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Review article

The lymphatics of the liver

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Abstract. An overview of our current knowledge of the hepatic lymph vessels is given, and the different lymph node stations that are related to the liver are described. The lymphatics of the liver itself can be divided into a superficial and a deep system. The superficial vessels are mainly situated in the liver capsule, the deep ones follow the triads of Glisson or the efferent hepatic veins. There are no direct communications between spaces in the liver parenchyma and the first lymphatic capillaries, which end blindly in the surrounding connective tissue. Nevertheless, the perisinusoidal space of Disse, the space of Mall, directly adjacent to the outer limiting plate of the parenchyma, and the space of Comparini, surrounding the sublobular hepatic veins can be regarded as prelymphatic spaces from which the hepatic lymph could originate. The extracellular matrix in the space of Disse is apparently continuous with the extraparenchymal areas of the connective tissue. Collagens and proteoglycans offer a morphological pathway for the transport of fluid, the physiological prerequisites of which are discussed.

Key words: Liver – Lymphatics – Prelymphatic spaces

Introduction

In describing the lymphatics of the liver, two morphological problems become simultaneously apparent. The first concerns the questions if and where the lymphatic fluid is produced in the liver, the architecture of its parenchyma being still under discussion (Sasse et al. 1992). The second difficulty is the smallness and transparency of the lymph vessels, attributes that have long been responsible for the neglect of their existence and the failure to realize their significance (Lord 1968).

Basic anatomical knowledge of the lymphatic system first emerged during the Renaissance. Eustachius (1563) observed the thoracic duct in the horse and Asellius (1627) demonstrated the mesenteric lymph vessels of the dog. Rudbeck (1653) was the first to describe lymph vessels on the surface of the liver. His contemporary, T. Bartholinus (1653) understood the general layout of the lymphatic system, including the cisterna chyli, thoracic duct, mesenteric and peripheral lymphatics. Detailed studies were later carried out by Mascagni (1787) and Hunter (1762).

Starling (1896) discovered that filtration through the walls of blood capillaries was responsible for the origin of the lymphatic fluid. Extensive descriptions of the lymphatic system were published by Bartels (1909) and later by Rouvière (1932).

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Macroscopy

In the liver it is possible to distinguish between superficial vessels, which are found predominantly in the liver capsule, and deep vessels, which lie either in Glisson's triads or accompany the efferent hepatic veins. Lymphatic vessels may therefore leave the liver at the porta hepatis, or together with the hepatic veins, or run in the coronary and falciform ligaments. The following description is based mainly on the work of Rouvière (1932).

Superficial lymphatics from the *convex surface* of the liver run through the coronary ligament, mainly the right or left triangular ligament as well as through the falciform ligament. They cross the diaphragm to enter the precardiac, superior phrenic and juxtaesophageal lymph nodes, or accompany the right or left inferior phrenic artery to reach the celiac nodes. Some lymph vessels cross the anterior margin of the liver and communicate with the hepatic lymph nodes at the porta hepatis.

Superficial lymphatics from the *concave visceral surface* mostly run to the hepatic lymph nodes with the exception of some lateral vessels of the right lobe, which pass directly to the right lateral aortic group. From the caudate lobe lymph vessels drain into the precaval nodes.

The *deep lymph vessels* leave the liver at the porta hepatis, where 12–15 separate vessels run together with

the hepatic artery or the bile ducts. These communicate with the foraminal node at the epiploic foramen and the superior pancreatic nodes, which are connected with the lateral aortic group (Hidden et al. 1973). Other lymph nodes are situated along the common and proper hepatic arteries and drain into the celiac nodes. The lymphatics that accompany the hepatic veins leave the liver as five or six separate vessels that continue in the wall of the inferior vena cava.

The further drainage of the hepatic lymph vessels is represented by four chains, of which the thoracic duct is the most important collecting vessel. The other chains consist of lymph nodes in the anterior and the posterior mediastinum and along the internal thoracic vessels (Fig. 1). Although there is apparently no exact relationship between liver segments and particular groups of lymph nodes, there are collecting lymph vessels that drain the lymph from two or three neighboring segments to the first regional lymph nodes. (Wolodjko 1967)

