

XIII. Tumours of the liver and biliary system

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In this histological classification of liver and gall bladder tumours the tumour types largely correspond to those found in man. The most common tumours in this group are liver cell adenoma, hepatocellular carcinoma, and cholangiocarcinoma.

Tumours of the liver and the intrahepatic biliary system are fairly common in most domestic animals, although absolute prevalence figures are generally not available. The most common tumours appear to be liver cell adenoma, hepatocellular carcinoma, and cholangiocarcinoma. Benign tumours of the bile ducts are infrequent and tumours of the gall bladder are seldom recognized. The series of tumours on which this classification is based includes examples from the dog, cat, ox, sheep, and pig but none from the horse. The tumours occurred in both male and female animals, but no information is available on sex predisposition.

In many respects, liver tumours in animals resemble the corresponding neoplasms of man. However, liver cell carcinomas of animals metastasized less frequently than might have been predicted from the histological features. In general, little difference in the histological characteristics of the tumours was found among the animal species studied except that in cattle, cholangiocarcinoma was usually a more scirrhous tumour than its canine counterpart and was more likely to show serosal dissemination over the abdominal organs.

The etiology of naturally occurring liver tumours in domestic animals is unknown. Cirrhosis of the liver in man is associated with liver cell carcinoma but, although cirrhosis is an important disease of the dog, co-existing liver cell carcinomas have been found only occasionally in cirrhotic dogs. Chronic hepatic fibrosis is a major disease of sheep and cattle, resulting from infestation by *Fasciola hepatica*, but again there is no evidence that this condition leads to subsequent neoplasia. No relationship between aflatoxin and liver tumours has been shown in domestic animals.

Hepatoblastoma similar to the fetal type in man occurs in domestic animals, particularly in lambs. Tumours of the extrahepatic bile ducts were not seen in the present series and are probably rare.

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HISTOLOGICAL CLASSIFICATION AND NOMENCLATURE OF TUMOURS OF THE LIVER AND BILIARY SYSTEM

Tumours of the liver

I. EPITHELIAL TUMOURS

- A. LIVER CELL ADENOMA (HEPATOCELLULAR ADENOMA)
- B. INTRAHEPATIC BILE DUCT ADENOMA (CYSTADENOMA)

- C. HEPATOCELLULAR CARCINOMA (LIVER CELL CARCINOMA)
- D. CHOLANGIOCARCINOMA (INTRAHEPATIC BILE DUCT CARCINOMA)
- E. HEPATOBLASTOMA

II. NON-EPITHELIAL TUMOURS

- A. HAEMANGIOMA
- B. HAEMANGIOSARCOMA
- C. FIBROSARCOMA

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III. MISCELLANEOUS TUMOURS

IV. HAEMATOPOIETIC AND LYMPHOID NEOPLASMS

V. UNCLASSIFIED TUMOURS

VI. SECONDARY TUMOURS

VII. TUMOUR-LIKE LESIONS

Tumours of the gall bladder

I. EPITHELIAL TUMOURS

A. ADENOMA (PAPILLARY ADENOMA)

B. ADENOCARCINOMA (PAPILLARY CARCINOMA)

II. TUMOUR-LIKE LESIONS

A. CYSTIC HYPERPLASIA

DESCRIPTION OF TUMOURS

Tumours of the liver

I. EPITHELIAL TUMOURS

A. *Liver cell adenoma (hepatocellular adenoma)* (Fig. 1, 2)

This is a well differentiated tumour composed of cells that resemble normal hepatocytes, although they are often larger and more varied in shape. The cytoplasm is often vacuolated and in some tumours the amount of glycogen and fat stored gives the tumour a predominantly clear-celled appearance. The nuclei contain prominent nucleoli but mitotic figures are rare.

Most liver cell adenomas show a predominantly trabecular or acinar pattern; mixed patterns may occur. Trabeculae are usually two or three cells thick and are separated by fine endothelial sinusoids. Some adenomas have a solid structure without acinar or trabecular differentiation. Very well differentiated adenomas may be distinguishable from normal liver tissue only by the absence of portal triads. The vascular element is seldom conspicuous in liver cell adenomas of animals.

Liver cell adenomas are not uncommon in young animals and in these cases, foci of extramedullary haematopoiesis are present. The latter feature is occasionally seen in tumours from adult animals.

