Developments in Nuclear Medicine 1

P. H. Cox (editor)

Cholescintigraphy

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CHOLESCINTIGRAPHY

DEVELOPMENTS IN NUCLEAR MEDICINE

VOLUME 1

FOREWORD

This book is timely and fills a void in the area of cholescintigraphy in Nuclear Medicine. It is true that many articles and papers from symposia on this subject are available but they are all scattered through a volumnous literature. Dr Cox and his colleagues have brought together in an orderly fashion the current available material on hepatobiliary scintigraphy in an excellent volume suitable for both the clinician as well as the clinical scientist.

This volume begins with a detailed discussion of anatomy and physiological functions of the liver and biliary tract followed by a section on scintigraphic functional imaging of the liver. A description of the chemistry and pharmaceutical considerations of Tc^{99m} labeled hepatobiliary agents, especially those of Ida-derivatives is included. Next the text follows the usual pattern of discussion on the pharmacodynamics of radiopharmaceuticals, followed by a description of various clinical disease patterns of the liver and the use of cholescintigraphy in evaluating these diseases. The last sections deal with computer applications in quantitation of liver function followed by a discussion of the clinical role for Tc^{99m} labeled hepatobiliary agents in comparison to ultrasonography, CT, radiography and in vitro laboratory tests.

One notable feature of this book is its discussion on the evaluation of new agents in normal experimental animals and in animals with induced liver disease, correlating this data to define the best radiopharmaceutical and then evaluating the same in patients. This type of methodological treatment of the subject matter is commendable.

This volume also reflects the change in the conduct of nuclear imaging from an organ imaging concept to dynamic functional imaging. Hepatobiliary studies using Tc^{99m} labeled radiopharmaceuticals have really opened up a new area of imaging and quantitation of hepatocyte function. Newer agents may fulfill this latter objective more effectively.

To help clinicians from various other disciplines, Nuclear Medicine physicians must find out where scintigraphic methods can eliminate diagnostic uncertainties better than other approaches. They must also know the various drawbacks and pitfalls associated with every Nuclear Medicine procedure. Books like this one can help Nuclear Medicine clinicians in that respect. Certainly this text discusses the fundamentals, clinical applications and more importantly the limitations of cholescintigraphy in Nuclear Medicine. Dr Cox and his colleagues have clearly provided an excellent perspective on this subject.

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INTRODUCTION

The importance of the liver has long been recognized. Around 2000 BC the Sumarians reported it as being a collecting centre for blood and therefore the seat of life. This point of view was assimilated into the Assyrian and Babylonian cultures and in Plato's timaeus the liver is described as mirror reflecting the thought of the intelligent spirit which appeared to have a moral function and was influenced by bile and sweetness.

In twentieth century western medicine the liver is still regarded as being the seat of life but for different reasons and much time and energy has been utilized to develop ways and means of evaluating liver function.

The use of scintigraphy to visualize the liver is a well known and trusted technique. This has primarily been centred around the use of radioactive colloidal substances which accumulate in the Kupffer cells. For a variety of technical reasons reagents, such as Iodinated rose bengal and bromsulphophtalein which localize in hepatocytes have been little used.

In recent years, however, the development of Technetium labeled compounds which accumulate in hepatocytes and are rapidly excreted in the bile have represented a potential major breakthrough in the use of non-invasive methods for the investigation of liver disease. Of these reagents the most widely used have been derivatives of iminodiacetic acid (IDA) and in particular Diethylida.

By following the biological distribution of this reagent with time by means of serial scintigrams obtained with a gamma camera and by recording quantitative information in the form of time activity curves or functional images it is possible to obtain macroscopic information concerning liver morphology, to demonstrate biliary obstruction and to evaluate hepatocyte function in one study.

In this volume the scientific basis of cholescintigraphy has been outlined together with the application of this knowledge to the clinical situation. The results have been compared with those obtained using other diagnostic methods to demonstrate its value to the clinician especially in the study of the highly jaundiced patient when other studies may be of little value or even contra-indicated.

There is little doubt that cholescintigraphy has not yet reached its full potential. We hope that this volume will stimulate the optimum usage of this technique by providing a comprehensive basis upon which clinicians can form their own opinions.

