The Fine Structure of Rat Liver Sinusoids, Space of Dissé and Associated Tissue Space [1]

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ABSTRACT Three structurally distinct zones are present in the liver sinusoid. The endothelium and basement (boundary) membrane of the portal vein extend uninterruptedly into the peripheral zone. The intermediate zone, comprising 90% or more of the length of the sinusoid, possesses a fenestrated lining and no basement membrane. The short central zone has unfenestrated endothelium and a basement membrane. Both are continuous with those of the central vein. The space of Dissé encircles all three zones of the sinusoid. It contains fat storage cells, perisinusoidal cells, numerous microvillae of liver cells and reticular fibers. These fibers are bundles of unit collagen fibers enclosed by cytoplasm of nearby cells. The space of Dissé is continuous with the tissue space at both ends of the sinusoid. The liver cells lack a basement membrane whether they abut on the space of Dissé or on the tissue space proper.

The unique feature of liver fine structure is the combination of fenestrations and lack of basement membranes in the intermediate zone of the sinusoid. Blood plasma is thereby afforded intimate contact with the parenchymal cells and has access to the tissue space at both ends of the sinusoid. This structural situation fits the known facts of liver function.

The relationship of fine structure in the liver lobule to blood vascular channels is a subject of more than ordinary interest. Early electron microscopic studies of the liver (Rouiller, '54, '56; Fawcett, '55; Parks, '57; Hampton, '58; Novikoff and Essner, '60) revealed fenestrations in the sinusoidal wall and absence of a basement membrane. Hampton ('60) observed "material indistinguishable from basement membrane" in the space of Dissé. However, he hesitated to interpret this material as membranous because of the rapid transit of intravenously injected colloidal particles across the space of Dissé into the parenchymal cells. Wood ('63) compared the sinusoids of calf and rat liver. He observed a basement membrane in the calf, but no fenestrations. Conversely, there was no basement membrane in the rat but fenestrations were present. Later, Hampton ('64) studied liver from rat, mouse, dog, human and newborn rabbits. He observed a basement membrane only at the periphery of the liver lobule, close to the interlobular tissue space containing branches of the portal vein, hepatic artery and hepatic ducts. His contribution is the only one that has related fine structure to its location within the liver lobule. More recently, Kuhn and Olivier ('65) have reported that hepatic sinusoids are not fenestrated in the goat and are surrounded by basement membranes. They agree with Wood ('63) that the structure of the sinusoids may vary in different species.

It appears that most observations of liver sinusoids have been made without realization of the highly systematic arrangement of basement membranes (boundary membranes; Low, '61; basal laminae, Fawcett, '61) throughout the body. These correspond to the PAS-positive membranes described in light microscopy by Gersh and Catchpole in 1949. In electron microscopy they are extracellular structures which generally define the limits of the tissue space (Low, '61, '64; Battig and Low, '61; Low and Burkel, '65). Although uninterrupted basement membranes are an integral part of tissue patterns in fine structure, incompleteness of this coat does characterize certain slow-flowing vascular channels (Farquhar, '61; Weiss, '61; Moe, '63).

The diversity of observations suggested that liver tissue could be fruitfully re-

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examined. This article accordingly describes fine structure in the rat liver sinusoid with special emphasis on the significance of basement membranes. The findings are interpreted with reference to the pattern of fine structure found elsewhere in the body, as well as with certain features of liver development, function and pathology.

MATERIALS AND METHODS

Liver tissue from 20 healthy, young adult, albino rats was fixed by two methods. (1) Thirteen rats were perfused through the left ventricle with 3% glutaraldehyde (Sabatini et al., '63) using a technique similar to that of Palay et al. ('62). Small pieces of liver were subsequently excised, minced, washed in buffer and post-fixed in 1% OsO_4. Both fixers were buffered with 0.1 M phosphate at pH 7.4. (2) Pieces of liver from seven rats were fixed by immersion in 1% OsO_4 buffered at pH 7.4 with either veronal acetate (Palade, '52) or phosphate (Millonig, '61). Tissue blocks were dehydrated in a graded series of alcohols or acetone. The 50% alcohol or acetone contained 1% phosphotungstic acid. Tissues were left in this solution for 30 minutes to one hour instead of the usual 10 to 15 minutes. Embedment was in either Vestopal W (Ryter and Kellenberger, '58) or Epon 812 (Luft, '61) followed by polymerization at 60°C for 24 hours.

Thick sections (1–2 μ) were made of the face of the entire embedded tissue block. These were stained with 1% toluidine blue in 1% borax for one minute. The orientation of liver lobules was studied in these sections by light microscopy. The block was subsequently trimmed and sectioned for electron microscopy. The area selected always contained a portion of a portal and/or central vein so that sinusoids communicating with these structures within the plane of section could be studied. Thin sections were mounted on single-hole grids with or without formvar membrane and stained with lead citrate (Reynolds, '63; Venable and Coggeshall, '65).

OBSERVATIONS

The structure of the liver sinusoid differs in various parts of the lobule. The presence or absence of basement membranes and cellular fenestrations determines three distinct zones through which blood must flow as it passes from the periphery of the lobule to the central vein (fig. 2). The *peripheral zone* is the first, where the branches of the portal vein and hepatic artery enter the lobule. The *intermediate zone* comprises most of the length of the sinusoid. At the third or *central zone* the sinusoid enters the central vein.

Peripheral zone. At the periphery of the lobule the sinusoid resembles a capillary of type A-1-α (Bennett el al., '59) for a distance of 10–50 μ (figs. 3, 4). Its endothelium is non-fenestrated and is enclosed in a continuous basement membrane without cellular investment. The perisinusoidal space of Dissé is between the sinusoidal wall and parenchymal cells. It contains microvillae of parenchymal cells and bundles of unit collagen fibers (reticular fibers). This portion of the space of Dissé resembles the interlobular tissue space and is continuous with it.