Liver cell adenomas are usually found as well demarcated, circumscribed, light-tan-coloured nodules. There is no invasion of adjacent liver tissue, which is usually compressed by the tumour. If such tumours reach a large size, they tend to become fragile and rupture. Small adenomas may be extremely difficult to distinguish from hyperplastic nodules; the latter are, however, usually multiple.

B. *Intrahepatic bile duct adenoma (cystadenoma)* (Fig. 3)

This tumour is a well circumscribed, small, solitary nodule composed of epithelium-lined tubules with a moderate amount of stroma. The epithelial cells are cuboidal and may have clear cytoplasm. At the margin of the lesion, there may be some infiltration by mononuclear cells.

Biliary cystadenomas are rather more common. They are multilocular cystic tumours composed of locules lined by epithelial cells. These cells are similar to normal biliary epithelium but may appear flattened. The cysts are supported on a fibrous connective tissue stroma and contain a clear mucinous fluid.

C. *Hepatocellular carcinoma (liver cell carcinoma)* (Fig. 4-8)

There is a wide range in the degree of differentiation of individual tumours. In well differentiated carcinomas, the cells retain a close resemblance to normal liver cells: they are large and polygonal with eosinophilic cytoplasm and have central vesicular nuclei with prominent nucleoli. The cytoplasm is often granular but may be vacuolated or clear owing to the presence of glycogen and fat. In less well differentiated tumours, the cells show pleomorphism with a high mitotic rate and tend to have more basophilic cytoplasm. Most carcinomas show a predominantly trabecular structure. The trabeculae may be 2-3 or several cells thick and are separated by endothelium-lined sinusoids. Acini or larger cystic spaces may occur within individual trabeculae. In some tumours, the cells are arranged in short cords and groups with focal acinar differentiation; non-mucinous PAS-positive material is often present

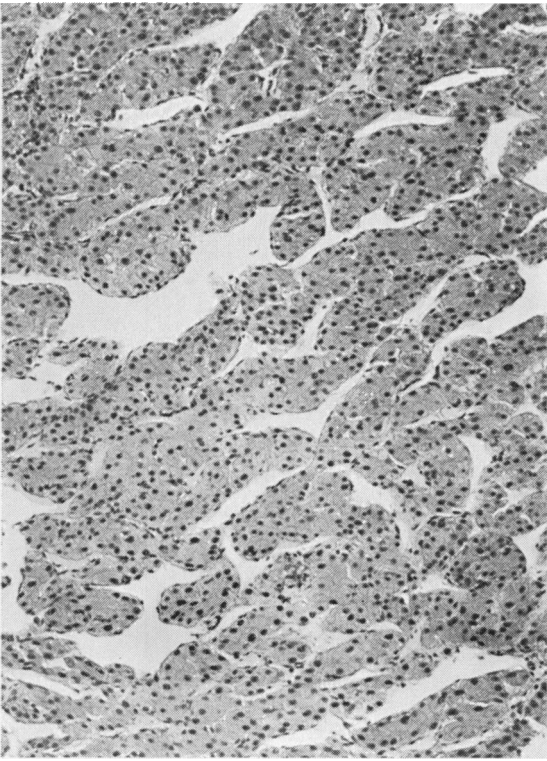


Fig. 1. Liver cell adenoma, trabecular pattern (cow).

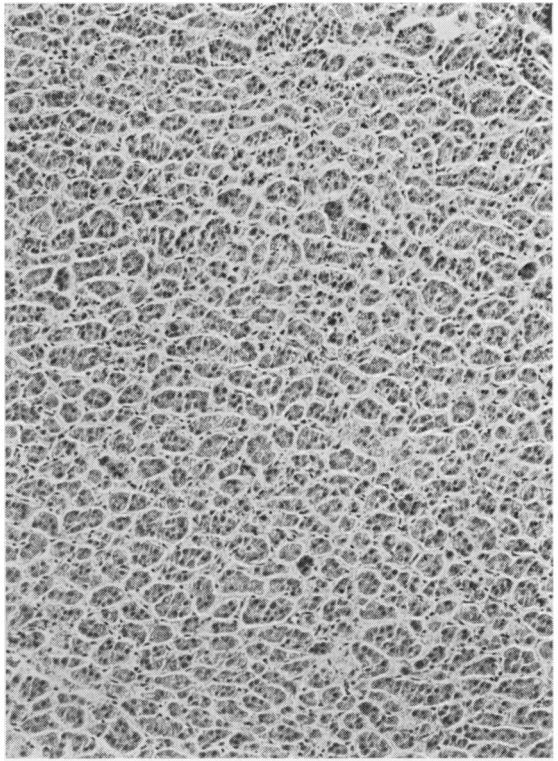


Fig. 2. Liver cell adenoma, acinar pattern (sheep).

