LIVER
Anaesthesia and Critical Care

Post graduate course
XIth internatonal meeting
of anaesthesiology and resuscitation
1979

SOCIÉTÉ FRANÇAISE d'ANESTHÉSIE, d'ANALGÉSIE et de RÉANIMATION

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publishers :

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Translation of french texts
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Librairie Arnette
2, rue Casimir-Delavigne
Paris

1980

Excerpta Medica
305 Keizersgracht
Amsterdam

Sole Distributors for the USA and Canada :
Elsevier/North-Holland Inc.
52 Vanderbilt Avenue
New York, N.Y. 10017

ISBN 90-219-0445-4
(ISBN 2-7184-0219-9 French edition)

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The histology and ultrastructure of the normal liver

G. FELDMANN*

Independently of the cells which form the walls of the portal vein, the hepatic artery, the bile ducts and the centrilobular vein, two varieties of cells are found in the liver : the hepatocytes and the sinusoidal cells [1, 3]. These cells are arranged within the organ in a characteristic order of which the elementory unit is the hepatic lobule [1, 3]. The lobule appears as a mass of cells that is occuped in its center by the centrilobular vein. Peripherally, it is limited by a variable number [3 to 6] of portal spaces. The portal spaces contain afferent vessels (branches of the portal vein and the hepatic artery) and the duct which drains the exocrine secretion of the parenchymal cells, the bile duct. The centrilobular vein constitutes the efferent vessel. The sinusoidal capillaries radiate outward from the portal spaces towards the centrilobular vein. The hepatocytes are disposed between the sinusoids. They form the liver cords that extend from the portal space to the centrilobular vein. The sinusoidal cells line the sinusoidal capillaries.

This description points out the unusual character of the vascularization of the hepatic lobule : the two afferent vessels, one arterial and the other venous, empty into a common capillary bed which is drained by a single vein. Because of the arteriovenous anastomoses, mixture of the venous and arterial blood takes place in the portal spaces and also in the sinusoids, since small branches of the vein and the artery empty directly into the sinusoidal capillaries. At the entrance to the sinusoids, there exist neuromuscular sphincters which are involved in the regulation of the intrabobular circulation [5]. However, there are no such sphincters where the sinusoid rejoins the centrilobular vein.

The histological definition of the hepatic lobule also corresponds to the elementary functional unit of the liver [1, 3]. Conventionally, the component cells are divided into 3 categories. In the periportal zone, the best-oxygenated cells are found ; their metabolism is the most intense. In

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the pericentrilobular zone, oxygenation is less satisfactory and cellular metabolism is much less marked. An intermediate situation exists in the mediolobular zone. The centrilobular zone appears to be the most fragile, and in the event of drug intoxication, lesions appear the most firstly in this zone.

The understanding of the structure of hepatocytes and sinusoidal cells has been greatly enhanced with the advent of the electron-microscope [1, 3, 7, 10]. The hepatocyte appears as a voluminous polyhedral cell (20-25 µm) (Fig. 1). Its nucleus is often situated in the center of the cell and is usually rounded. Two faces of the cell are in relationship with the neighbouring hepatocytes ; the othe faces are lined by the sinusoids (Fig. 1

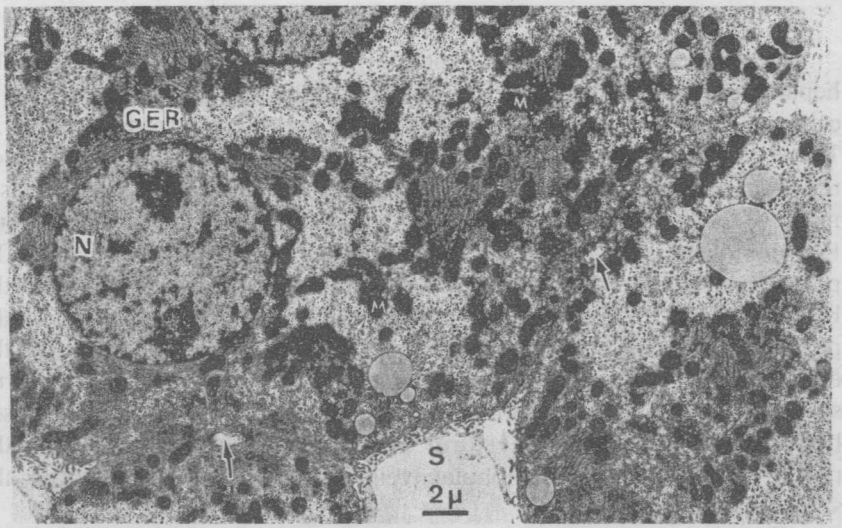

Fig. 1. — General appearance of hepatocytes in the electron microscope. Two faces of the hepatocyte are in contact with adjacent cells ; one face is in contact with the sinusoid (S) (N : nucleus ; GEG : granular endoplasmic reticulum ; M : mitochondrion ; the arrow indicates a bile canaliculus) (× 3000).