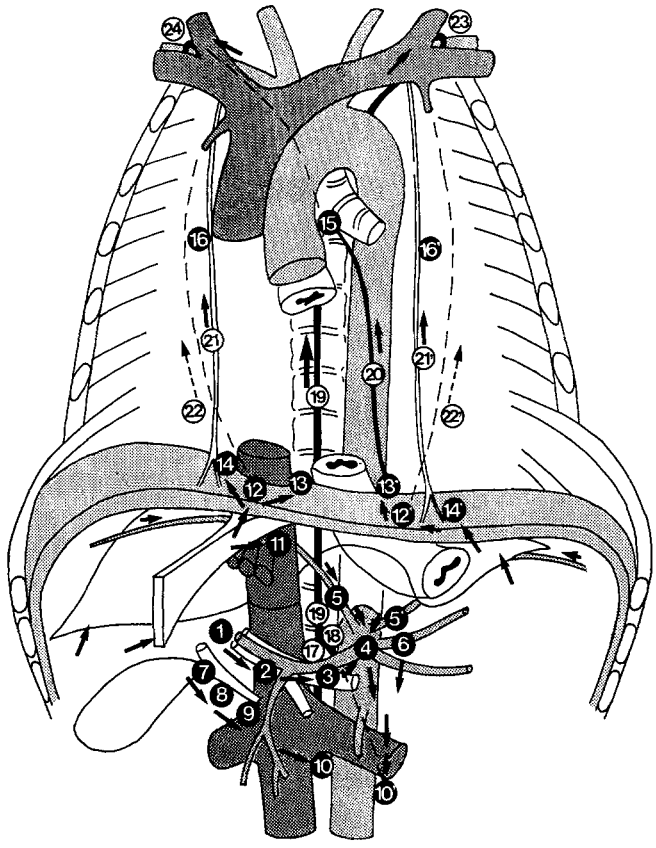

Fig. 1. Lymphatic drainage of the liver. *Lymph nodes* (Lnn.): *1*, Lnn. hepatici; *2/3*, Lnn. along the A. hepatica propria/communis; *4*, Lnn. coeliaci; 5/5′, Lnn. along the A. phrenica inferior dextra/sinistra; *6*, Lnn. along the A. gastrica sinistra; *7*, Lnn. along the bile duct; *8* Lnn. foraminalis; *9*, Lnn. pancreatici superiores; *10* Lnn. aortici laterales; *11*, Lnn. praecavales; *12/12′*, Lnn. praepericardiales dextrae/sinistrae; *13/13′*, Lnn. iuxtaoesophageales dextrae/sinistrae; *14./14′*, Lnn. phrenici superiores dextrae/sinistrae; *15*, Lnn. tracheobronchiales; *16/16′*, Lnn. mediastinales anteriores dextrae/sinistrae. *Lymph vessels*: *17*, truncus lumbalis dexter; *18*, truncus lumbalis sinister; *19*, ductus thoracicus; *20*, posterior mediastinal lymph chain; *21/21′*, right/left anterior mediastinal lymph chain; *22/22′*, Lnn. along the A. and V. thoracica dextra/sinistra; *23*, left venous angle; *24*, right venous angle. *Arrows* indicate direction of lymph fluid

The existence of afferent lymph vessels is controversial. The transport of intraperitoneally administered Indian ink by lymph vessels in the hepatoduodenal ligament has been described (Goldmann 1912). Furthermore, anastomoses between efferent hepatic and mesenteric lymph vessels have been detected. Mesenteric lymph can therefore enter the hepatic lymph vessels (Tso et al. 1983). Whether such anastomoses play a physiologically important role is not known.

Microscopy

The *superficial lymph vessels* of the liver capsule are arranged in three layers (Comparini 1969). The deep layer consists of a network of capillaries that lies directly between the parenchyma and the connective tissue. In the middle layer, the lymph capillaries are more sparse but have a wider lumen. In the superficial layer, lymph capillaries are found together with collecting vessels that are equipped with valves. According to Magari (1968), the collagen fibers between the lymph vessels and the parenchyma have a "peculiar" structure which, in her opinion, resembles the "maculae cribriformes" of the diaphragm described by Tsubouchi (1950). These maculae are thought to be able to resorb even particles from the peritoneal cavity. A detailed description of these "maculae cribriformes" has been given by Kihara (1956). It may be supposed that the maculae are the structures called stomata by von Recklinghausen (1869), who detected them on the peritoneal surface of the diaphragm. They have also been described by MacCallum (1903), Allen (1936) and Tsilibary and Wissig (1977), and definitely confirmed with the electron microscope (Leak and Rahil 1978). The maculae are characterized by openings with a diameter varying from 1–12 μm (Allen 1936; Tsilibary and Wissig 1977). The underlying lymph capillaries are either covered with a fenestrated basal lamina, or else they communicate directly with the stomata and through them with the fluid of the peritoneal cavity (Leak and Rahil 1978). The expression "macula cribriformis" is misleading, since Magari (1968) uses it for the "peculiar" collagen networks and not for gaps in the mesothelium. Whether "stomata" are present in the liver capsule is not known, but a description of such openings in the falciform ligament has been published by Tesch et al. (1990).