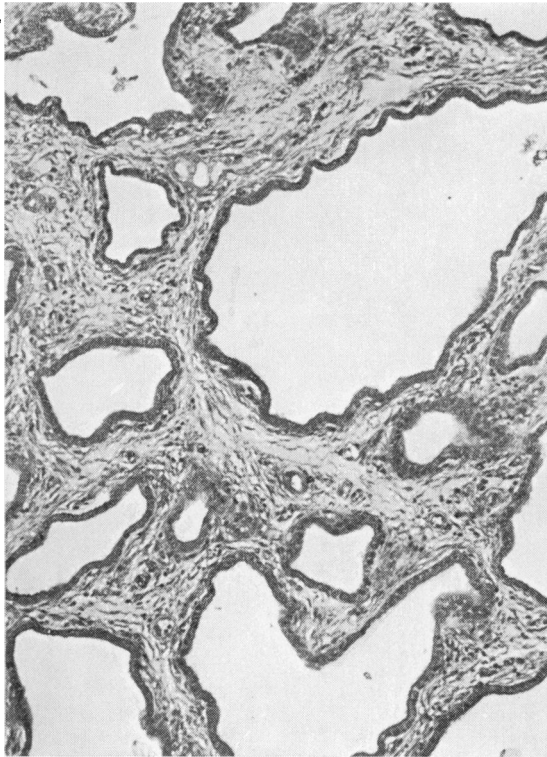


Fig. 3. Intrahepatic biliary cystadenoma (dog).

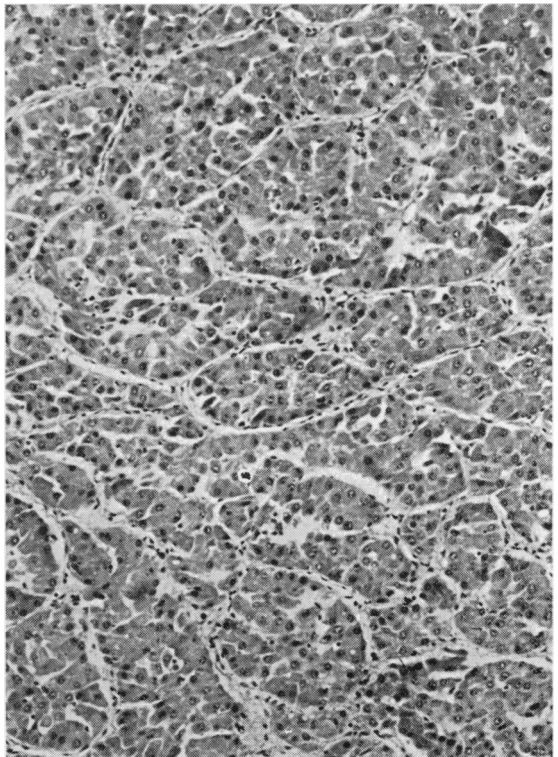


Fig. 4. Hepatocellular carcinoma, trabecular pattern (dog).

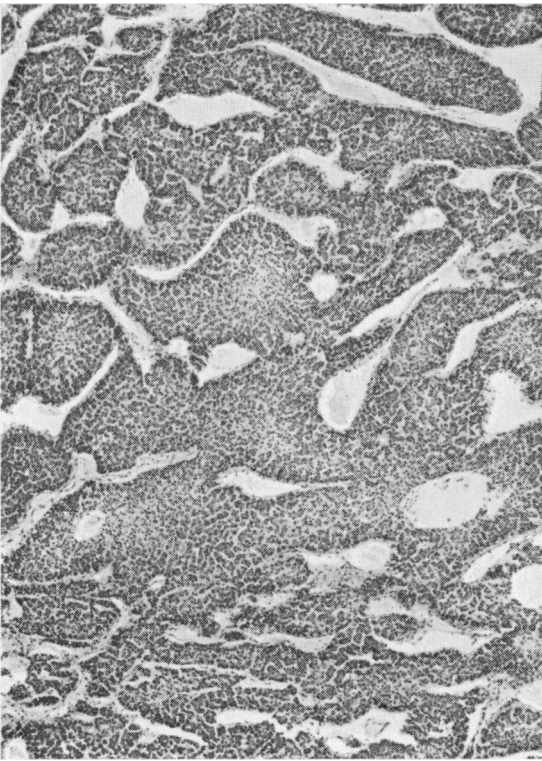


Fig. 5. Hepatocellular carcinoma, trabecular pattern (cow).