and 7). The surfaces of two adjacent hepatocytes are separated by a thin intercellular space in which the bile canaliculus is situated (Fig. 1). On either side of the canaliculus, space communicates freely with the sinusoid (Fig. 7).

Within the cytoplasm of the hepatocyte, several kinds of organelles are found [1, 3, 7], which may be divided into three categories.

1) Organelles responsible for the great majority of the metabolic functions of the cell, namely, the granular endoplasmic reticulum (GER), the smooth endoplasmic reticulum (SER) and the Golgi apparatus (GA) (Fig. 1, 2, 3, 4 and 5).

The GER appears as a network of membrane bounded cavities, commonly referred to as cisternae. This network is usually situated around

the nucleus of the cell (Fig. 1). It consists of a variable number of elements, continuous one with the next. The external surface of the membranes is studded with another round organelles, the ribosomes, with or diameter of about 20 nm (Fig. 2 and 5). Ribosomes are found either isolated on the

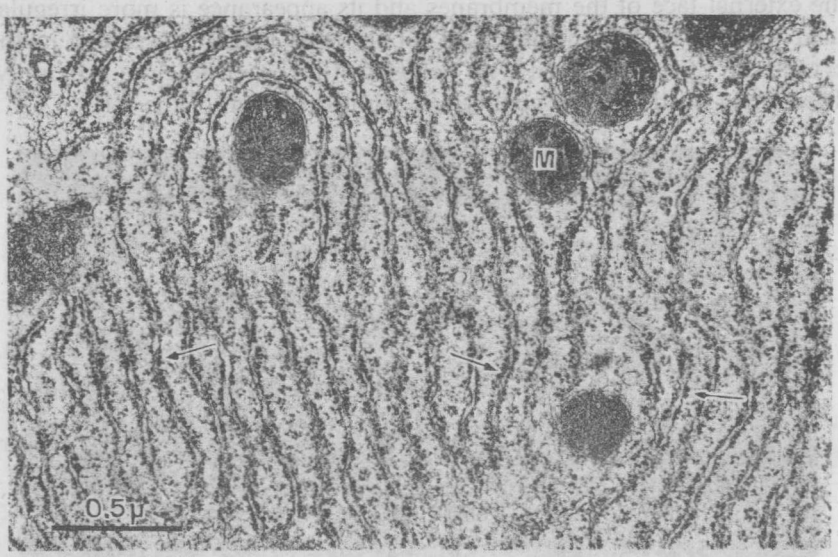

Fig. 2. — Hepatocyte. Ultrastructure of the granular endoplasmic reticulum. The ribosomes (arrow) are situated on the external surface of the membranous network (M : mitochondrion) (× 32000).