Intermediate zone. The transition from peripheral to intermediate zones is abrupt, often occupying only 5–10 μ (figs. 3, 4, 5). The basement membrane disappears after becoming spotty. The lining cells become somewhat thinner and develop fenestrations (fig. 6). This is the sinusoid described in early electron microscopic investigations of the liver (Rouiller, '54, '56; Fawcett, '55; Parks, '57; Hampton, '58; Novikoff and Essner, '60; Wood, '63). Its structure corresponds to capillary type B-3-α of Bennett et al. ('59). Here the space of Dissé is essentially vascular. No demonstrable structure hinders access of the blood plasma to the numerous microvillae of the parenchymal cells. The intermediate zone comprises 90% or more of the length of the sinusoid.

Central zone. As the central vein is approached the structural situation again changes (fig. 7). The endothelium becomes continuous and a basement membrane appears. This change is more abrupt than the transition from peripheral to intermediate zones. The space of Dissé becomes typical tissue space and is continuous with this space around the central vein. The central zone of the sinusoid is the shortest of the three. It is often diffi-

cult to demonstrate because of its extreme brevity.

The basement membrane that is present at both ends of the sinusoid is continuous with the same structure surrounding the endothelium of all connecting blood vessels.

Von Kupffer cells possess no basement membranes. They usually have the same relation to parenchymal cells as lining cells, but often span the sinusoidal lumen (fig. 8). Their cytoplasm possesses more endoplasmic reticulum and mitochondria, but does not always contain particulate material. Positive identification is sometimes difficult.

The parenchymal cells of the rat liver possess no basement membranes. Their basal surfaces are characterized by microvillae which are most numerous along the sinusoids (figs. 6, 9). Here they extend into the perisinusoidal space of Dissé. Where parenchymal cells abut on the interlobular tissue space (fig. 4) or surround a central vein (fig. 7), microvillae are also present, but are less numerous.

The space of Dissé itself contains microvillae, reticular fibers and bits of cytoplasm. The microvillae nearly fill the space in many localities (fig. 9) and sometimes project into the sinusoid through fenestrations (figs. 5, 9). Reticular fibers traverse the space, usually running in cytoplasmic gutters. The cytoplasm which isolates them may be derived from the cell bodies of parenchymal cells (figs. 4, 5, 7), or lining cells (fig. 9). Unidentifiable pseudopod-like processes in the space of Dissé, larger than microvillae, also invest reticular fibers (fig. 10). These may be derived from perisinusoidal cells (Wood, '63; Kuhn and Olivier, '65) or fat storage cells (Ito and Nemoto, '52; Yamagishi, '59; Nakane, '63) of the sort shown in figures 10 and 11. Positive identification is difficult because the cell body usually lies out of the plane of section.

DISCUSSION

It is evident that there is an orderly variation of fine structure in different parts of the rat liver lobule. Figure 1 illustrates the chief regional characteristics observed in this study. In the intermediate portion of the lobule the presence of fenestrations and the absence of basement membranes provide the blood plasma with unimpeded access to the liver cells. This occurs in the space of Dissé, which is continuous not only with the sinusoidal lumen but also with the tissue space at both ends of the sinusoid. An unusual relationship results, involving vascular system, parenchyma and tissue space (Rhodin, '64). It is, however, best understood as a variant of similar relationships found elsewhere in the body, and may be interpreted along the lines suggested below.

Basement (boundary) membranes generally define the limits or boundaries of the tissue space. They form a structural framework which isolates epithelium (including endothelium and mesothelium), muscle, nerve and fat from the tissue space. Within this space lie the formed elements of the connective tissues (Low, '61; Battig and Low, '61; Low and Burkel, '65). As an expression of this pattern the endothelium of the blood vascular system is separated from the surrounding tissue space by its basement membrane. This is especially notable in capillaries. Likewise, the parenchyma of organs, usually epithelial, is separated from the tissue space by its own basement membrane. A small amount of tissue space usually persists between the basement membranes of different tissues. This situation characterizes all but a few areas of the body, of which the liver lobule is a notable exception.

Where the common bile duct and the portal vein enter the liver they possess "normal" basement membrane relationships. A typical epithelial basement membrane continuously encloses the bile ducts and continues to the ends of the ducts of Hering. Here the basement membranes end (fig. 1). The parenchymal cells themselves lack basement membranes whether they abut on the tissue space proper or on the space of Dissé. The endothelium of the portal vein is likewise sheathed by a basement membrane to its smallest branches. This basement membrane continues to enclose the peripheral portion of the sinusoid where it terminates. The same situation in reverse applies to the hepatic veins, the central veins, and the central portions of the sinusoids. It follows that no basement membranes are

