TUMORS OF THE LIVER AND INTRAHEPATIC BILE DUCTS

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ARMED FORCES INSTITUTE OF PATHOLOGY

ATLAS OF TUMOR PATHOLOGY

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TUMORS OF THE LIVER AND INTRAHEPATIC BILE DUCTS

by

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INTRODUCTION

The human liver, probably as a consequence of its anatomic location, size, dual blood supply, and favorable nutritional elements, is the site of neoplastic lesions which are greater in number and diversity than those seen in any other organ. Primary tumors as well as metastatic carcinoma and sarcoma, leukemic infiltrations, and lymphomas flourish in the hepatic environment. The problems associated with these lesions have for a long time chiefly concerned the autopsy surgeon. The advent of the needle biopsy and a bolder surgical attack on neoplasms of the liver, however, now make the understanding of liver tumors a matter of practical importance for all pathologists. This has made it necessary, utilizing present stains and technics, to differentiate primary malignant tumors from both benign lesions and metastatic cancer.

Although primary carcinoma of the liver is uncommon in the United States and Europe, significant differences in frequency are noted in other parts of the world (fig. 1). It is the most common malignant tumor among Javanese males and among Negro males in some areas of Africa. It is likewise prevalent among Japanese and Filipino males. The widespread occurrence of liver cancer in the animal kingdom, the ease of production of liver tumors in experimental animals, and the problem of the relationship of cirrhosis of the liver to primary carcinoma add further to its significance. In the United States, patients with cirrhosis of the liver, especially those living to the advanced or atrophic stage of the disease, are increasing in number. This has resulted in such a rise in the frequency of carcinoma of the liver that the clinician must be familiar with the differential diagnosis of the disease.

Table I emphasizes the variety and number of primary liver tumors seen in a large general hospital.

CLASSIFICATION AND EMBRYOLOGY

Primary neoplasms of the liver may arise either from the hepatic cord cells, bile duct epithelium, blood vessels and other mesodermal structures, or from combinations of these tissues. Numerous problems exist in regard to specific tumors because study has been too limited to allow the formulation of criteria necessary for proper terminology and classification. It is not surprising that tumors of widely different histologic appearance have received the same diagnosis or that many with a similar appearance have been given a variety of names. Many of these problems will be discussed in appropriate sections of this fascicle.

Table I

LIVER TUMORS IN THE FIRST 50,000 AUTOPSIES, LOS ANGELES COUNTY HOSPITAL, 1918 TO 1954

Tumors	Number	
Adenomas	.....	6
Liver Cell	2	.....
Bile Duct Cell	4	.....
Adrenal Rest Tumors	.....	0
Carcinomas	.....	107
Liver Cell[1]	81	.....
Bile Duct Cell	26	.....
Carcinoma of Infancy and Childhood	.....	0
Hemangiomas	.....	176
Hemangioendotheliomas	.....	0
Myxoma	.....	1
Hemangioendothelial Sarcoma	.....	1
Sarcoma (type uncertain)	.....	1
Miscellaneous Tumors	.....	2
Hepatic Mixed Tumors	0	.....
Carcinoma and Sarcoma combined[2]	2	.....
Focal Nodular Hyperplasia	.....	14
Mesothelioma of Glisson's Capsule	.....	1
Total	.....	309

[1] Includes 5 combined liver and bile duct cell carcinomas

[2] Also included among the liver cell carcinomas

A better understanding of liver tumors and their classification results from a study of the embryology of the organ. This applies to the possible relationship of tumors of both epithelial and mesodermal origin to the primitive tissue from which the liver is derived. The following discussion on embryology is based on the studies of Streeter at the Carnegie Institution, and of Horstmann. In the 16-somite embryo, the entodermal anlage of the liver can be seen just prior to the time it forms a ventral outpouching of the primitive foregut with a mass of undifferentiated mesenchyme situated just caudal to the heart and in front of the yolk sac (figs. 2, 3). This mesoblastic tissue is derived from the coelomic tract. Its earliest differentiation is toward the formation of angioblasts. It is usually stated that one anlage gives rise to the entire biliary tract, gallbladder, and liver parenchyma. The primitive entodermal cells form a single mass which invades the primitive mesenchyme and rapidly proliferates. At the same time, there is rapid angiogenesis in the mesenchyme with formation of the sinusoids. These sinusoids and the cells within their walls become the chief blood-forming organ in the embryo as the bone marrow is as yet undifferentiated. Since the primordial mesenchyme that gives rise to the vessels and connective tissue of the liver arises early in the growth of the embryo, it might properly be expected to retain some of its potentialities for differentiation into widely different types of tissue. This I believe occurs in many of the tumors of

infancy. As the liver grows, the bile ducts can be seen to penetrate farther and farther into the mass of liver cell sinusoidal tissue. For example, in the 12 mm. embryo the bile ducts can be seen for only a short distance in the hilar area where they are intimately associated with blood vessels and highly cellular connective tissue. The channels lined with bile duct epithelium fade imperceptibly into tiny canaliculi lined with pink-staining liver cells. This has led Streeter to suggest that the bile duct cells do not grow into the liver but that the existing cord cells change to a bile duct type of cell (fig. 4). This occurs in conjunction with the ingrowth of the mesenchyme of the portal tracts. Bile duct epithelium may be seen on one side of a duct where it is in contact with connective tissue, while liver cells bordering upon sinusoids complete the circumference of the duct (fig. 5). Following this redifferentiation of the liver cells they are probably unable, even in diseased states, to again form functioning hepatic parenchymal units. If this concept is correct, carcinomas arising from liver cells may, in the presence of mesenchymal tissue, form bile duct components, but those arising from bile ducts have forever lost the ability to form liver cell units. It must be kept in mind, however, that while the transition between the cholangioles and the peripheral intralobular bile canaliculi is a sharp one, the cells in this location may be capable of differentiation in either direction.