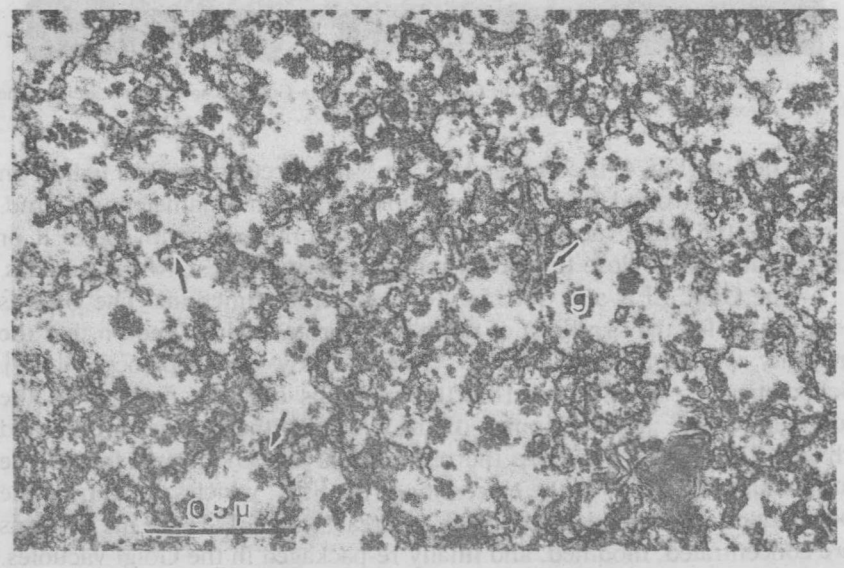

Fig. 3. — Hepatocyte. Ultrastructure of the smooth endoplasmic reticulum. The surface of the membranous network is free of ribosomes. It is composed of tubules and vesicles (arrow) (g : glycogen) (X 40000).

surface of the endoplasmic reticulum, or grouped in bundles of 5 or 10. The latter are referred to as polysomes.

The SER (Fig. 3) also appears as a membranous network but may be distinguished from the GER by two criteria. There are no ribosomes on the external face of the membranes and its appearance is more irregular than the G.E.R. It is made up of tubules and vesicles dispersed in the cytoplasm, often associated with deposits of glycogen in close proximity. The lumen of the SER is continuous with the lumen of the GER.

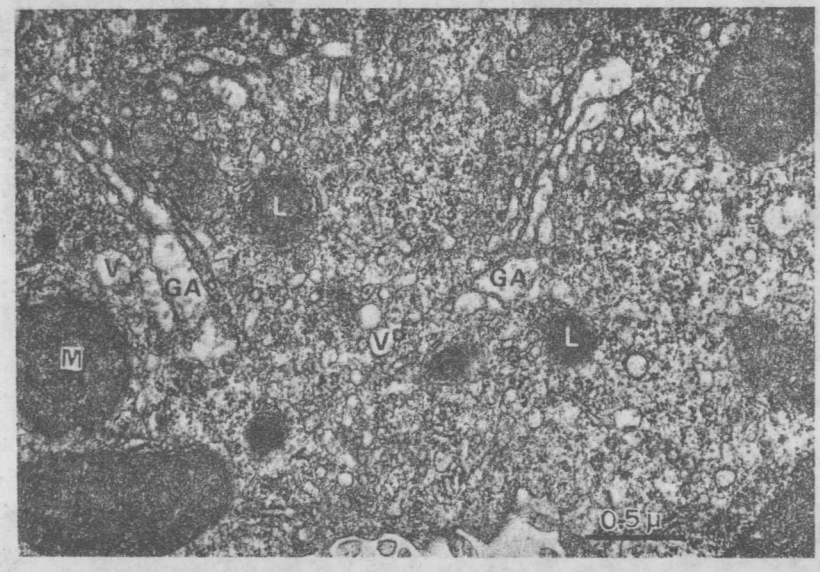

Fig. 4. — Hepatocyte. Ultrastructure of the Golgi apparatus (GA). Golgi vacuoles (V) are seen around the Golgi saccules (M : mitochondrion ; L : lysosome) (X 26000).

The GA (Fig. 4) is composed of 2 or 3 flat saccules, stacked tightly on one another. Around the saccules, vacuoles of variable diameter are found. These are the Golgi vacuoles. The GA is not continuous with the SER or GER, but it has a close functional relationship with these two organelles.

The GER, SER and GA carry out numerous functions. The GER is responsible for the synthesis of the plasma proteins. It is known that the majority of these proteins are synthesized by the hepatocyte [4, 9]. Schematically, we may describe the synthesis of these proteins in the following way : the polysomes of the GER synthesize the amino acid chains. The chains penetrate the cisternae of the GER, and follow the lumen upto the SER. At the extremity of the SER, vesicles containing the polypeptide chains bud off the SER and reach the GA. Here, the proteins are concentrated, modified, and finally re-packaged in the Golgi vacuoles. The Golgi vacuoles release their contents into the sinusoid by a mechanism of exocytosis. As the proteins pass from the SER to the GA, they

progressively aquire their definitive structure, for example, when glycoproteins are synthesized, carbohydrates from the cytoplasm are transfered and attached to the polypeptide chains by means of specific enzymes, the transferases, which are contained within the menbranes of the SER and GA. The synthesis of lipoproteins proceeds in a similar way.