P.H. Cox.

CONTENTS

1. THE LIVER AND BILIARY TRACT. ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

H.S.L.M. TJEN

1.1. The liver

The liver is the largest organ in the body weighing in the adult of 1200-1500 g comprising one fiftieth of the total body weight. It is located in the upper part of the abdomen where it occupies the right hypochondriac and the greater part of the epigastric region. A part of its surface is associated with the diaphragm. The location of the liver is dependent on the position of the body and varies with respiration. The topography is altered in some diseases and can be changed by displacement of the organ due to thoracic processes which may push the liver downwards (1). In contrast to the multilobulated liver of many mammals, the human liver is a compact and continuous mass of parenchyma. There are two anatomically distinct lobes, divided conventionally by the line of insertion of the falciform ligament. The right lobe is larger than the left lobe and has on its posterior-inferior surface two smaller lobes: the caudate and the quadrate lobes. The whole organ is covered by the fibrous capsule of Glisson. In the porta hepatis which is situated on the visceral surface of the right lobe, the branches of the hepatic artery and portal vein enter the liver and the common bile duct leaves the liver. At this point the capsule of Glisson enters into the liver following the blood vessels and biliary ducts.

The liver plays an important role in the intermediate metabolism and storage of carbohydrates, the metabolism of fats and amino-acids and the synthesis of proteins. It serves as a depository for numerous vitamins, enzymes and hormones and a large number of chemical syntheses are carried out. Bile is secreted into the bile ducts, synthetized from bile-salts and bile pigments.

The mammalian liver is made up of polygonal prisms, each representing a defined unit known as a lobule. Hepatic lobules were already discribed by Malpighi (2) in 1666 and Mascagni (3) in 1819. A more definite concept of hepatic lobulation as basic architecture was introduced by Kiernan (4) in 1833 who described the hexagonal lobule centered around the radicles of the hepatic veins. Running through the center of the lobule along its longitudinal axis, is

the central vein. At the periphery are situated the branches of the portal vein (intra-lobular vein), the interlobular bile ducts, branches of the hepatic artery and the lymphatics, which form a network about the portal vein and its branches. Many authors however have questioned the existence of the classic hexagonal lobule (5,6,7,8,9). Rappaport described acinar units and demonstrated that a lobule is centered around a terminal portal venule and adjoined at its periphery by one or more hepatic veins (10). Scanning electron microscopy of the liver confirmed this finding (11).

The plates of liver cells are separated from one another by the
The lining of the hepatic sinusoids is composed of an irregular alternation of two kinds of cells connected by many intermediate forms. One of these two lining cells are fixed macrophages, the phagocytic stellate cells of Von Kupffer which may contain phagocytosed material (12).

1.2. The blood supply of the liver

The importance of blood flow for hepatic function has long been appreciated and much attention has been given to methods of measurement. Abnormalities of the hepatic circulation cause reduced hepatocyte uptake capacity (13).

The liver circulation is characterized by its dual blood supply. It receives blood from the hepatic artery and the portal vein, which latter transports blood that has already passed through the capillaries of the gastro-intestinal tract and the spleen. The terminal vessels of the hepatic artery enter the portal fissure and follow the branches of the portal vein quite closely. The distribution of the vascular tree is just like the biliary tree within the liver and is strictly segmental. The hepatic arterial and the portal venous streams meet in the lateral portions of the liver lobules, where they enter the sinusoids. This mixed blood proceeds through these wide channels to the center of the lobule and enters the branches of the hepatic veins. After a short course it joins the inferior caval vein (14,15,16,17). By means of the Fick principle reliable estimates of the flow through the liver are possible, also (18,19,20,21,22,23) used infusion of bromsulphalein for the estimation of blood flow. Somewhat better is the estimation of blood flow by means of indocyanine green as described by Caesar (19) but a disadvantage is the instability of this compound in plasma. Radionuclides have also been used to estimate blood flow: ^{131}I-Rose Bengal was used by Winkler (22). In 1962 Ueda (24) used ^{198}Au for the determination of the ratios of flow through the hepatic arterial and portal vein. Pabst et al (25) found the clearance of radioactive gold to be useful for

measuring liver blood flow. Rees (20) and Mackenzie (23) described the use of ^{133}Xenon for this purpose.

