder, Office of Education, NZP.

intrahepatic type, reported mainly in felids, dogs, and cattle (*6–8*).

These tumors in our bears were similar to 5 that occurred in a group of bears at the San Diego Zoo in 1964 (*9*). Four were sloth bears living in the same grotto. The grotto was previously occupied by 2 grizzly bears, 1 of which also developed a biliary tumor. The proposal was made that the bears may have been exposed to some carcinogen. Similar tumors were reported and cited (*10*) in several Asiatic bears before the San Diego Zoo episode and subsequently have occurred in a sloth bear at the London Zoo (*11*), 2 sun bears in Norway (*12*), and in the 2 bears reported herein.

Although once plentiful in nature, these Asiatic bears are becoming a vanishing species (*13, 14*). As of 1975, only 72 sloth bears were known in captivity (Jaffeson RC: Unpublished data). Nothing is known of the occurrences of these tumors in wild bears; however, their relatively high incidence and worldwide distribution would appear to be very significant.

Although a carcinogen in such a cluster of unusual tumors must be considered, no agent, either infectious or chemical, was recovered in any of the bear cases. Clonorchid flukes have been associated with bile duct tumors in humans and experimental animals, mainly in Southeast Asia, but no evidence was found of any flukes or other hepatic parasites in either of these bears. Also, the bears were not fed raw fish, which are required to contract parasites of this type. A few ascarid nematodes were observed in the small intestine, but these are relatively common in most bear species. Other factors, such as genetic predisposition that renders the bear sensitive to some element common in the environment, must be considered. These Asiatic bears are known to hybridize with each other in nature (*13*) and therefore might have similar susceptibilities.

Another possibility is that alteration of their natural diet of insects and plants to red meats and dog food could be responsible for rendering their bile carcinogenic.

Although perhaps not a feasible model to deal with practically, the study of the natural history and pathology of these cases may add some important comparative knowledge to the biology of cancers in domestic animals and humans. Other cases that occur should be studied in detail. In particular, bile should be obtained and studied for possible carcinogenicity. This procedure was not considered in our first case, and in the second case no bile was available. Bile was obtained and frozen for subsequent studies from an old sun bear that died recently of a gastric torsion. It had no evidence of neoplasia.

REFERENCES

(*1*) BISMUTH H, MALT RA. Carcinoma of the biliary tract. N Engl J Med 1979; 301:704-706.

(*2*) HOCH-LIGETI C, CONGDON CC, DERINGER MK, STEWART HL. Adenocarcinoma of the gallbladder in guinea pigs. JNCI 1979; 62:381-386.

(*3*) STERNBERG SS, POPPER H, OSER BL, OSER M. Gallbladder and bile duct adenocarcinomas in dogs after long-term feeding of aramite. Cancer 1960; 13:780-789.

(*4*) FORTNER JG, LEFFALL LD. Carcinoma of the gallbladder in dogs. Cancer 1961; 14:1127-1130.

(*5*) FORTNER JG. Experimental induction of primary carcinoma of the gallbladder. Cancer 1955; 8:689-700.

(*6*) MOULTON JE. Tumors of the pancreas, liver, gallbladder, and mesothelium. In: Moulton JE, ed. Tumors in domestic animals. 2d ed. Berkeley: University of California Press, 1978:279.

(*7*) STRAFUSS AC, VESTWEBER JG, NJOKU CO, IVOGHLI B. Bile duct carcinoma in cattle: Three case reports. Am J Vet Res 1973; 34:1203-1205.

(*8*) MCCLURE HM, CHANG J, GOLARZ MN. Cholangiocarcinoma in a margay (*Felis weidii*). Vet Pathol 1977; 14:510-512.

(*9*) DORN CR. Biliary and hepatic carcinomas in bears at the San Diego Zoological Gardens. Nature 1964; 202:513-514.

(*10*) MOULTON JE. Bile duct carcinomas in 2 bears. Cornell Vet 1961; 51:285-293.

(*11*) APPLEBY EC, KEYMER IF. Some tumors in captive wild mammals and birds. In: Tenth International Symposium Uber die Erkrankungen der Zootier, Berlin, 1968. Berlin: Academie-Verlag, 1968:199-200.

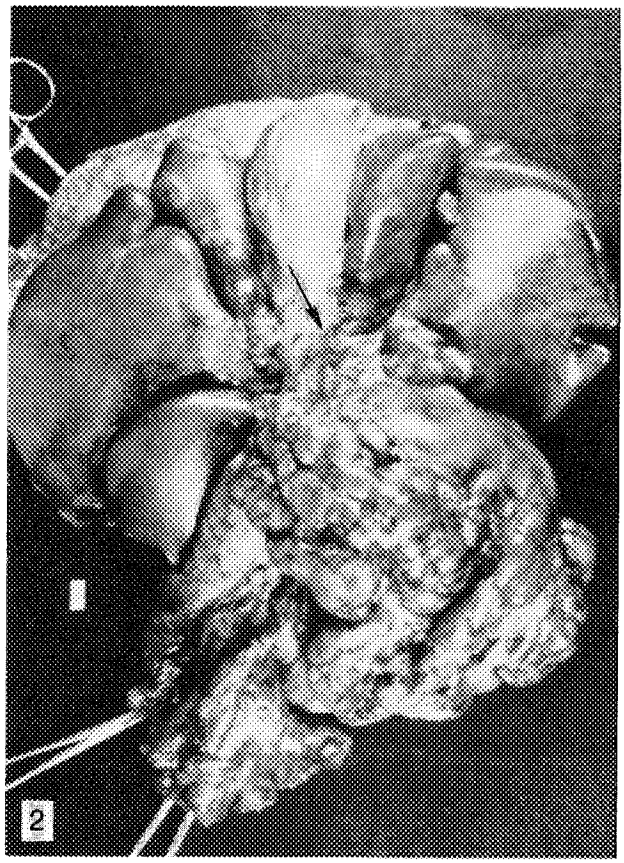
(*12*) KRONBERGER H. Tumors in zoo animals. Nord Vet Med 1962; 14 (suppl 1):297.