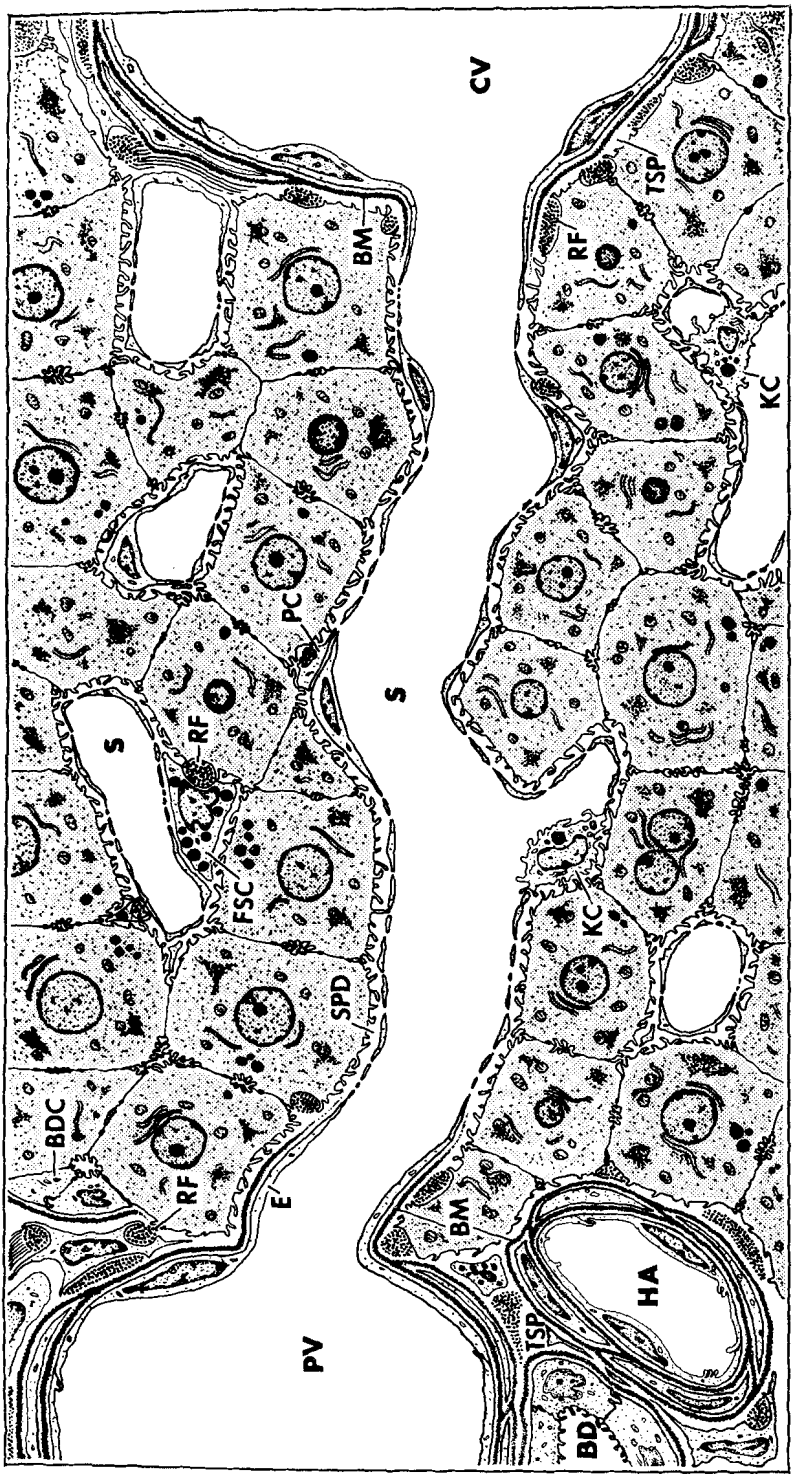

Fig. 1 *Fine structure in the rat liver lobule.* The periphery of the lobule is at the left where branches of portal vein (*PV*) hepatic artery (*HA*) and bile duct (*BD*) lie in the tissue space (*TSP*). Above, bile duct cells (*BDC*) abut on liver cells. The sinusoid (*S*) connects the portal vein with the central vein (*CV*). In the peripheral portion of the sinusoid both the endothelium (*E*) and its basement (boundary) membrane (*BM*) are continuous with those of the portal vein. In the intermediate portion the lining is fenestrated and there is no basement membrane. Centrally the cellular lining is continuous with the endothelium of the central vein and a basement membrane is present. Reticular fibers (*RF*) are found in the tissue space and in the space of Dissé (*SPD*) which surrounds the sinusoids. In places the sinusoids are lined by the cells of von Kupffer (*KC*). Perisinusoidal cells (*PC*) and fat storage cells (*FSC*) are in the space of Dissé. See text for interpretation.

present in the intermediate portion of the lobule where the sinusoidal lining is fenestrated. It is here that blood plasma has free access to the liver cells. This circumstance collates well with certain features of hepatic development and pathology as well as with normal liver function.

The lining cells of the liver sinusoids are derived from or closely associated with the mesenchyme (Aterman, '63). These cells have accordingly been described as "undifferentiated" (Wolf-Heidigger, '41; Maximow and Bloom, '57; Hampton, '64), "embryonic" (Altschul, '54; Gasser, '55), or "primitive" (Rüttner et al., '56; Rondez and Rüttner, '60; Ham and Leeson, '61). Their primitiveness is attested to by their multipotential response to stimulation. They may become hemopoietic stem cells (Sorenson, '60; Ham and Leeson, '61) or phagocytes (Hampton, '58, '64; Ham and Leeson, '61). In certain pathological conditions they organize to form non-fenestrated endothelium and even develop basement membranes (Schaffner and Popper, '63). In this condition they are indistinguishable from capillaries. These changes are comparable to the normal development of the mesodermal derivatives other than the connective tissues. Muscle, urogenital epithelium, mesothelium and most endothelium acquire basement membranes as their specialization progresses. It appears then, that the lack of basement membranes around the sinusoids is in accord with the primitive status of the lining cells.