The *deep lymph vessels* of Glisson's triads (the so-called portal lymph vessels) are at first associated with arterioles, venules and bile ductules. Later they become preferentially attached to the arterial branches (Wassermann 1958; Comparini 1969), where they build up a periarterial plexus in the adventitia. Near the porta hepatis the collecting lymph vessels accompany the portal vein (Comparini 1969). Magari et al. (1981), however, found a lymphatic network that is as much associated with the branches of the portal vein as with the bile ductules. These findings have been corroborated by the electron microscope studies of Yamamoto and Phillips (1986) on corrosion casts. Other lymph vessels have been found to originate from the surrounding connective tissue of the intrahepatic bile ductules (Johnson and Mann 1950).

Those deep lymph vessels that accompany the efferent hepatic veins are called central, sublobular or venous lymphatics. They originate in the connective tissue surrounding the sublobular veins, and later run with the branches of the hepatic veins, together with which they leave the organ. Some of them anastomose with the lymph vessels of the diaphragm (Magari et al. 1981). An intramural network of three layers has been described for the hepatic veins; it is found subendothelially, in the tunica media and in the adventitia, and is continued into the wall of the inferior vena cava (Magari et al. 1981). With the exception of the adventitial vessels, the intramural capillaries have never been confirmed in the literature, so this finding requires critical examination.

There are numerous descriptions of anastomoses between the superficial and the deep lymph vessels (Herring and Simpson 1906; Baum 1922; Witte et al. 1968; Comparini 1969; Szabo et al. 1975; Magari et al. 1981), between portal and venous lymph vessels (Herring and Simpson 1906; Lee 1923), between lymph vessels of the liver and those of the gall bladder (Nisimaru 1969), and also between lymph vessels and intrahepatic branches of the portal vein (Job 1918; Baum 1922). No special function has been ascribed to them.

All terminal lymph capillaries, characterized by a flat, single-layered, nonfenestrated endothelium, end in the interlobular connective tissue (Niiro and O'Morchoe 1986). They are mostly situated in the periphery of the portal field, in the vicinity of the space of Mall (Comparini 1969, Niiro and O'Morchoe 1986). Other terminal lymph vessels are present in the connective tissue surrounding the sublobular veins (Comparini 1969). Magari et al. (1981) observed terminal lymph capillaries even in the connective tissue between the central and sublobular veins. Magari (1968) also described the reticular architecture of the collagen fibers between the outer limiting plates of the parenchyma and portal lymph capillaries; they form a structure which in her view resembles the macula cribriformis of Tsubouchi (1950). The outside of the lymph capillaries is connected by delicate fibers of 10 nm diameter to the surrounding connective tissue (Hahn et al. 1980, Niiro and O'Morchoe 1985a, b, 1986), and these serve as anchoring filaments that maintain the patency of the lumen (Leak and Burke 1968).

The interstitial compartments

The whole organism, including of course the liver, is subjected to the requirements of homeostasis: so the size of the compartments and the composition of the body fluids must be balanced between supply and depletion. It is the function of the lymphatic system to drain the fluid and dissolved substances that have been filtered through the blood capillaries. In the presence of surplus fluid, the lymphatics serve as a safety valve, so they help to keep the composition and volume of the interstitial fluid constant.

Like other organs, the liver possesses an intracellular and an extracellular compartment, the latter consisting of intravascular and the interstitial spaces. It is mainly the interstitial compartment that serves as the morphological basis for lymph formation. Special interstitial spaces of the liver include the space of Disse, the space of Mall and a sublobular space, described by Comparini (1969). For historical reasons, and because the source of the lymph is supposed to be here, they are summarized under the term "lymph spaces of the liver". The other interstitial sources of lymph fluid include the periportal and perivenous connective tissue.

The space of Disse is the the perisinusoidal cleft bordered by the endothelial cells of the sinusoid, which lacks a basal lamina, and the sinusoidal surfaces of hepatocytes, which are covered with numerous microvilli. Apparently the width of this space changes under various metabolic conditions (Cossel 1964), the most often cited value being 0.2–0.5 μm. The space of Disse was the first to be regarded as a prelymphatic space, the components of which serve as "leitstruktur" for the interstitial transport of fluid (Magari 1968). Of these components, at first only the reticulin fibers around the endothelial tube were known (Schiller 1943), and the existence of a basal lamina remained for a long time an open question (Wassermann 1958).

