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A Histological Study of the Structural and Functional Unit of the Liver of the Mouse:

I. On the Distribution of Mitochondria*

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ABSTRACT

The hepatic structural and functional unit of the mouse was demonstrated by quantitative distribution of mitochondria in preparations which were cut serially 5 micra thick after embedding in paraffin and stained with Heidenhain's iron hematoxylin.

In the hepatic structure of the mouse there were three different geometrical areas: the perivascular area of the portal stem, which continued to the preterminal portal branch, of the preterminal vein and of the terminal portal twig, which were considered to be the real functional unit and extended into the neighbouring hepatic lobules.

Mitochondria of the hepatic cells were contained in the perivascular portion adjacent to the portal vessels and were deposited less toward the peripheral portion of the portal vessels.

The pericentral area of the central vein in the hepatic lobule or the structural unit, and the perivascular area of the sublobular vein corresponded to the peripheral zone of the actual functional unit described above.

As the structural unit of the hepatic tissue, the hepatic lobule was first recognized grossly by Wepfer (1664), and Malpighi (1666) isolated the smallest parenchymal masses attached to the finest portal vessels by the teasing method and called them hepatic acini.

Kiernan's (1833) hepatic geometrical concept of the morphological organization, which was based on the secretory activity of the liver, was not satisfactorily adopted.

Brissaud and Sabourin (1888) considered the secretory hepatic unit, which represented the amount of liver parenchyma that was drained by the bile canal of the portal triad, as the functional or actual unit of the liver.

Mall (1906) presented the portal unit of the liver as the hepatic structural unit. Elias (1948 a, b) presented the new structural theory of the liver as being composed of parenchymal plates tunnelled by a network of lacunae.

Rappaport et al. (1954) described the structural unit in the dog and rabbit as a small, irregular, berry-like, parenchymal mass situated around the terminal branches of the portal triad by the use of portal venous injection with Ranvier's carmine gelatin and india ink. Rappaport (1958) demonstrated the hepatic structural and functional units or acini in the human liver post mortem by the portal injection of india ink.

The present investigation was made in an attempt to determine whether the cytological or functional characteristics of the hepatic cells in different parts of hepatic lobule are in accordance with the general concept of the hepatic lobule described in the textbooks of histology or Rappaport's presentation of the hepatic acini.

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MATERIAL AND METHODS

The livers of male and female mice were freshly obtained after decapitation. Small pieces of liver tissue measuring about 3 mm in the longest diameter were fixed in Helly's and Regaud's fixatives and then were cut serially 5 micra thick after embedding in paraffin. The sections were stained with Heidenhain's iron hematoxylin for mitochondria and with hematoxylin and eosin.

RESULTS

In preparations of the mouse liver stained with hematoxylin and eosin and iron hematoxylin, the boundary of each hepatic lobule was not demonstrable because of scant interlobular connective tissue. Also the interlobular hepatic artery was hardly recognizable in the portal space.

According to the quantitative distribution of mitochondria in hepatic cells in different areas of the hepatic lobule, as demonstrated in preparations stained with iron hematoxylin, if the long hepatic lobule were cut transversely, the area heavily deposited with mitochondria could easily be differentiated from the scantily contained area around the central vein. Mitochondria contained in hepatic cells became denser toward the periphery of the hepatic lobule. In such a preparation, the most heavily deposited area might correspond to the boundary of the hepatic lobule.

In observing the perivascular area around the portal stem which continued to the preterminal portal branch, the hepatic cells composed of several layers around the portal stem contained many mitochondria which were granular in shape, as a rule. This periportal area was one of the areas with the heaviest concentration of mitochondria in the hepatic lobule. Also the short and slender collateral twigs arising from the portal stem usually coursed perpendicularly or obliquely to it and opened into the sinusoids near the portal stem.

Both perivascular areas of the portal stem and of the terminal portal branches were densely deposited with mitochondria, being will nourished with fresh blood, the former from the collateral twigs arising from the portal stem and the latter from the terminal twigs of the portal veins opening into the sinusoids. The fact that mitochondria were packed densely in those areas could be explained by the above findings. In the areas densely deposited with mitochondria, hepatic cells containing enzymes related to certain metabolic processes might be more active than the other hepatic cells were.

The perivascular area of the preterminal portal branch, which mainly ran perpendicularly or obliquely to the long axis of the hepatic lobule, revealed a marked deposition of mitochondria in the hepatic cells, while the pericentral area adjacent to it showed less or almost no amount of mitochondria in the hepatic cells.

Similarly, the perivascular area of the portal terminal branch which ran as the former, showed almost the same results in the hepatic cells.

If the portal stem, preterminal portal branch and terminal portal branch were cut transversely, the densely deposited perivascular area with mitochondria around them appeared circular in shape, and if longitudinally, columnar in shape.