1.3. The liver cell

The liver cells are arranged more or less regularly in columns extending radially from the central vein to the periphery of the lobule. In adults fine bile canaliculi run between the hepatic cells and form a condensation of the membrane of the hepatic cells (7). The structure and function of the hepatocyte is mostly polarized: materials are absorbed from the blood at the sinusoidal surfaces and bile constituents are secreted at the surfaces exposed to the bile canaliculi (26). Damage to the liver cell can therefore impair its function in two directions each independent of the other. The cytoplasm of the liver cell presents an extremely variable appearance which reflects to some extent the functional state of the cell.

The extensive use of electron microscopy correlated to cytochemical and histiochemical analysis has resulted in a new dimension in the understanding of liver disease in that disorders of organelles of the cells are being recognized. The absorptive and secretory surfaces of the liver cells are increased by the microvilli, projected into the lumen of the bile canaliculi and peri-sinusoidal tissue space (26,27). The mitochondria are the main and probably exclusive sites of oxidative phosphorylations (26), glycogeen synthesis also occurs there. In 1918 Cowdry (28) stressed already that mitochondria are much more sensitive indicators of cell damage than are nuclei. This statement has been confirmed by others (29,30). The endoplasmatic reticulum is a system of submicroscopic tubuli and flattened vesicles in the cytoplasma. It is possible to distinguish between a rough or granular reticulum and a smooth or agranular reticulum. The first is responsible for the synthesis of albumin and some globulins including fibrinogen (31). It has a high content of RNA. The latter has great importance for glycogenesis as pointed by Porter (32,33). Further it is the site for bilirubin conjugation and detoxification of many drugs and other foreign compounds (34). Other intrecellular structures are the lysosomes: pericanalicular dense bodies adjacent to the bile canaliculi (35). The nucleus containing DNA and the Golgi apparatus, which is also situated near the canaliculi and plays a role in the secretion of ingested material (36).

1.4. The biliary system

The biliary system commences with the intercellular bile capillaries and

canaliculi which empty into the smallest bile ducts. Ellinger and Hurt (37) first visualized the bile capillaries with fluorescence microscopy. The bile capillaries form an intercommunicating network within the center of the liver cell plates and appear to lie within grooves in them, though they actually constitute a part of them. The network of bile canaliculi drains to the smallest intralobular bile ducts, the cholangioles. In the portal tracts the cholangioles communicate with the smallest interlobular bile ducts. When the ducts become wider due to confluence of the smaller ones and approach the hilus, their epithelium becomes high columnar and mucus producing. The right and left lobar ducts which leave the liver in the porta hepatis become the right and left hepatic ducts and fuse to form the common hepatic ducts with a length of 2-3 cm. After the common duct is joined by the cystic duct on its right side, it forms the common bile duct. The normal internal biliary duct pressure is regulated by the secretory pressure of the liver, the distensibility of the gall-bladder and the resistance of the choledochal and ampullary sphincters (38). Recent studies have shown that there is no peristalsis in the common bile duct, only a milking action of the several sphincter muscles at its distal end (39,40). The physiological regulation of the flow bile into the duodenum can be thought of as the result of a balance between two types of pumps and one major resistance (41). The principal resistance to bile is provided by the sphincter of Oddi. Neural and hormonal stimuli can increase the flow of bile by contracting the gall-bladder and relaxing the sphincter of Oddi (42).

1.5. The gall-bladder

The gall-bladder is a pear-shaped, hollow structure, closely attached to the posterior surface of the liver. It consists of a fundus, a body and a neck which progresses into the cystic duct. It shows marked variations in shape and size and is frequently the site of pathological processes which change the size and thickness of the wall. The major functions of the gall-bladder are to concentrate and store bile and to deliver it to the duodenum during meals. When stimulated by cholecystokinine the gall-bladder also delivers the concentrated bile through the cystic duct into the common bile duct and the intestine (43). The mechanism of concentrating bile is an active process in and through the wall of the gall-bladder which absorbs fluid and electrolytes (44,45).