The SER of the hepatocyte has other more specific functions. Among others things it is responsible for the transformation of non-conjugated bilirubin into conjugated bilirubin, again by means of a membrane enzyme system [9]. The SER is also involved in the enzymatic hydrolysis of glycogen [7], and actively participates in the metabolism of certain drugs [6]. Several years ago it was shown that is is possible to increase the latter function, for example by using inducing drugs such as phenobarbital. This induction is characterized biochemically by an increase in the activity of the enzymes of the SER. From a morphological standpoint, visible evidence of induction is revealed by an enormous increase in the volume of the SER. This modification is referred to as proliferation [6].

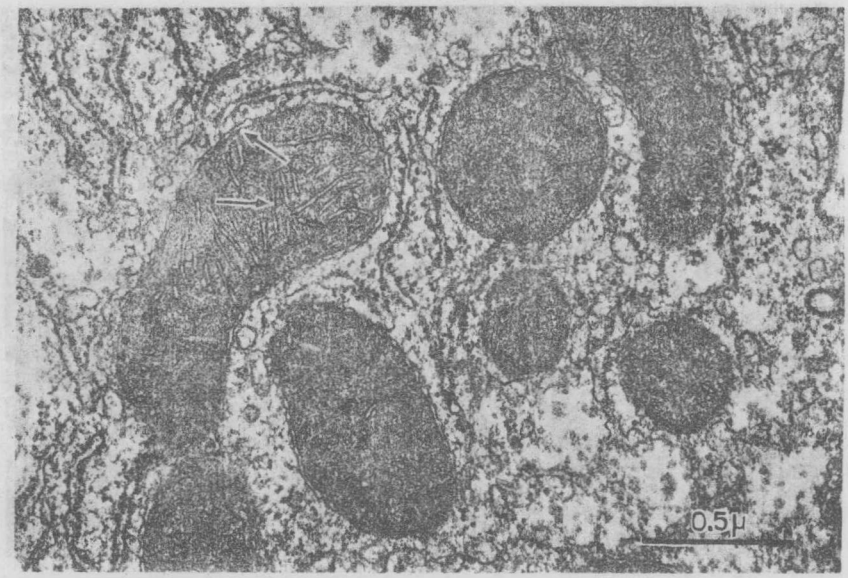

Fig. 5. — Hepatocyte. Ultrastructure of mitochondria. Oxidative phosphorylation takes place on the cristae and on the inner membrane of the organelle (arrow). Some mitochondria are situated at close proximity to the ribosomes of the granular endoplasmic reticulum (X 40000).

2) Organelles responsible for the production of energy, namely, the mitochondria (Fig. 5)

Mitochondria are round or elongated organelles whose diameter varies between 1 and 3 microns. Their structure is complex : a double peripheral membrane encloses the mitochondrial matrix, where expan-

sions of the inner mitochondrial membrane, the cristae, are found. The various biochemical elements of the enzymatic systems responsible for oxidative phosphorylation are found on the inner membrane and on the cristae. The function of mitochondria is to product ATP, which is released into the cytoplasm of the cell according to its energy requirements. The highest density of mitochondria in the cell is usually observed in the areas where the energy is needed the most, for example near the GER (Fig. 5).

3) Organelles responsible for the removal of waste and debris, namely, the lysosomes (Fig. 4 and 6)

Lysosomes are spherical organelles that measure between 0.5 to 1 micron in diameter. They are essentially membranous sacs containing numerous hydrolytic enzymes. Lysosome functions are autophagy (destruction of degenerate organelles) and heterophagy (destruction of substances forcing substances captured by the hepatocyte).