The parenchymal cells of the liver also possess characteristics that suggest primitiveness. Their regenerative capacity is well known (Leduc, '63) and their fine structure is so lacking in specialization that they have become the cellular prototype of the cytologists. The absence of a basement membrane between them and the tissue space is difficult to understand if one accepts the idea of entodermal origin. If, as is generally held (Patten, '53; Arey, '54) they are entodermal extensions of the ducts of Hering, then they are the only known entodermal derivatives without a basement membrane. On other hand, mesodermal origin for these cells (reviewed by Bloom, '26) has been claimed by investigators over a span of more than half a century (Elias, '55) and still finds occasional support (Wilson et al., '63). Although no new embryological evidence is offered here, the absence of basement membranes, the unspecialized fine structure of the cell itself and the idea of mesodermal origin all fit together.

The fine structural situation responsible for intimate contact between blood plasma and parenchymal cell naturally focuses attention on the space of Dissé. Close examination shows that this unusual space communicates freely with the vascular lumen through the fenestrations and likewise with the tissue space at the periphery and center of the lobule. This provides a pathway for the seepage of blood plasma into these areas that has been suspected to account for the large volume and high protein content of hepatic lymph (Trowell, '46; Bloom and Fawcett, '62; Brauer, '63). The bundles of unit collagen fibers (reticular fibers) in the tissue space at the margins of the lobule are in their "normal" environment. As they course through the space of Dissé to the intermediate portion of the lobule they enter a primarily vascular zone. Here they are enclosed by cytoplasmic sheaths which tend to isolate them from this unusual environment.

The species variations appearing in the sinusoids of calf (Wood, '63) and goat (Kuhn and Olivier, '65) are not incompatible with the interpretations presented herein. The presence of unfenestrated endothelium and basement membrane in these forms may be interpreted as extended development to the point reached by capillaries in most areas of the body. The pathology of chronic liver disease reflects similar changes, since Schaffner and Popper ('63) observed essentially this process in cases of long standing cirrhosis.

The unique fine structure of the liver lobule really represents an alteration of a master pattern that is found throughout the vertebrate body in general (Low, '64; Low and Burkel, '65). All published reports, although differing in specific detail, can be interpreted as variations of this pattern. Normal developmental processes and certain of the abnormal changes of pathology alike bear coherent relationship to the conceptual norm. This concept, that of variable but patternized fine structure,

provides an interesting framework for interpreting the complex and ever-changing events of liver metabolism.

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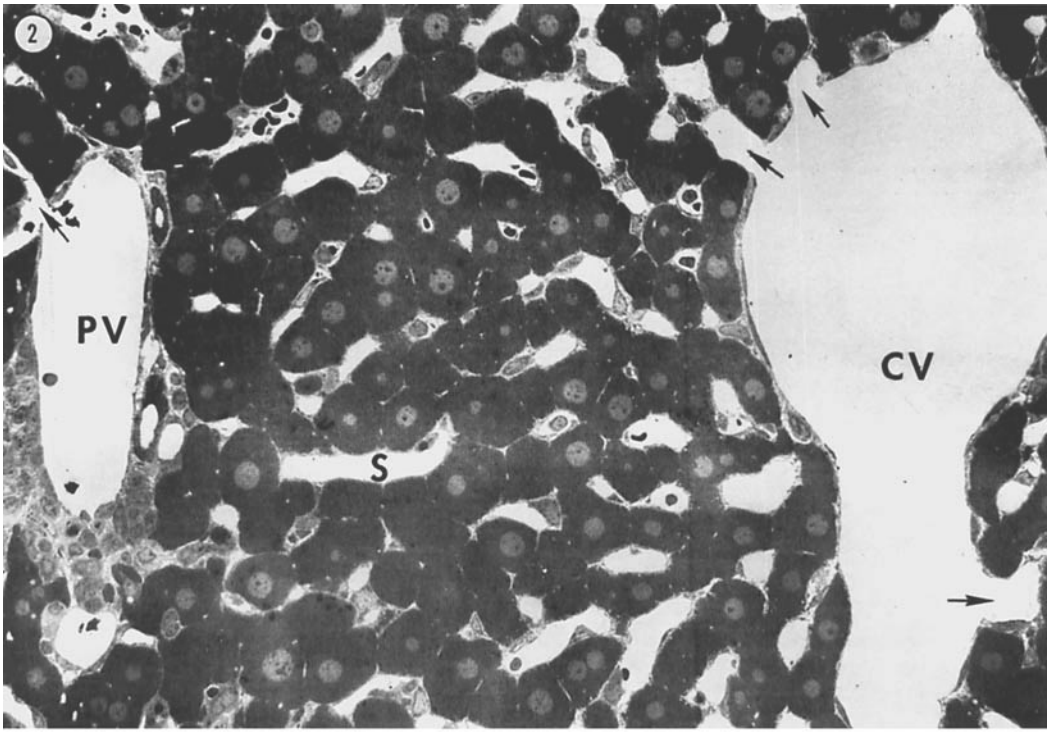
Note added in proof: Stenger ('66) has recently reported capillarization of liver sinusoids with development of basement membranes in carbon tetrachloride poisoning. This is essentially the reaction described by Schaffner and Popper ('63) in long standing cirrhosis and may be similarly interpreted.

PLATE 1

EXPLANATION OF FIGURES

2 Low power micrograph of lobule. Open vascular channels, some of which contain a few residual blood cells, characterize perfused liver preparations. The portal vein (PV) connects with the central vein (*CV*) by sinusoids (*S*), which open freely into both vessels (arrows). The irregular path followed by the sinusoids prevents demonstration of their entire course in the plane of a single section. The complete traverse of a sinusoid from portal to central vein is diagrammatically represented in figure 1, which summarizes fine structure in the rat liver lobule. Glutaraldehyde; OsO_4; Epon; 360 ×.