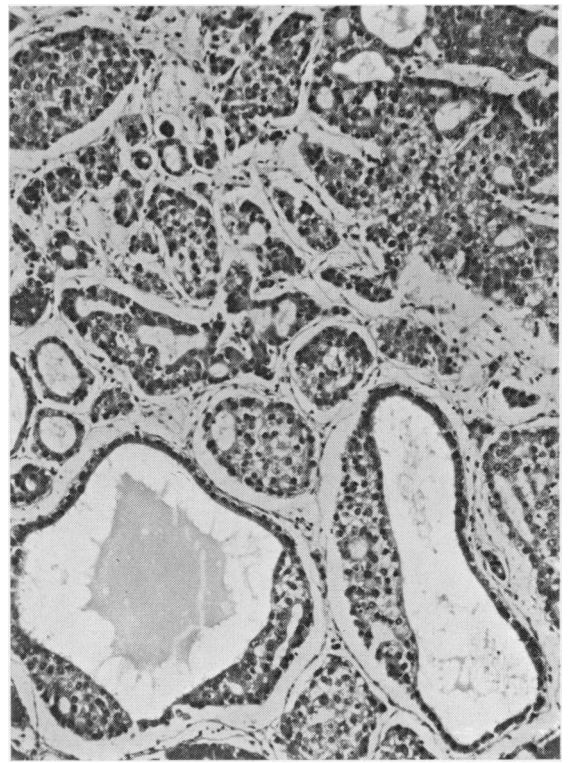


Fig. 6. Hepatocellular carcinoma, trabecular pattern with focal acinus and cyst formation (cow).

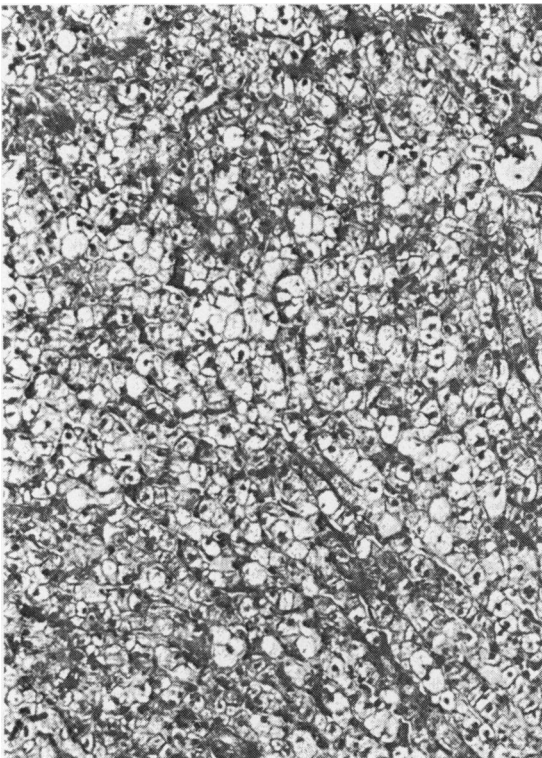


Fig. 7. Hepatocellular carcinoma with clear cells (dog).

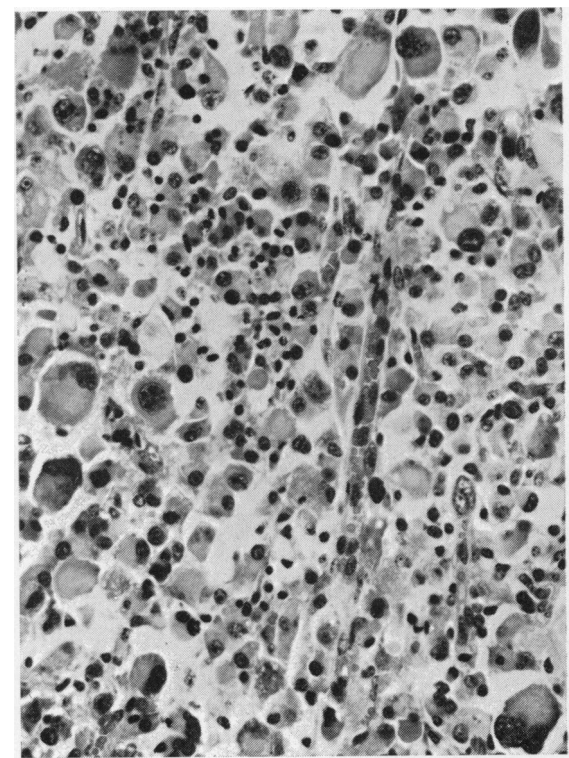


Fig. 8. Hepatocellular carcinoma, poorly differentiated (cow).