1.6. Bile formation and secretion of organic compounds in bile

Bile is produced in man at the rate of 15 ml per kg body weight in 24

hours (46,47). Total bile flow is largely determined by the flow of the blood through the liver (48). Bile flow varies with the portal blood flow, although sudden interruption of the latter decreases, but does not stop bile flow. In first instance the relationship between blood flow and bile production is controlled by hepatic cell function. The total amount of what is produced is defined by bile secretion in the canaliculi, in the ducti and by the biliary system (49). Bile acids induce bile flow, i.e. they induce fluid movement during their secretion into the biliary canaliculi (50,51,52) and it has been proved that the initial phase of the formation of bile is the active transport of bile-acids from parenchymal cells into the bile canaliculi. The osmotic effect of these substances results in a flow of water and solutes into the bile canaliculi. The total amount of bile that finally reaches the duodenum is further dependent on the entero-hepatic cycle of the bile acids (53,54).

Much of what we know about the secretion of bile originates from observing the livers of animals following the administration of fluorescent dyes (Grafflin (55), Mendeloff (56), Hanzon (57), described the behaviour of the dye sodium-fluoresceïn:

- within 3-10 seconds after intravenous injection the dye appears in the blood plasma of the hepatic sinusoids, then in the Kupffer cells and after 15-32 seconds traces of the dyes are found within the liver cell. Bile canaliculi contain the dye 26-27 seconds after it reaches the sinusoids. In 30-60 minutes the liver cells are cleared of the dye, although it can be detected in the canaliculi as long as two hours after injection.

In the last years kinetic analysis has been carried out with radioactive tagged substances (58,59). When the excretion of bile is abruptly interrupted by mechanical obstruction of the bile ducts, bile continues to be formed and is absorbed from the liver at first through the lymphatics and later by the blood vessels of the liver (57). Hanzon (57) suggests a leakage from the bile canaliculi into the blood, either between or through the liver cells. Leakage most often develops in injured liver cells of which the permeability has been altered because of the raised pressure in bile ducts. However the toxic action of a high consentration of bile acids may be important. In prolonged biliary obstruction there is an astonishing degree of biliary hyperplasia and liver cell atrophy, perhaps due to chemical irritation, that commences within a few days of obstruction (47).

Organic substances can enter the bile by diffusion, secretion or filtration. Mechanisms by which many substances enter the bile are closely associated

with the mechanism of bile formation (51). Extracellular fluid to cell transfer may consist of active transport, facilitated by diffusion, pinocytosis or a combination of these processes. Accumulation within the cell often results from binding to cell components and it is possible that active transport contributes to the accumulation (60). The nature of the transfer process is determined by the kind of organic compound.

1.7. Types of compound present in bile

Two kinds of substances are present in hepatic bile.

1. Those which are found in concentrations that differ slightly from those found in plasma; they represent a protein free ultrafiltrate of plasma formed by the liver cells. The chief examples are Na^+, K^+, Cl^-, creatinine, glucose and cholesterol (47).
2. Others such as bilirubin and p-aminohippurate, are much more strongly concentrated in bile than in plasma and reach the bile by an active secretory mechanism. In addition bile acids are secreted after their synthesis by liver cells.

ad 1

The organic compounds which appear in bile in a concentration similar to or smaller than in plasma include lipid-insoluble molecules, highly lipid soluble weak electrolytes and a miscellaneous group or organic ions. Studies of the hepatic uptake and biliary excretion of lipid-soluble drugs are complicated by the fact that most of these substances are metabolized by the liver (61). Large, lipid-insoluble molecules enter the bile via restricted diffusion or filtration (62). Large insoluble molecules could enter the liver cells either by diffusing through pores in the cell membrane, or by being taken up by some non-specific transport process such as pinocytosis (63,64). An alternative pathway for these substances from extracellular fluid to bile would be through intracellular spaces (62). When this latter pathway may be open to all substances it is to a degree dependent on the size of molecules.

ad 2

The compounds which appear in bile in a concentration greatly exceeding that of plasma, are transfered against a sizeable concentration gradient and have to pass at least two membranes between plasma and the bile: a substrate must penetrate a liver cell before it can be secreted into bile. Therefore there is strong evidence that plasma-to-cell and cell-to-bile transfer takes place by a process of active transport. Mendeloff (56) showed an accumulation of Rose Bengal in