3 Junction of portal vein with sinusoid. The portal vein (PV) is identified by nearby bile duct (*BD*). Numerous cells in the tissue space (*TSP*) also characterize the periphery of the lobule. The sinusoid (*S*) is bridged over at one point by lining cells in the plane of this section, but communicates freely with the portal vein. The endothelium (*E*) and basement membrane (*BM*) of the portal vein continue without interruption into the peripheral zone of the sinusoid. The inset illustrates the transition from the peripheral to the intermediate zones of the sinusoid. Here the basement membrane ends. Fenestrations appear deeper in the sinusoid (arrows). This situation is illustrated at far left above and in figure 6. Note the continuity of the tissue space and the space of Dissé (*SPD*) from the portal vein to the sinusoid. Glutaraldehyde; OsO_4; Epon; 3,200 × (inset 8,700 ×).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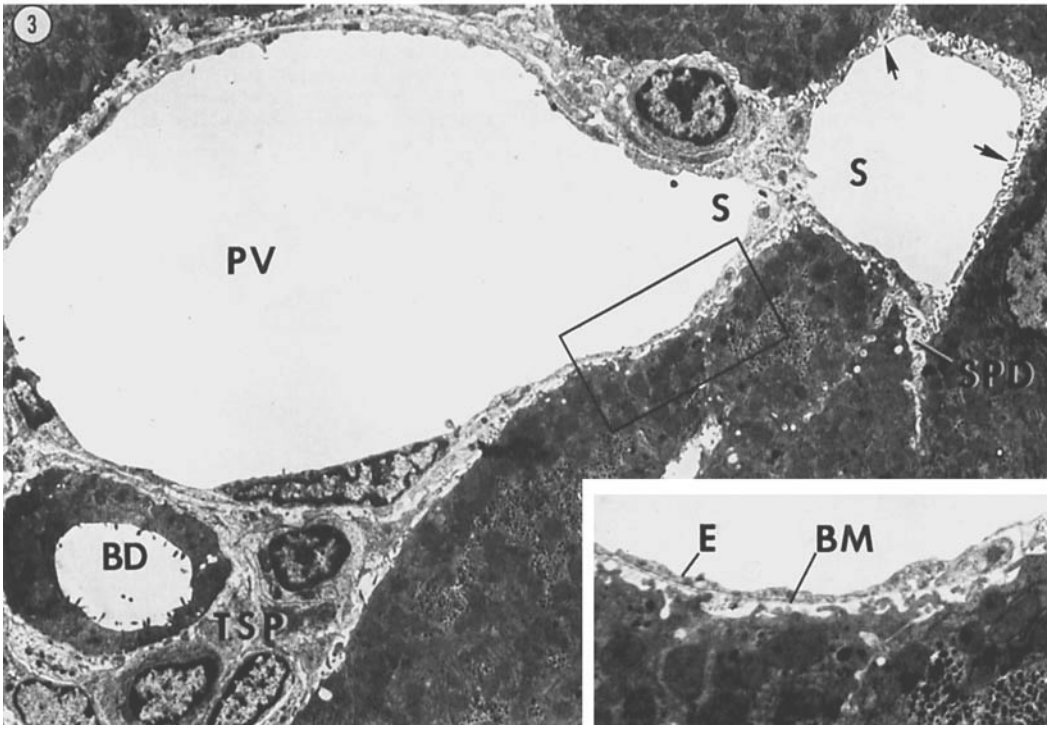
3
PV
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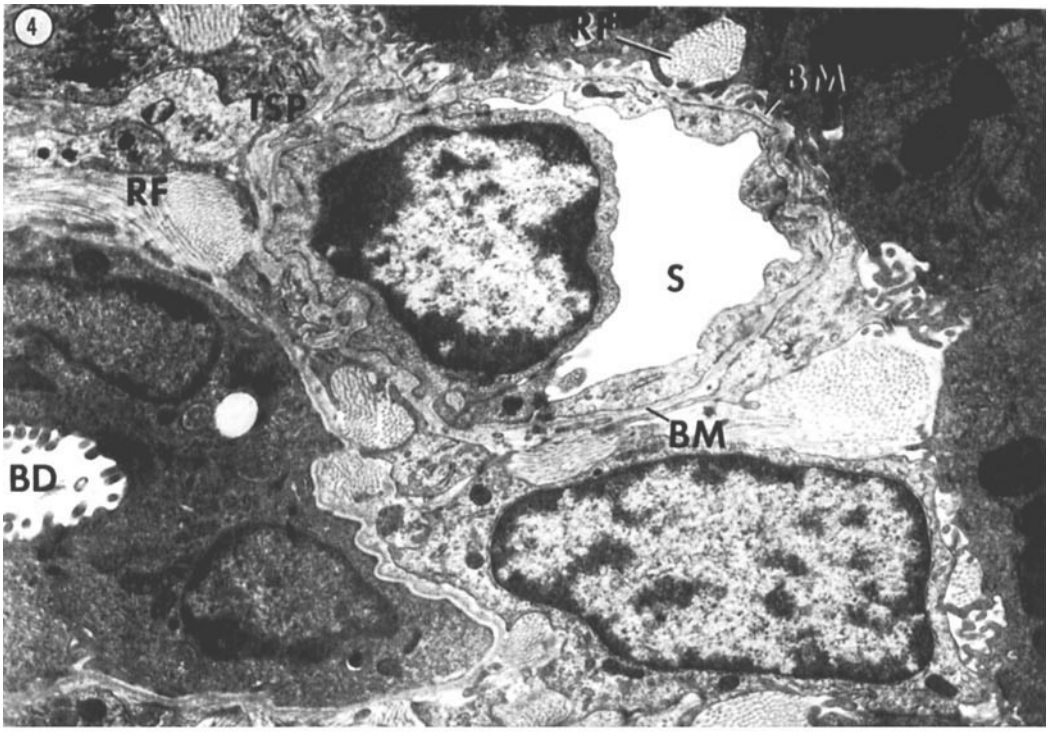
BD
TSP
E
BM