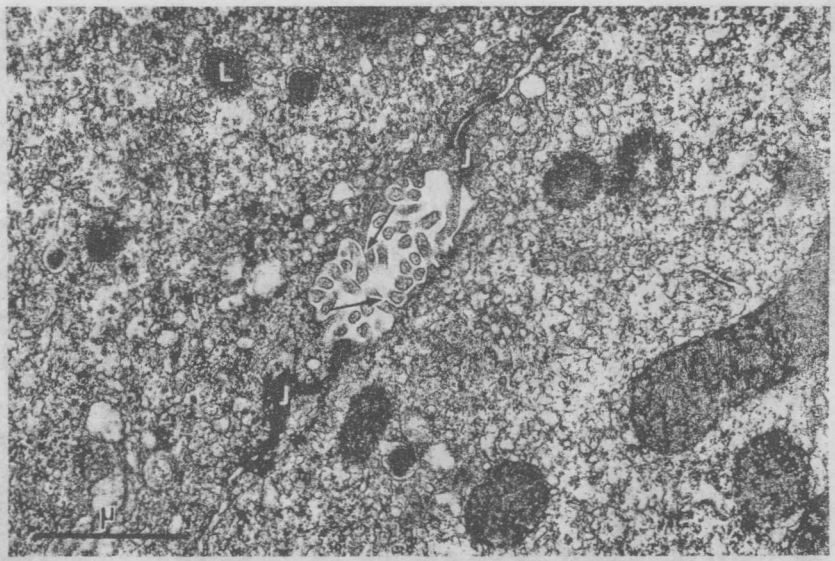

Fig. 6. — Hepatocyte. The bile canaliculus appears in the electron microscope as a dilation of the intercellular space. The microvilli that extend from its wall obstruct the lumen (arrow). Tight junctions (J) on both sides block the passage of bile into the intercellular space (L : lysosome) (X 40000).

The compounds synthesized or metabolized by the hepatocyte may be exported by two possible routes. This cell has the particularity of possessing two different modes of secretion at the same time : an exocrine mode and an endocrine mode. The product of the exocrine function is the bile. The different biliary components are excreted into the bile canaliculi. These have a round or oval shape (Fig. 6). Their walls are formed by the

plasma membrane of 2 neighboring hepatocytes. Microvilli project into the lumen of the canaliculus. The bile canaliculi are not connected to the intercellular space : tight junctions block the passage of biliary elements into this space. Around the canaliculus, on the cytoplasmic side, there exist microfilaments composed of actin, a contractile protein, that has recently been shown to be involved in cholestasis [2]. The bile canaliculi form a continuous network that extends from the pericentrilobular hepatocytes to the periportal hepatocytes. When the canaliculus reaches the area around the portal space, it is no longer surrounded by hepatocytes, but by cells of a distinctly different nature, the biliary cells. This structure is called a bile duct.

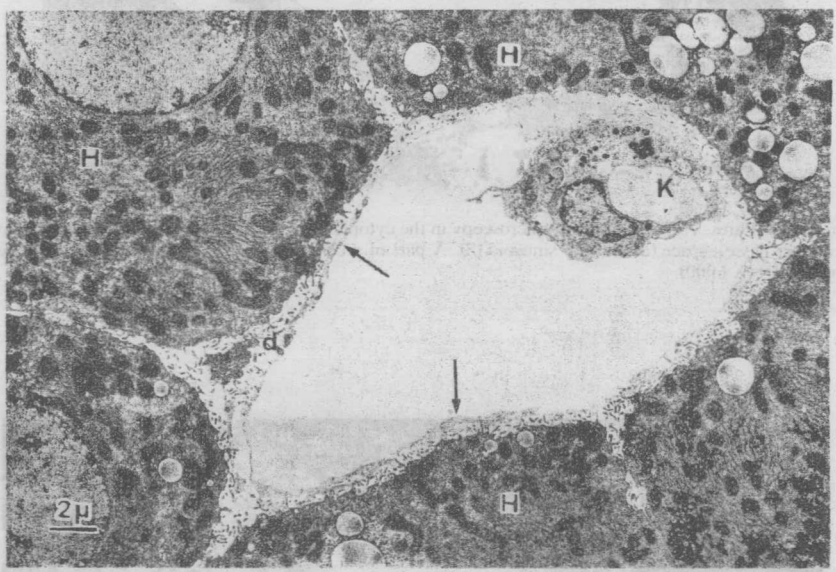

Fig. 7. — Ultrastructure of a sinusoidal capillary. Disse's space (d) is between, the hepatocytes (H), the Kupffer cell (K), and the endothelial cells, of which only the extensions of the cytoplasm are visible. The absence of erythrocytes in the lumen of the sinusoid is due to a technical artifact (X 3000).

The endocrine function of the hepatocyte involves the numerous compounds that are excreted into the sinusoids. The arrangement of the capillaries with respect to the hepatocytes facilitates this function [10]. There are three kinds of sinusoidal cells (endothelial cells, Kupffer's cells and Ito's cells) which line the sinusoids, but they are not pressed close to the plasma membrane of the hepatocytes. There is a narrow space which separates the cells, called the space of Disse (Fig. 7 and 8). Microvilli protruding from the hepatocyte are visible in this space and in some areas, reticular fibers are present. There is no basement membrane, however. Moreover, there are no junctions between the sinusoidal cells ; between each of them there are spaces which facilitate the passage of the products