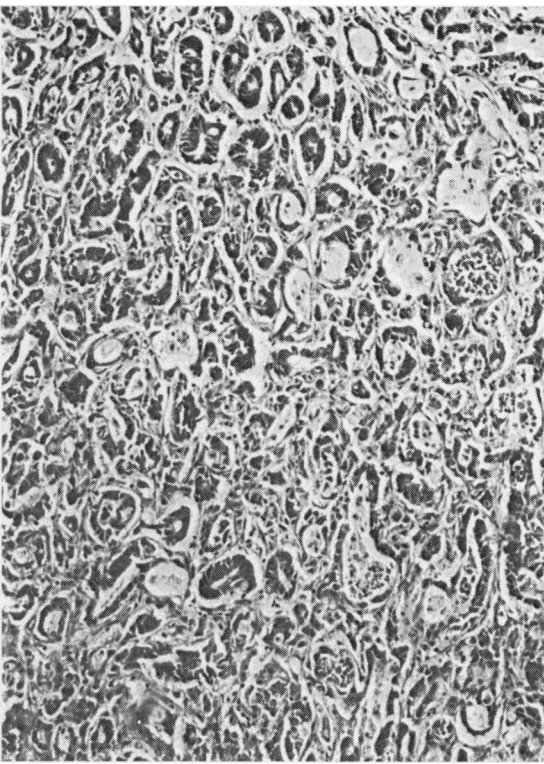


Fig. 9. Cholangiocarcinoma, moderately differentiated (sheep).

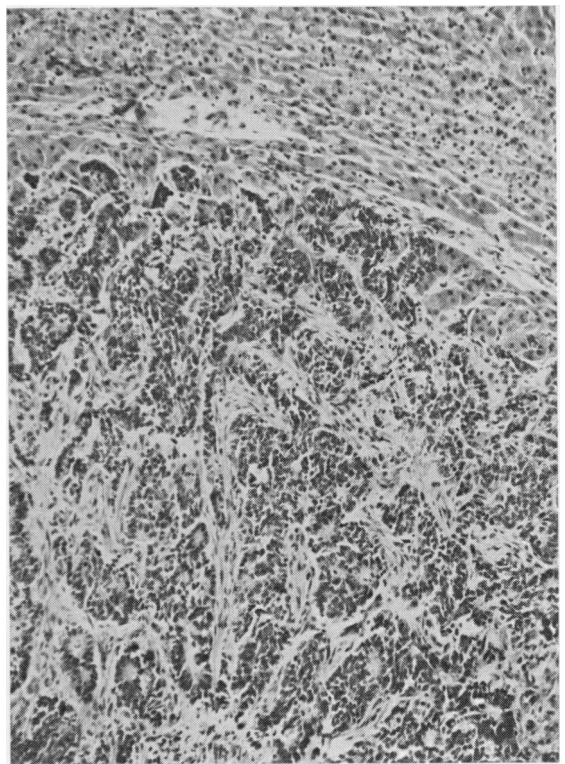


Fig. 10. Cholangiocarcinoma, moderately differentiated (cow).