In Mall's view (1901), the perisinusoidal space of Disse is in direct continuity with the perilobular lymph space (space of Mall). This space is situated in between the outer limiting plate of the liver parenchyma and the periportal connective tissue. Mall was able to demonstrate the existence of this space by injecting coloured gelatin into the portal vein. The dye first appeared in the space of Disse, and then reached the periphery of the hepatic lobule. Here, from the "perilobular space", it enters the terminal lymphatics. This experiment was responsible for the now classical view that the spaces of Mall and Disse are the places of origin of lymph formation in the liver. It is worth pointing out that the space of Mall itself is not lined by endothelial cells, and is therefore not strictly speaking a lymphatic vessel but a prelymphatic space. It is important to realize that the clear definition of the "space of Mall" became somewhat blurred when certain authors described collagen fibers as being *in* this space (Schatzki 1978), because it is defined as a space lying *between* the hepatocyte and the connective tissue.

Since its first description, the existence, definition and function of the perilobular space of Mall have been subjected to numerous investigations. Viragh et al. (1978) deny the existence of this space, regarding it as an artifact. Using the electron microscope, they concluded that collagen fibers and fibrocytes are directly in contact with the hepatocytes of the limiting plate. Only where the surface of the liver cells is covered with microvilli, is a submicroscopic space to be found between the processes. Virágh et al. (1978) also recognized that this perilobular space is traversed by fibers that penetrate from here to the limiting plate and then enter the liver parenchyma. In their opinion, these fibrous structures support the lymph flow from the space of Disse to the terminal lymphatics.

For Schatzki (1978), the only possible communication between the space of Disse and the terminal lymphatics must lie in the interspaces between the hepatocytes. These observations are, in principle, supported by those

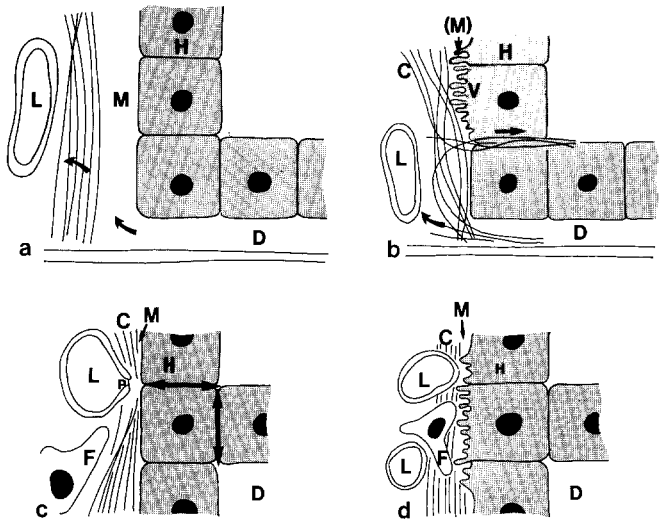

Fig. 2a–d. Schematic drawings of possible communications between the space of Disse and the space of Mall. *H*, Hepatocyte; *L*, lymph capillary; *P*, pores; *D*, space of Disse; F, fibroblasts; *M*, space of Mall; *C*, periportal connective tissue; *V*, microvilli. **a** Mall (1901): After injection of coloured gelatine into the portal vein a perilobular space appears. **b** Virágh et al. (1978): at sites where hepatocytes are covered with microvilli, a submicroscopic space is recognizable. Lymph flows along collagen fibers (*curved arrows*) that are entering the limiting plate (*straight arrows*). **c** Schatzki (1978): the space of Mall is a virtual space between the periportal connective tissue and the limiting plate of the liver. Lymph vessels with *P* can be very close to this space if *F* are not intercalated between them. A communication between the space of Mall and the space of Disse is theoretically possible through intercellular spaces of hepatocytes (*arrows*). **d** Niiro and O'Morchoe (1986): the lymph capillaries are separated from the space of Disse by the limiting plate of the liver and by the periportal connective tissue and *F*. The space of Mall is recognizable in between the microvilli on the surface of the hepatocytes

of Niiro and O'Morchoe (1986). Although these authors agree that there is close contact between this intermicrovillous space and the lymph capillaries, the terminal lymphatics are separated from the space of Disse by hepatocytes and the connective tissue in Glisson's triad, which consists mainly of collagen fibers and fibrocytes (Fig. 2a–d).

Another space that is occasionally included in the prelymphatic spaces was described by Comparini (1969). It is the sublobular space which, like the space of Mall, is bordered by the liver parenchyma and the connective tissue around the sublobular veins. This space is supposed to have a direct communication with the space of Disse (McGee and Patrick 1972).