PLATE 2

EXPLANATION OF FIGURES

4 Peripheral sinusoid. The bile duct (*BD*) and the numerous reticular fibers (*RF*) in the tissue space (*TSP*) characterize the periphery of the lobule. The left and the lower portions of the sinusoid (*S*) abut on the interstitial tissue. Above and to the right its relations to the parenchymal cells and the reticular fiber are typical of the peripheral sinusoidal zone. Note the basement membrane (*BM*) around its entire circumference and the absence of endothelial fenestrations. This sinusoid was traced well into the liver lobule in nearby sections. Glutaraldehyde; OsO_4; Epon; 13,800 ×.

5 Transition between peripheral and intermediate zones. This sinusoid is deeper in the lobule than the one illustrated in figure 4. The terminal portion of the basement membrane of the peripheral sinusoidal zone is visible along the upper sinusoidal wall (arrows). Elsewhere the structure of the wall defines the zone as intermediate as illustrated in figure 6. The cytoplasmic sheath separating the reticular fiber (*RF*) from the space of Dissé (*SPD*) is typical. Note the microvillus (*MV*) projecting through the fenestration. Glutaraldehyde; OsO_4; Epon; 10,700 ×.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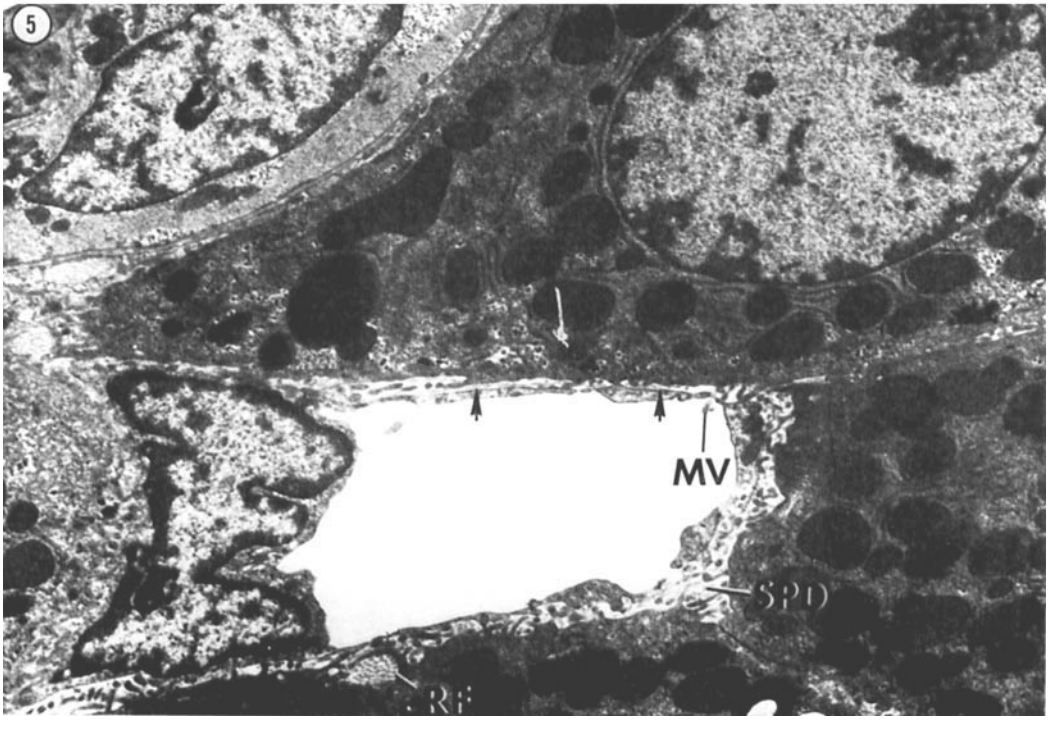
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SPD
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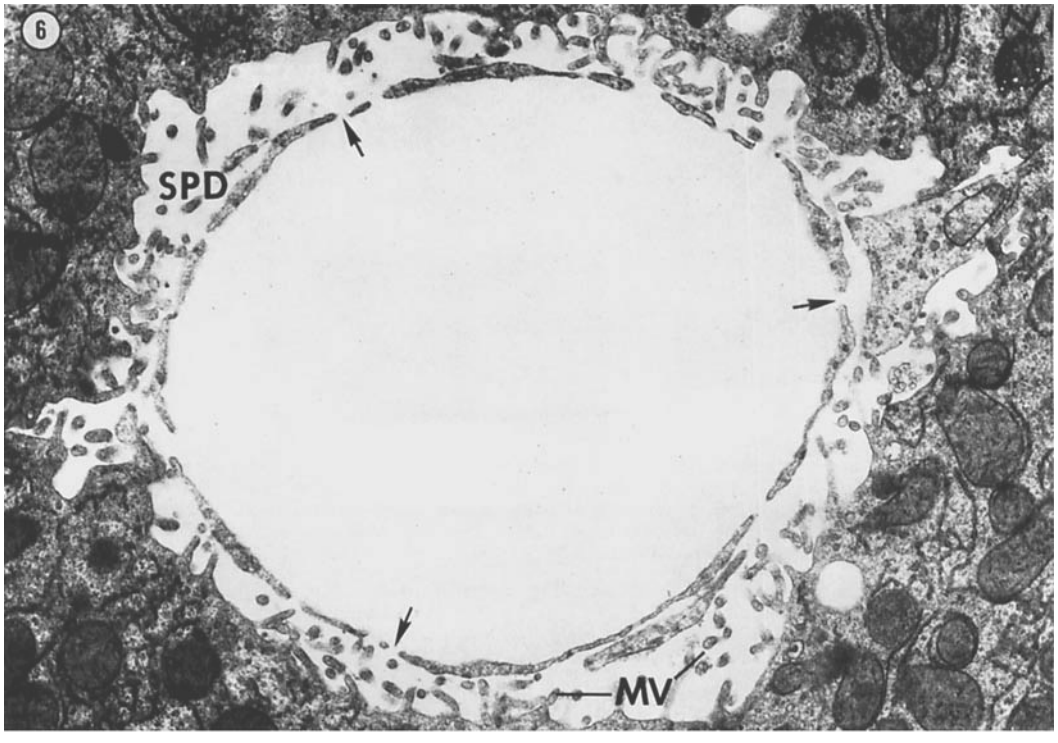
PLATE 3