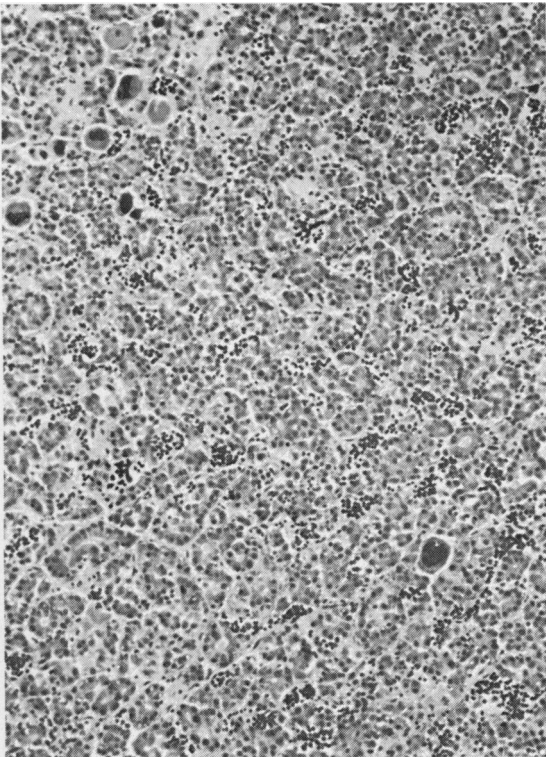


Fig. 11. Hepatoblastoma, fetal type (sheep).

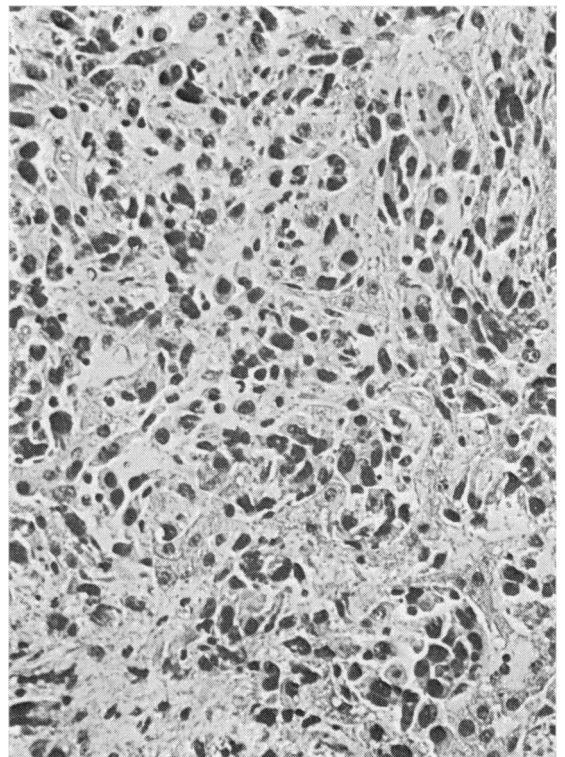


Fig. 12. Haemangiosarcoma of the liver (dog).

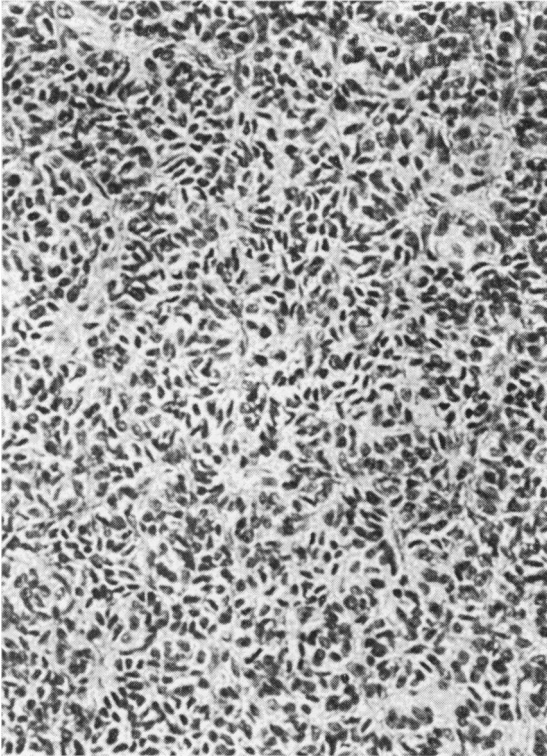


Fig. 13. Carcinoid tumour of the liver (cow).