The extracellular matrix

Since the interstitial space is considered to be the source of the lymph drainage, it must be described as an integral part of the lymphatic system of the liver. However, its anatomical description is not completed by the delimitations of spaces, but must also take into account the molecules contained in them, in other words; the extracellular matrix. In the liver, this contains three main components, collagens, glycoproteins and proteoglycans.

Collagens in the liver mainly serve to support the parenchyma. They are represented by the types I, III, IV, V and VI, of which the collagen types I and III alone make up 40–50% (Rojkind et al. 1979). These are mainly found in the portal stroma, whereas in the space of Disse they appear only discontinuously (Martinez-Hernandez 1984). Collagen type IV, or basement membrane collagen, is not only present in the basal laminae of blood vessels, but also in the space of Disse (Hahn et al. 1980; Martinez-Hernandez 1984), where it is functionally equivalent to the missing basal lamina.

Glycoproteins are the main non-collagenous extracellular matrix proteins that, by their multidomain-structure, primarily serve for matrix-cell interactions (Baranov et al. 1990). Fibronectin is the oldest known glycoprotein which is also found regularly in the space of Disse (Hahn et al. 1980; Martinez-Hernandez 1984). Laminin was at first thought to be localized in the portal stroma and around the efferent veins only, but later it was also found in the perisinusoidal space (Maher et al. 1988; Schuppan 1990). Closely associated with laminin is the glycoprotein entactin (Ramadori et al. 1990). Undulin forms undulating bands in the space of Disse. Tenascin has a high affinity to fibronectin; it is found surrounding the sinusoids in the vicinity of the Ito cells (van Eyken et al. 1990).

Proteoglycans are built up from a protein core and covalently linked glycosaminoglycans. They regulate tissue hydration and historheology, and are responsible for interactions with other matrix components and cells. They also serve as receptors for growth factors at the cell surface (Ruoshlati 1988, 1989). Other proteoglycans in the liver include hyaluronic acid (10–21%), dermatan sulfate (7–13%) and chondroitin sulfate (4–7%) (Geerts et al. 1986; Gressner and Bachem 1990). The proteoglycans are characterized by their strong negative charge, and therefore they have a great influence on the interstitial transport of charged molecules in the space of Disse (Gressner and Bachem 1990; Griffiths et al. 1991). Because of their high capacity for binding water they are able to increase their dry-weight volume some 30–50 times.

The production of matrix proteins is mainly brought about by the Ito cells (Gressner and Bachem 1990; Rieder et al. 1991), but endothelial cells are also able to produce collagen type IV (Irving et al. 1984), laminin (Tsutsumi et al. 1988) and fibronectin (Rieder et al. 1987).

The components of the extracellular matrix in the space of Disse seem to be continued into the portal spaces (Hampton 1958; Grimaud et al. 1980; Hahn et al. 1980). Ohtani (1988, 1992) was able to demonstrate that the collagen fibrils in the space of Disse are continuous with those in Glisson's triads, those around the central and sublobular veins, and those in the liver capsule, thus forming a continuous collagen fibrillar network throughout the liver as a whole. His SEM pictures show collagen fibrils forming a three-dimensional system of anastomosing channels. Furthermore, Reid et al. (1992) have recently described extracellular matrix gradients in the space of Disse. These authors suppose that, while the hepatocytes

of the lobular periphery proliferate in the direction of the central vein, the concomitant differentiation processes are also reflected by the varying composition and concentration of the matrix components in the space of Disse. In this way, for instance, the still intact basal lamina surrounding the afferent vessels in the vicinity of the Hering canals alters with increasing distance from the periportal stem cells, so that a matrix gradient develops, containing different concentrations and types of collagen, glycoprotein and proteoglycans.

In support of the assumption that the space of Disse is the origin of the hepatic lymph, the collagen continuum in the interstitial spaces of the liver and the concentration gradients are certainly of great importance.

Physiology

Two capillary systems are under discussion as possible sources of hepatic lymph, namely, the peribiliary plexus and the sinusoids. It is assumed that the hepatocytes contribute to the composition of the lymph, but quantitative data are missing. The bile ducts and the gall bladder are also supposed to produce some of this fluid (Földi 1974). The role of the efferent veins is still unclear (Fig. 3).