EXPLANATION OF FIGURES

6 Intermediate sinusoid. The lining cells possess fenestrations (arrows) and there is no basement membrane. The space of Dissé (*SPD*) is voluminous. The surface of the parenchymal cells is characterized by numerous microvillae (*MV*). The blood plasma has free access to the liver cells. Glutaraldehyde; OsO_4; Epon; 13,500 ×.

7 Sinusoid entering central vein. The extremely short central zone is established by the presence of the basement membrane (*BM*); note inset. The reticular fiber (*RF*) at the left is surrounded by a cytoplasmic sheath typical of the space of Dissé. The reticular fibers on the right are more openly located to the tissue space (*TSP*). OsO_4; Epon; 11,900 × (inset 29,000 ×).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SPD
MV

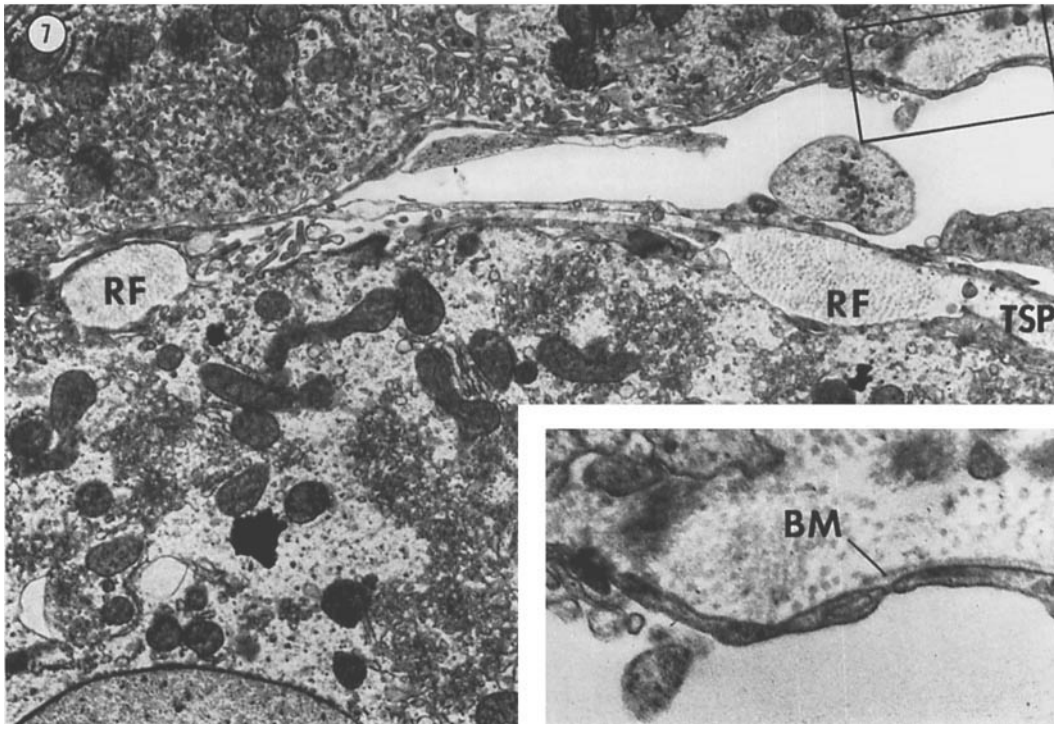

7
RF
RF
TSP
BM

PLATE 4

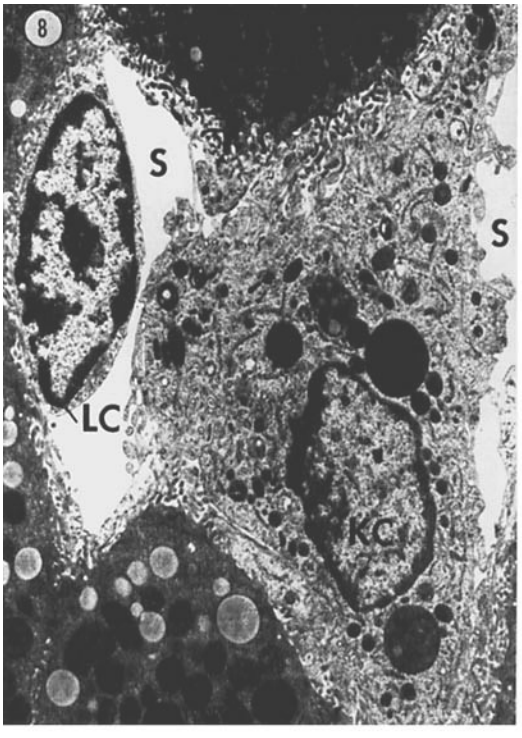
EXPLANATION OF FIGURES

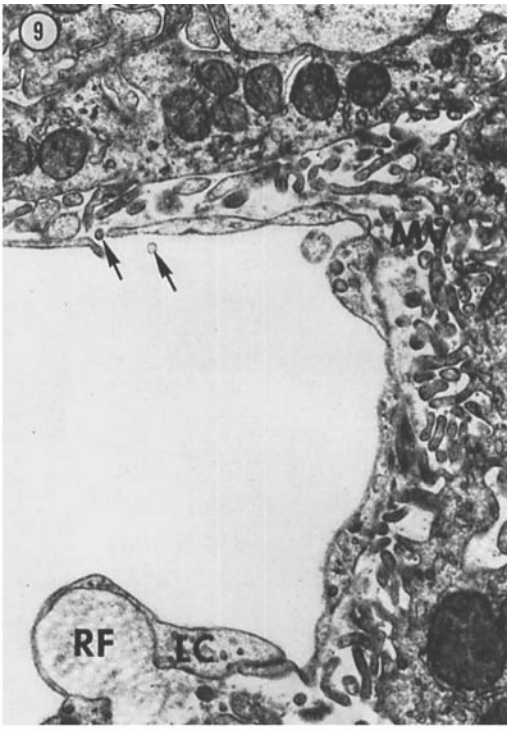
8 Intermediate sinusoid with von Kupffer cell. The large von Kupffer cell (*KC*) spans the sinusoid (*S*). It is in intimate contact with both blood and parenchymal cells. There is no basement membrane. The abundant cytoplasm contains more organelles than that of the lining cell (*LC*). Glutaraldehyde; OsO_4; Epon; 6,500 ×.