In pursuing the course of the sublobular vein, the perivascular area of it showed almost the same result as the pericentral area.

Analyzing the areas densely deposited with mitochondria and the less deposited areas, the former might correspond to the central portion of the hepatic acinus described by Rappaport which extended into the neighbouring hepatic lobules, and the latter correspond to be the peripheral area of the acinus.

The geometrical concept of the hepatic lobule which was depicted in the textbooks of histology and was composed of a parenchymal plate tunnelled by hepatic sinusoids, is considered to be nothing but a structural idea.

Both the perivascular areas densely deposited with mitochondria surrounding the nutrient vessels, and the peripheral areas less deposited with them surrounding the above mentioned vessel, together might form the so-called acinar structures described by Rappaport et al.

DISCUSSION

Knisely (1939) Wakim and Mann (1942) and others paid attention to the vascular architecture of the hepatic circulation in vivo and differentiated the active circulatory portion of the hepatic lobule from the quiescent portion near the former. Rappaport et al. (1954) believed that the neighboring 2 different portions mentioned by Knisely belonged to different structural units and indicated the small piriform mass of parenchyma surrounding the terminal afferent vascular twigs as the unit of the hepatic tissue or the functional hepatic unit.

Reviewing the nutrition of the hepatic parenchyma in the hepatic lobule, the fact that the peripheral portion of the lobule was first nourished with fresh blood entering from the terminal twigs of the interlobular artery and the portal vein into the sinusoids, was described by Mann (1926). In the hepatic unit or grape-like irregular acinar agglomerations of hepatic parenchyma which were situated perpendicular to the central veins and surrounding terminal and the preterminal twigs of the portal triad presented by Rappaport et al, the parenchymal cells best supplied with fresh blood were thought to be those adjacent to the terminal vascular twigs, even though distant from the portal space.

Mall (1906) presented the new hepatic lobule or unit; the portal unit or lobule which was cylindrical in shape and its parenchyma was arranged around the axis of the portal triad in the portal space. Mall's portal unit adoped by Arey (1932) and Opie (1944), failed to correlate structure with function.

Elias and Sokol (1953) found an inclination to present the liver as an indivisible mass and to consider lobulation as a matter of conjecture. They believed that the hepatic lobulation changed with the variation in pressure in the afferent and efferent vessels. The inversion of the lobular pattern would be hard to interpret. The sudden transformation of one real lobular system into another by pressure changes, which used to be quite common in veins, was not comprehended by others.

Lipp (1952) described the embryology of the human liver and stated that the hepatic parenchymal plates developed from the cell cord were organized along their nutrient vessels, and Rappaport et al considered that Lipp's finding was in accordance with the basic law that all tissues in our body depended upon their nutrient vessels and that the basic law held also for the liver, and therfore the units of the liver were presented as organized around their nutrient vessels.

The presence of an identical zonal blood flow pattern in the areas around the terminal afferent vascular branches had been observed by Brauer (1955) in the isolated and perfused rat liver. Rappaport (1958) presented the outline of circulatory zone 1, 2, 3 which were concentric to the axis of the simple acinus.

It would be expected that the normal enzymatic and chemical activities of the hepatic cells would vary in the different portions of the hepatic lobule. Schumacher (1957) pointed to the activities of respiratory enzymes, such as succinic dehydrogenase and cytochrome oxidase, and showed that they were particularly concentrated in the peripheral portion of the hepatic lobule, while DPN- and TPN-diaphorases were confined to the pericentral portion of the hepatic lobule of the rat, the horse, and the pig. Schumacher concluded that the differential distribution of the enzymes was closely related to the blood flow, especially the oxygen tension, in the hepatic lobule and further speculated that since the enzymes under study reflected only part of an integrated metabolic system, it might be assumed that other chemical components would reveal similar distribution patterns in the liver. Similarly the author found that the quantitative distribution of mitochondria in the liver of a mouse varied in different portions of the hepatic lobule, as mentioned above.

As described above, the perivascular zone of the sublobular vein contained a less amount of mitochondria in the hepatic cells than the pericentral zone of the hepatic lobule showed.

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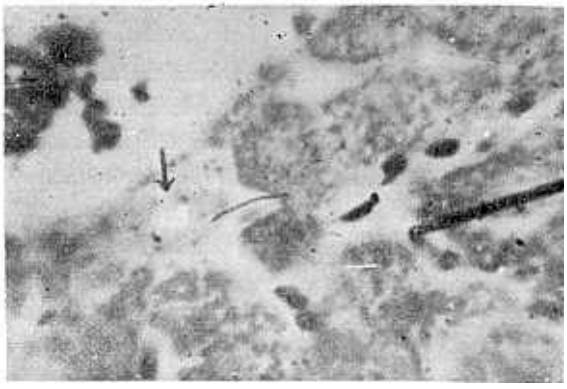

Fig. 1. Hepatic cells deposited with a great amount of mitochondria near the preterminal portal vessel located at the upper left corner. One bile duct is indicated with an arrow.
Iron hematoxylin stain. × 1000.