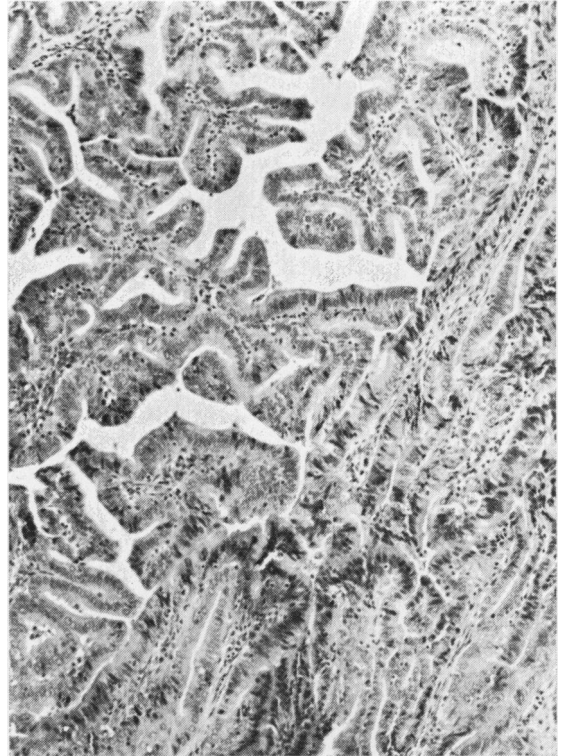


Fig. 14. Adenocarcinoma of the gall bladder (pig).

within the acini. More than one histological pattern may occur in different parts of the same tumour. In poorly differentiated carcinomas, there may be no distinctive organization, the tumour cells simply forming diffuse invasive sheets. Occasionally, foci may be seen where the tumour cells resemble biliary rather than hepatic epithelium. However, these are not true combined hepatocellular and cholangiocarcinomas, since there is no evidence of mucin production.

Well differentiated carcinomas may be difficult to distinguish from adenomas, because mitotic figures are infrequent and in both cases the tumour cells retain a close resemblance to normal hepatocytes. Carcinomas do not always show obviously invasive growth at the primary site even when metastasis has occurred. They may reach a large size and cause extensive destruction of the normal liver before metastasising. The usual sites for metastasis are the regional lymph nodes and the lungs.

D. *Cholangiocarcinoma (intrahepatic bile duct carcinoma)* (Fig. 9, 10)

These tumours are composed of epithelium resembling biliary tract epithelium. The cells are cuboidal or columnar and have clear or, less often, granular eosinophilic cytoplasm. The cells are arranged, at least in places, in a micro-acinar pattern. In many instances there is a striking scirrhous reaction, giving the tumour its fibrous consistency. The histological appearance of individual tumours varies according to the degree of differentiation: in well differentiated tumours, there is regular formation of small acini; in moderately differentiated cases, such acini are less well defined; and in poorly differentiated carcinomas solid cords of tumour cells show only occasional lumen formation. Mucin production is always demonstrable. Bile may be seen within the acini but not within the tumour cells. Within predominantly acinar tumours areas showing a papillary structure may occur. In occasional cases, mucin production is particularly marked and may accumulate to form "lakes" within the tumour tissue. In rare instances, the tumour may be of the adenosquamous type, in which foci of squamous differentiation occur in an adenocarcinoma.

Cholangiocarcinomas form dense, white, firm multinodular masses showing invasive growth within the biliary tract and into the surrounding parenchyma. They commonly spread to the liver capsule, resulting in widespread serosal dissemination, as well as metastasising to the lymphatic system and lungs.

E. *Hepatoblastoma* (Fig. 11)

Tumours resembling hepatoblastomas of the fetal type in man occur occasionally in domestic animals, particularly in lambs. Hepatoblastoma of the embryonic type has not been encountered. These tumours appear to be benign and are composed of cells resembling fetal hepatocytes; these are smaller than hepatocytes in adults and have granular or vacuolated cytoplasm. The mitotic rate is low. The cells are arranged in an orderly pattern of trabeculae and micro-acini separated by sinusoids. Foci of extramedullary haemopoiesis are always present within the tumour. Unlike most hepatoblastomas of man, there is little or no evidence of a non-epithelial component. The above cytological features distinguish the condition from liver cell adenoma.

II. MESENCHYMAL TUMOURS

A. *Haemangioma*

This is a benign, solitary or multiple, vasoformative tumour. Capillary haemangiomas are composed of small vascular channels lined with endothelial cells and separated by a delicate fibrous stroma. In cavernous haemangiomas, the vascular channels are generally larger and more varied in size. Individual blood-filled spaces in the tumour may reach several centimetres in diameter. The lining endothelial cells may be flattened and, in some places, desquamated. The vascular channels are supported by a fibrous stroma. In all haemangiomas, the cytological features tend to be regular and mitotic figures are rare.

B. *Haemangiosarcoma* (Fig. 12)

This is a malignant tumour of endothelial cells, which form irregular, anastomosing, vasoformative channels. The cells tend to be large, plump, and spindle-shaped, but frequently show marked pleomorphism and an extremely high mitotic rate. Such tumours are invasive and fragile with little supporting stroma and are therefore liable to rupture and haemorrhage. The terms angiosarcoma and malignant haemangioendothelioma have been applied to this condition.