The arterial capillaries of the peribiliary plexus are covered by a continuous endothelial layer (Barrowman and Granger 1984). Rappaport (1981) suggests that a main function of this plexus is the regulation of arterial flow, as well as of water and solute transport across the biliary epithelium, so it can be assumed that, in accordance with the forces of Starling, fluid is filtered into the surrounding connective tissue. It is estimated that this capillary plexus contributes less than 10% to the total lymph output from the liver (Földi 1974). For understanding the possible importance of both the capillary and sinusoidal systems, the geometric and hydrodynamic data must be regarded as fundamental.

The liver sinusoids have a length of about 300 μm, and a diameter of about 5 μm. According to Mall (1906), the total number of sinusoids is 1.85×10^9. The endothelium is characterized by fenestrations that form sieve plates. There are on an average 25 sieve plates per square millimeter of endothelium, so the total surface of a sinusoid is about 7,800 μm^2. With 25 sieve plates containing 30 fenestrae each, a total of 200,000 fenestrae/sinusoid can be calculated, corresponding to a total area of 1.57×10^{-9} m^2, or a porosity of 20% (Henriksen et al. 1984). Hampton (1958) has shown that a free bidirectional exchange of macromolecules through the pores of the endothelium is possible, so that the space of Disse is a perivascular rather than a lymphatic space (Henriksen et al. 1984). On the basis of these theoretical assumptions, only molecules with molecular weight of less than 1,000,000 and a diameter of less than 20 nm can pass through (Laine et al. 1979). This sieve effect seems therefore not to be relevant for most of the plasma proteins (Lautt and Greenway 1987), and the space of Disse can therefore be regarded as a mixing pool (Barrowman and Granger 1984). Whether the extracellular matrix is able to select will be discussed later.

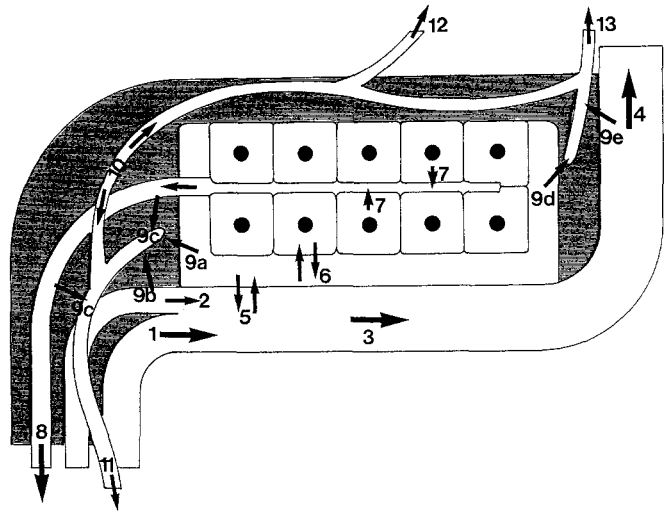

Fig. 3. Schematic representation of known and still hypothetic fluid movements in the liver. *1*, Blood flow from the V. portae; *2*, blood flow from the A. hepatica; *3*, blood flow in the hepatic sinusoid; *4*, venous blood flow; *5*, filtration through the sinusoidal endothelium; *6*, secretion and resorption between hepatocytes and the space of Disse; *7*, bile secretion; *8*, bile flow in the ductus biliferus; *9*, origin of lymph fluid from *9a*,. the space of Mall; *9b*, the periarterial plexus; *9c*, the peribiliar plexus; *9d*, the sublobular lymph space (Comparini) and *9e*, the efferent veins; *10*, lymph flow between the superficial and the deep lymph system; *11*, lymph flow in portal lymph vessels; *12*, lymph flow in lymph vessels of the Ligg. hepatis, *13*, lymph flow in perivenous lymph vessels

The normal blood pressure is 7 mmHg in the portal vein and 2 mmHg in the inferior vena cava; with an interstitial pressure of 5.8 mmHg. Laine et al. (1979) assumed a transsinusoidal hydrostatic pressure gradient between 1 and 1.2 mmHg. The sinusoid/lymph filtration coefficient is estimated to be between 0.08 and 0.3 ml/min × mm Hg × 100 g (Laine et al. 1979). The Starling forces which determine the microvascular exchange of fluid and the production of lymph are essentially modified by the morphological peculiarities of the liver sinusoids. The high permeability of the sinusoidal wall for proteins could also account for the high concentration of protein in the hepatic lymph, and therefore only a negligible oncotic gradient is to be expected. Since, however, the lymph/plasma quotient for proteins is less than 1, it can be assumed that the interstitial matrix acts as a filter for proteins. This assumption requires that the matrix components in the space of Disse and the portal fields serve as a continuous bridge. Whether such an oncotic gradient can be built up in such a gel-like compartment remains undecided (for discussion see Goresky, in Barrowman and Granger 1981).