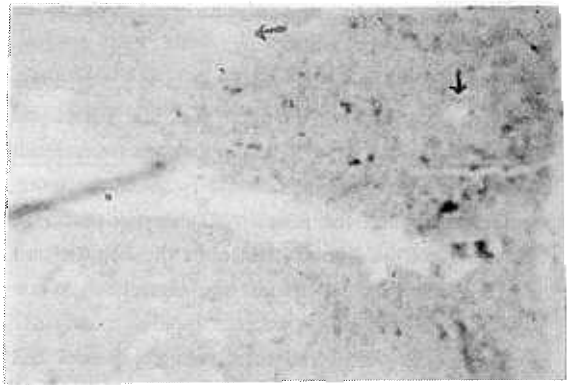

Fig. . Perivascular area, densely deposited with mitochondria, of the portal stem which gives off a few collateral twigs to the liver parenchyma. 2 pericentral areas, less deposited with them, are indicated with arrows.
Iron hematoxylin stain. × 1000.

Fig. 3. Collateral twigs, indicated with an arrow, arising from the portal stem and perivascular area and densely deposited with mitochondria are shown. Iron hematoxylin stain. × 400.

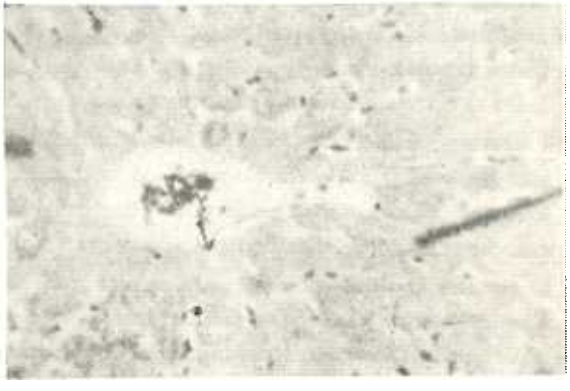

Fig. 4. Perivascular area, densely deposited with mitochondria, of the preterminal portal vessel. One bile duct is indicated with an arrow.
Iron hematoxylin stain. × 400.

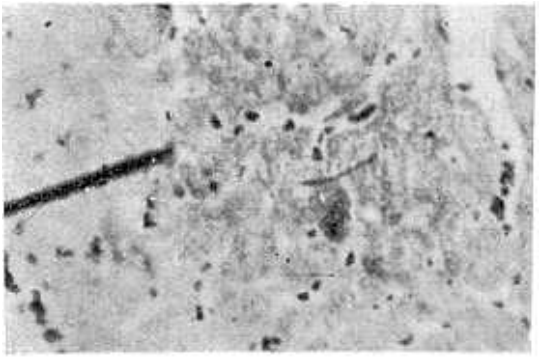

Fig. 5. Perivascular area, densely deposited with mitochondria, of the terminal twigs located at the right upper corner. Iron hematoxylin stain. × 400.

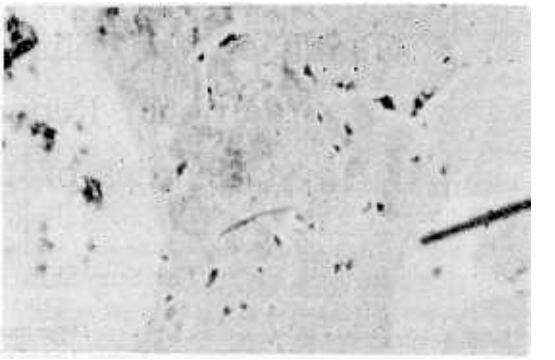

Fig. 6. Perivascular area of the portal stem, at the left side and pericentral area of the central vein, at the right side. Iron hematoxylin stain. × 400.

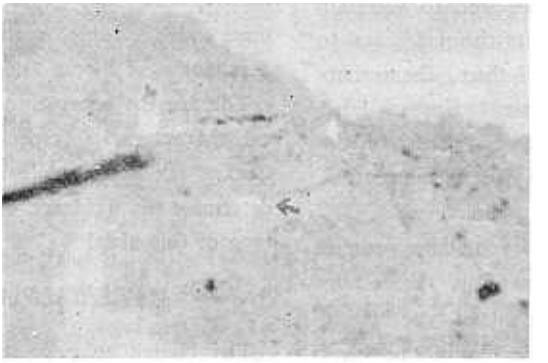

Fig. 7. Pericentral area of the central vein indicated with an arrow and the portal stem at the lower portion, the preterminal portal branch which is interrupted at the left and the terminal portal twig with darkly stain stained erythrocytes at the upper portion. Iron hematoxylin. × 100.