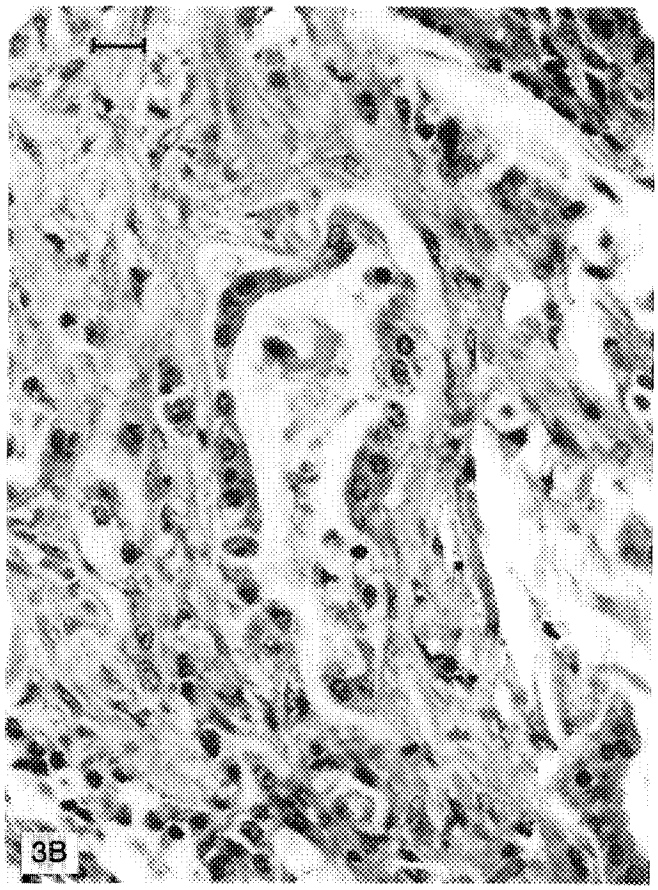
(*13*) LAURIE A, SEIDENSTICKER J. Behavioral ecology of the sloth bear (*Melursus ursinus*). J Zool Proc Zool Soc Lond 1977; 182:187-204.

(*14*) LEKHAKUN B, MCNEELY J, eds. Mammals of Thailand. Bangkok: Association for the Conservation of Wildlife. 1977:529-531.

(*15*) MONTALI RJ. An overview of tumors in zoo animals. In: Montali RJ, Migaki G, eds. Comparative pathology of zoo animals. Washington, D.C.: Smithsonian Institution Press, 1980:531-542.

FIGURE 1.—Sloth bear.





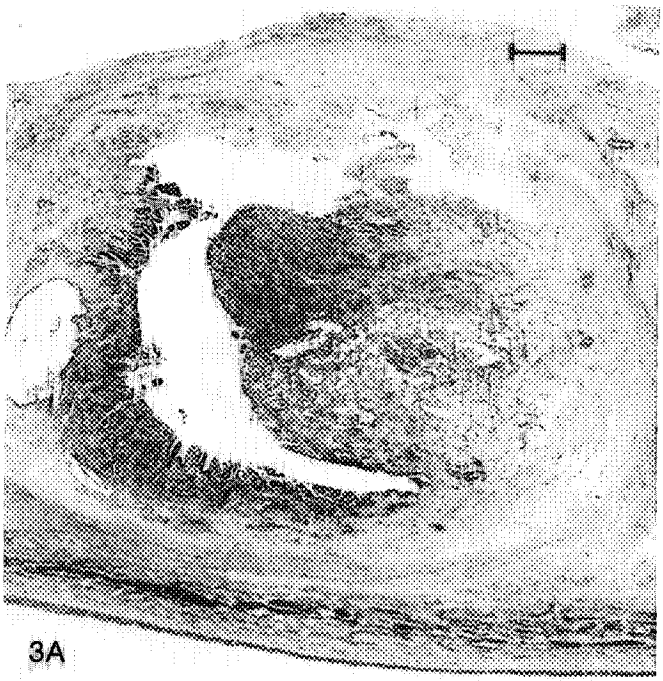


FIGURE 2.—Liver from sloth bear with large tumor mass extending from the neck of the gallbladder (*arrow*) and incorporating extrahepatic bile ducts. Reprinted with permission. (*15*).

FIGURE 3.—A) Hepatic duct from sloth bear shows adenocarcinoma involving the luminal epithelium. *Bar*=2 mm. × 12. B) Neoplastic glands lie within a scirrhous stroma. Hematoxylin and eosin. *Bar*=20 μm. × 300

FIGURE 4.—Malayan sun bear.

FIGURE 5.—Metastatic biliary tract tumor in liver of sun bear shows marked cyst formation. Hematoxylin and eosin. *Bar* = 100 μm. × 55