Assuming that the oncotic pressure along the liver sinusoids is zero, the only decisive force remaining is the hydrostatic pressure. Filtration of fluids may then be imagined as depicted below (Fig. 4).

Hypothetical consideration of hepatic lymph production

Since a mathematical solution of this geometric hydrodynamic problem was not available, a very simple model of

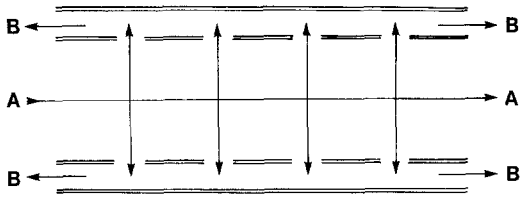

Fig. 4. Model of the sinusoidal and the perisinusoidal flow. *A*, Flow through the "hepatic sinusoid"; *B*, filtered fluid leaving the "perisinusoidal space"

what may really happen in vivo was put forward by Trutmann (1993). Fluid enters from one side into a porous inner tube, and is then filtered through the pores into a continuous, "perivascular" outer tube. It can be demonstrated that the fluid leaves this space in both directions, *with and against* the current in the inner tube. Thus, reduced to the physical requirements alone, it is feasible that the hepatic lymph originates in the space of Disse. This fluid moves in the direction of the portal fields as well as in the direction of the efferent terminal venule. Such a movement would only be impossible if all the structures in the space of Disse were to prevent this transport. It can be assumed, however, that the components in the space of Disse probably only slow down the movement and modify its composition, so that at least a part of the filtrate can arrive at the terminal lymph capillaries. It is therefore at least *physically* possible that the hepatic lymph is formed in the space of Disse.

The morphological basis of the prelymphatic spaces in the liver is still not understood. As pointed out earlier, the composition of the extracellular matrix in the space of Disse and in the periportal fields is similar, if not identical. Therefore, a continuity of the spaces of Disse and Mall is also feasible, either along the blood vessels that penetrate the outer limiting plate of the parenchyma, or along collagen fibers that are continuous in both spaces. We believe that those who deny the existence of continuity between the two spaces are overlooking the continuity of their extracellular matrices. Both spaces are extracellular compartments lying between the microvilli of the hepatocytes and filled with collagens and proteoglycans. These two substances could therefore ideally serve as reliable prelymphatic pathways. In other words, we think that the prelymphatic pathways of the liver will not be found by searching for open gaps, but by searching for "bridges" of extracellular matrix. We have tried to express this idea in Fig. 5.

Finally, it is to be noted that the terminal lymph vessel is attached to anchoring filaments that keep the gaps open. With this model a *morphological* basis for the space of Disse as the origin of the hepatic lymph is presented. This concept, which is based on physical and morphological observations, is still hypothetical, although it is supported by many data from the literature. So the high protein concentration, which is about 80% of the concentration of plasma proteins is an indication of the high permeability of the sinusoidal endothelium (Barrowman and Tso 1989). The fact that high concentrations of hepatic enzymes (Lindena and Trautschold 1986) and of lipoproteins which are secreted by hepatocytes (Tso et al. 1983) can also be detected in the hepatic lymph leads to the assumption that there is a connection between the space of Disse and the lymph vessels. The recirculation of lymphocytes and Kupffer cells from the sinusoids via the space of Disse to the portal lymph vessels (Fichtelius and Groth 1963; Hardonk et al. 1986; Matsuno et al. 1990; Hardonk and Atmosoerodjo-Briggs 1992) also strongly suggests a morphological basis for such a communication (Hardonk and Atmosoerodjo-Briggs 1992).