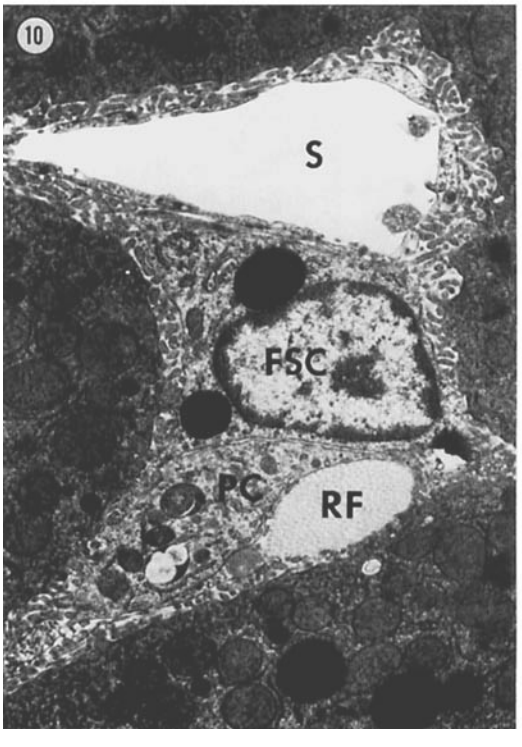
9 Sinusoidal lining cell enclosing reticular fiber. The reticular fiber (*RF*) is encircled by a lining cell (*LC*). The space of Dissé is nearly filled with microvillae (*MV*), which occasionally project through fenestrations (arrows). OsO_4; Epon; 8,000 ×.

10 Contents of space of Dissé. A fat storage cell (*FSC*) lies below the sinusoid (*S*). The perisinusoidal cell (*PC*) partially encloses the reticular fiber (*RF*). The remainder of the space of Dissé is largely occupied by the microvillae of surrounding parenchymal cells. Glutaraldehyde; OsO_4; Epon; 9,600 ×.

11 Fat storage and von Kupffer cells. Lipid inclusions (*L*) in the cytoplasm and the perisinusoidal position of the upper cell (*FSC*) identify it as a fat storage cell. It is separated from the sinusoidal lumen by the attenuated cytoplasm of a lining cell (arrows). Although the von Kuffer cell (*KC*) is almost completely separated from the lumen, a small part of it abuts on the vascular channel on the right. Glutaraldehyde; OsO_4; Epon; 6,600 ×.


8
S
S
LC
KC


9
RF
EC


10
S
FSC
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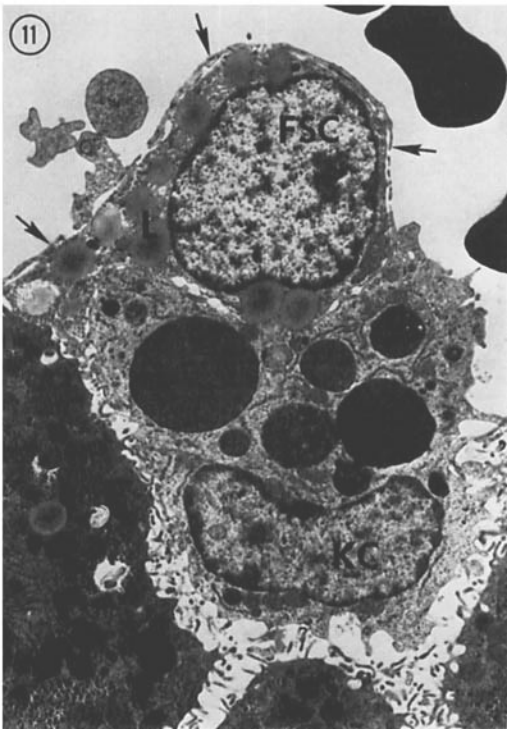
11
FSC
KC