C. *Fibrosarcoma*

These tumours are similar to fibrosarcomas at other sites.^a

^a WEISS, E. *Bulletin of the World Health Organization*, 50: 101-110 (1974).

III. MISCELLANEOUS TUMOURS

Carcinoid of the liver (Fig. 13) is a rare neoplasm in domestic animals. The tumour appears to originate from the cells with argentaffin properties in the bile duct epithelium and is composed of uniform cells with hyperchromatic, round or oval nuclei. The cells are typically arranged in small groups, separated from each other by a delicate fibrous stroma. The cells within the groups are orientated towards the basement membrane to form pseudolobules. Mitotic figures are infrequent. Silver impregnation should be used to show the granules in the cytoplasm of carcinoid tumour cells to distinguish this tumour from cholangiocarcinoma.

IV. HAEMATOPOIETIC AND LYMPHOID NEOPLASMS

The liver is commonly involved in disseminated malignancies of the haematopoietic and lymphoid systems and these conditions have been described elsewhere.^a Very occasionally, lymphosarcoma and mast cell tumours may apparently involve only the liver with no demonstrable lesions at other sites.

V. UNCLASSIFIED TUMOURS

These are primary tumours of the liver that cannot be placed in any of the above categories.

VI. SECONDARY TUMOURS

The liver is an extremely important site for metastases of primary tumours situated elsewhere. The great majority of malignant tumours originating in extrahepatic tissues may produce secondary tumours in the liver. If the primary site is closely related to the liver anatomically or by vascular supply, metastases to the liver may occur early, e.g., carcinoma of the pancreas.

VII. TUMOUR-LIKE LESIONS

Hyperplastic nodules occur as focal and often multiple lesions, and are extremely common in middle-aged and old dogs. They are clearly circumscribed, seldom more than 3 cm in diameter, often fatty in consistency, and are found in otherwise normal livers. Multiple nodular hyperplasia of cirrhosis involves the entire liver, with the formation of irregular nodules that vary in size and are separated by fibrous tissue. Histologically, hyperplastic foci consist of cords of hepatocytes of regular appear-

ance, which do not form normal lobules but which may include small bile ducts. They often contain more fat than normal cells, giving them a vacuolated appearance. Occasional mitotic figures and binucleate cells may be found.

Telangiectasis (Peliosis hepatis) consists of small, blood-filled, vascular or sinusoidal spaces, which often occur throughout the liver. It is particularly common in cattle. The individual lesions vary from a few millimetres to two centimetres in diameter. Histologically, an endothelial lining is sometimes but not always apparent.

Tumours of the gall bladder

I. EPITHELIAL TUMOURS

A. Adenoma (papillary adenoma)

Adenoma of the gall bladder is a simple tumour of mucus-secreting epithelium, which forms a nodule composed of acini separated by a delicate stroma. The acini are lined with tall columnar epithelium and they may be distended by mucin. Papillary adenoma is composed of papilliform structures covered with cuboidal or columnar epithelium. The stroma may be abundant and acini within the tumour may show cystic dilation. Some tumours may show features of both simple and papillary adenoma.

B. Adenocarcinoma (papillary carcinoma) (Fig. 14)

Malignant tumours of the gall bladder epithelium are composed of mucin-secreting columnar epithelium. Such tumours often show a papillary pattern in addition to the formation of acini. They may include less well differentiated areas where the cells are less regularly arranged. The tumour is composed of tall columnar cells that have basal nuclei, mucin containing cytoplasm, and usually a low mitotic rate. The stromal connective tissue is often well vascularized and may contain an infiltrate of mononuclear cells.

II. TUMOUR-LIKE LESIONS

A. Cystic hyperplasia

Cystic hyperplasia of the gall bladder epithelium causes diffuse thickening and may produce a honey-combed structure. The individual cysts are lined with tall, columnar, mucin-secreting epithelial cells of normal appearance. Infiltration of the stroma by lymphocytes is frequently seen. There may be proliferation of smooth muscle within the stroma. Accumulation of mucin secretion causes individual cysts to show different degrees of distention.

^a JARRETT, W. F. H. & MACKEY, L. J. *Bulletin of the World Health Organization*, 50: 21-34 (1974).