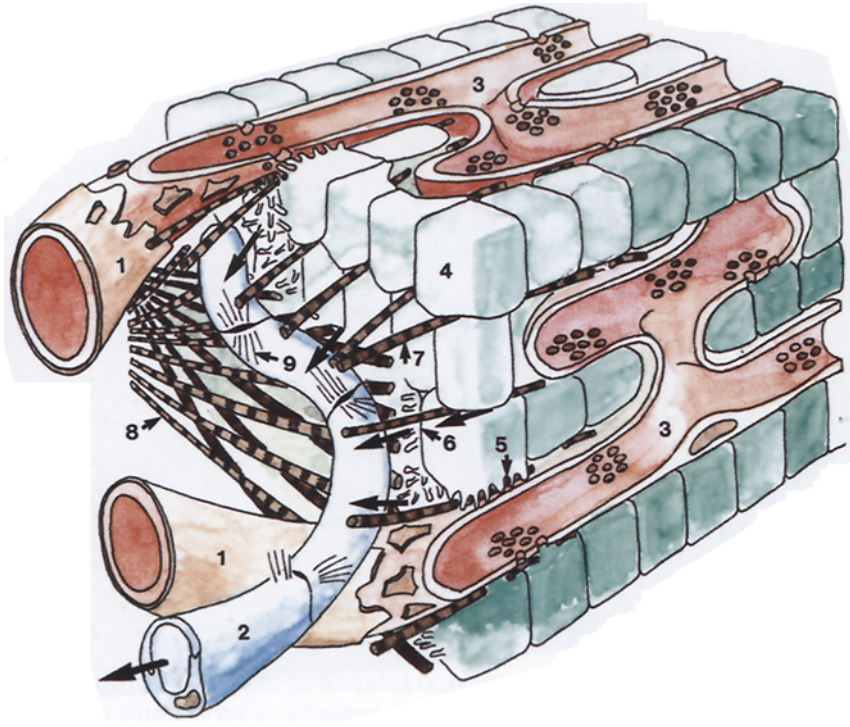

Fig. 5. Terminal lymphatics of the periportal area. The *thick arrows* indicate the possible lymph flow, coming from the space of Disse and entering a terminal lymphatic. The continuity between the space of Disse and the periportal area is represented by collagen fibers. *1*, blood capillary entering the liver parenchyma; *2*, terminal lymph vessel; *3*, sinusoid; *4*, periportal hepatocyte; *5*, space of Disse; *6*, space of Mall; *7*, collagen fibers entering the limiting plate; *8*, network of periportal collagen fibers; *9*, anchoring filaments

Experiments modifying the inflow and outflow from the liver also indicate this possible origin for the hepatic lymph, although pathological conditions can only to a limited extent be interpreted as physiological facts. An increase of blood pressure in the hepatic veins leads to an augmentation of hepatic lymph production (Starling 1896; Brauer et al. 1959), so when the blood pressure is increased by 1 mmHg in the inferior vena cava, the lymph flow is augmented by 50% (Laine et al. 1979). This situation resembles the clinical aspect of right heart insufficiency leading to ascites or the Budd-Chiari syndrome. The ascitic fluid is then delivered by the liver capsule into the peritoneal cavity ("tropfende Leber"; Witte and Witte 1981). Ascites is also supposed to develop in a similar fashion at the beginning of liver cirrhosis (Cain et al. 1947).

Ligation of the hepatic lymph vessels produces a lymphostatic condition of the liver which is histologically characterized by dilatation of the spaces of Disse (Babics et al. 1955; Cremer et al. 1972). Similar results are seen after liver transplantation when the lymphatic vessels are cut through (Lie et al. 1974).

After cholestasis, bile is regurgitated via the lymph vessels (Herring and Simpson 1906; Gonzalez-Oddone 1946; Carlsten et al. 1961; Witte et al. 1968; Dumont 1973). The passage of bile into the lymph is possible from the bile canaliculi to the space of Disse, or from the periphery of the parenchyma to the terminal lymph vessels, or from bile ducts to lymph vessels, or finally, from the lymph vessels of the gall bladder to the lymph vessels of the liver. Stains that have been injected into the portal vein can also be detected in the efferent lymph vessels of the liver (Godart 1966; Meyer-Burg et al. 1974). All these data suggest that the spaces of Disse, Mall and Comparini may be the source of the hepatic lymph. So far, however, direct transport of fluids or solutes from these "prelymphatic" spaces has not been verified.

In conclusion, it cannot be stated with certainty that the space of Disse is a source of the hepatic lymph. There are morphological and physiological facts arguing in favor of this concept, but convincing evidence is not so far available. It is difficult to study in vivo a fluid stream that lies beyond the resolving capacity of the light microscope. It is quite possible that Mall, working at the beginning of the century (Mall 1901) designed the best experiment that has yet been achieved when he injected dyes into the portal vein and examined sections of the liver under the light microscope, although it is certainly true that the injection of an electron-dense substance would offer more precise results.

Furthermore, there are also certain anatomical details that still require investigation; the exact course of the sublobular lymphatics and those under the mesothelial surface of the liver. These details are of great importance when it is necessary to collect, for any purpose whatever, a sample of hepatic lymph that is as complete as possible. So long as these facts remain unclear, no physiological experiment can be said to rest on a solid foundation. We certainly agree with Child (1954) that "the story of the relationships of the liver to the lymphatic system is long and complicated, and the last chapter has yet to be written".

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