The liver on occasion gives rise to tumors composed of derivatives of one or more of the primitive germ layers, such as bone, muscle, or cartilage, which are not a part of the normal development of the organ. Although given a wide variety of names, these neoplasms are usually assembled under the terms "mixed" or "teratoid" tumors (Milman and Grayzel). They occur primarily in infancy and childhood. In this fascicle they are discussed in the sections on Hepatic Mixed Tumors, Malignant Hepatic Mixed Tumors, Teratomas, and Carcinoma of Infancy and Childhood.

Logic dictates that an attempt should be made to subdivide or segregate certain entities in this conglomeration: (1) the true teratomas as defined by Willis* are classified and described as such; (2) tumors composed of mesodermal elements only, such as blood vessels, fibrous tissue, and muscle, are classified as mesenchymomas and discussed under the section on Mesodermal Tumors; and (3) liver cell carcinomas with osteoid stroma seen in infants are discussed in two different sections. Many of the tumors in the last category differ very little from other liver cell carcinomas, since they contain only minimal amounts of osteoid, while others show osteoid as an outstanding gross and microscopic feature. For this reason the tumors in the third group are mentioned in both the section on Carcinoma of Infancy and Childhood and the section on Hepatic Mixed Tumors.

There remains a group of tumors containing epithelial and mesodermal elements which may be placed in the category of "mixed tumors." This is not

*Fascicle 9, "Teratomas."

a satisfactory term because of the unavoidable confusion with tumors of salivary gland origin which have a historical priority and carry the same name. The use of the term "hepatic mixed tumor" prevents any confusion in terminology on an anatomic basis.

Some of the problems in classification must be left unsolved, but whenever possible preferable terms were chosen with the realization that they may have to be changed at a future date. For example, it is difficult at present to be sure of the nature of some of the vascular tumors of the liver in infancy and childhood. The use of the term "hamartoma" constitutes another problem. In the sense that it denotes a developmental error, it is used only for a small group of cystlike lesions in infants, which do not appear to be true tumors. Any other usage of the term "hamartoma" as applied to liver lesions should be left, as Landing and Farber* have said in discussing the same problem, to the individual pathologist in accord with his beliefs in regard to the theories of origin.

Lastly, is the use of the term "hepatoma" desirable? In the literature, the inexact use of this term serves only to bewilder the reader. Most authors use it as a synonym for liver cell carcinoma in the human. Others have reported benign and malignant epithelial tumors as well as non-neoplastic proliferative lesions as hepatomas. The experimentalist is more likely to use it for benign tumors of the liver. Because of these wide differences in meaning, its use in human pathology seems unjustified.

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*Fascicle 7, "Tumors of the Cardiovascular System."

GEOGRAPHIC DISTRIBUTION OF PRIMARY LIVER CANCER

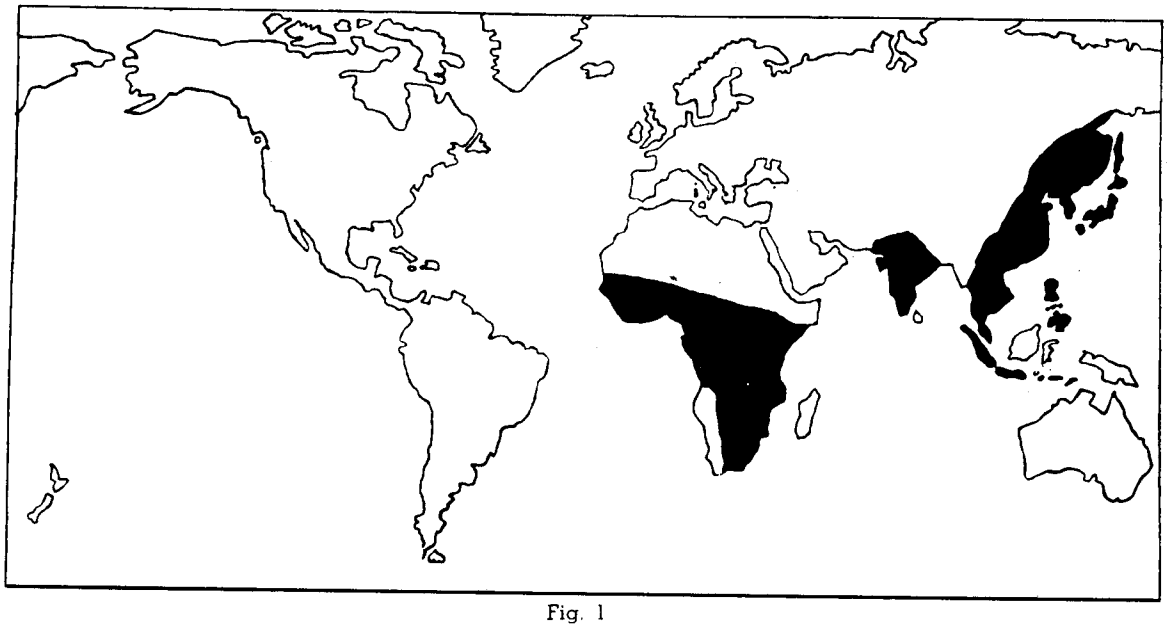

Fig. 1

Figure 1. Map showing geographic areas of known or suspected high primary liver cancer incidence. (This is adapted from figure 3 in Berman, C. Primary Carcinoma of the Liver. A Study in Incidence, Clinical Manifestations, Pathology and Aetiology. London: H. K. Lewis & Co., Ltd., 1951.) A. F. I. P. Acc. No. 218891–238.