PROPERTIES OF THE MESOTHELIUM OF THE SEROUS MEMBRANE OF THE LIVER DURING EXPERIMENTAL LIVER PATHOLOGY

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In experimental disturbances of the hemodynamics, of the secretion of bile, or of protein metabolism the mesothelium of the serous membrane of the liver, which is normally flat, swells, mitoses appear in it, and its surface area increases through the appearance of external folds and channels with a mesothelial wall. These channels appear as a result of contact between the apex of the fold of the serous membrane with its surface and they are located in the connective tissue. Initially numerous and greatly dilated, they collapse and undergo reduction as repair processes begin or when advanced changes have taken place in the liver. Judging from the morphological evidence, the excretory mesothelium of the liver exerts a drainage function at certain stages of the pathological process.

According to the few facts available the mesothelium of the liver has cells which are not flat but cubical or cylindrical in shape [4], it does not contain multinuclear cells, and it accordingly shows a very low level of physiological activity in response to direct stimulation [9, 10]. A close connection has been found between the continuous mesothelial layer and the lymphatic capillaries of the peritoneum covering the liver [11], evidently indicating that the mesothelium plays a role in exchanges between the tissue and peritoneal fluids.

This paper describes the results of observations on the mesothelium of the serous membrane of the liver in dogs with various types of experimental pathology.

EXPERIMENTAL METHOD

Material was obtained by biopsy (280 specimens) and at autopsy (100 specimens) from 125 dogs with various experimental disturbances of liver function: portocaval anastomosis, constriction of the inferior vena cava or compression of the hepatic veins, ligation of the common bile duct, intravenous injection of an excess of amino acids and polypeptides, injection of a sclerosing substance, etc. Pieces of liver were fixed in 10% formalin solution and in a mixture of ethanol with formalin and acetic acid. Frozen and paraffin sections of these tissues, 5-10 μ in thickness, were stained with hemotoxylin-eosin, basic brown, Sudan III, carmine by Best's method, and picrofuchsin by Van Gieson's method. To describe the morphological characteristics of the mesothelium, measurements were made with an ocular micrometer.

EXPERIMENTAL RESULTS

In the healthy dogs before the experimental procedures the mesothelium of the serous membrane was flat. With the ordinary stains it appeared in the sections as a syncytium up to 2-3 μ in thickness, with flat-oval nuclei 7-10 μ and 2-3 μ in diameter without figures of mitosis and amitosis. Neither glycogen nor fat could be found in the mesothelial cells, and they gave a weak positive reaction for acid mucopolysaccharides.

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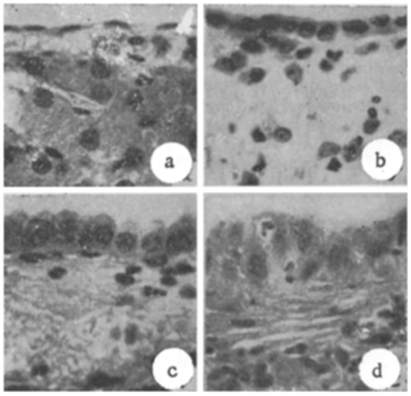

Fig. 1. Mesothelium of serous membrane of the dog liver: a) above hemorrhage; b) swollen; c) swollen with cell borders; d) with phagocytosis of leukocyte. Hematoxylin-eosin, biopsy, 630× (immersion).

In some intact dogs and also in dogs under experimental conditions (after injection of an excess of protein, or of sclerosing solution, or in the picture of "meat poisoning" after portocaval anastomosis) the formation of a type of brush border was observed on the surface of the liver mesothelium. A similar brush border was detected experimentally by Anikin [1] in the mesothelium of the spleen. According to Anikin it developed as the result of the accumulation and excretion of urea. The appearance of a structure typical of excretory organs suggests that the mesothelium of of the liver is capable of excretion. Under pathological conditions of the liver the thin layer of mesothelium remained intact even above foci of edema and hemorrhage (Fig. 1a). Where the mesothelium was absent, this was mainly due to its stripping off during removal of the piece of tissue or histological treatment.

In the biopsy material taken during the experiments lasting from a few days to 3 years the liver mesothelium was swollen in some places or over a wide area (Fig. 1b). Sometimes cell boundaries appeared in it without any special staining, outlining the cubical or cylindrical shape of the swollen cells (Fig. 1c). In response to sudden changes in the hemodynamics or in protein metabolism, the mesothelium swelled within 1.5-2 h, whereas under other conditions, during dilation of the stomach, for example, no changes were observed during an experiment lasting 5-6 h, although swelling nevertheless did appear after 4-15 days (liver biopsy). The swollen mesothelium contained many vacuolated cells with polymorphonuclear leukocytes in the vacuoles (Fig. 1d); mitotically dividing and binuclear cells also were observed. Figures of mitosis were found not only on the 1st days, but even in later stages after the beginning of the experiments.

Folds of the serous membrane appeared on the surface of the liver under pathological conditions (Fig. 2a-f). By contrast with villi [2] they did not possess an organoid structure and they evidently appeared as the result of mitotic activity of the mesothelium. Simultaneously in the connective tissue of the liver capsule, and frequently in the immediate vicinity of foci of hemorrhage, cavities lined with mesothelium were found. They were round or oval in frontal sections (Fig. 2d, h) and elongated in saggital sections (Fig. 2g), and they were evidently divided tubular structures. The mesothelium inside them was flat, especially on the inner wall, or cubical, and it was cellular or syncytial in structure, sometimes with a brush border (Fig. 2f). Solitary leukocytes, erythrocytes, desquamated mesothelial cells, a finely granular, reticular mass, and sometimes long, birefringent crystals were seen in the lumen. Acid mucopolysaccharides were clearly visible in the structures with a widely dilated lumen.

As a result of these observations the appearance of tubular structures lined with mesothelium in the liver capsule can be connected with the formation and growth of external folds on its surface. It will be clear from Fig. 2a-d that the morphological picture can be compiled by tracing the individual stages of this process: folding of the serous membrane, lengthening, followed by its assuming a sloping and, later, horizontal position. When its apex comes into contact with the surface of the mesothelium, a cavity lined with mesothelium is closed between them. Separated from the mesothelial layer, it may retain its angular outline for some time at the points where it has been cut off (Fig. 2f). Since the inner wall of these cavities is part of the liver surface, it is always at the same level (Fig. 2h). After separation of the mesothelial cavities on the liver surface, fresh folds can form above them, and in these cases the cavities formed with their participation are also as the same level, but this time in a layer above. The tubular structures with their mesothelial wall remain within the connective-tissue capsule of the liver.

Cavities arising beneath the thin folds lie close to the surface of the liver. They are not commonly seen for they are easily ruptured, together with the surface layer of mesothelium, if care is not exercised when the section is prepared. In the thickened liver capsule the mesothelial tubules remain intact if the surface mesothelium is torn. Their sections are frequently seen at the boundary with the parenchyma (Fig. 2h). This may be the result of edema or sclerosis of the capsule, and also of the formation of the tubules with the aid of thick horizontal folds (Fig. 2e). Apart from their connection with the mesothelium, they resemble atypically situated bile ducts, which is what the writer originally considered them to be [5],

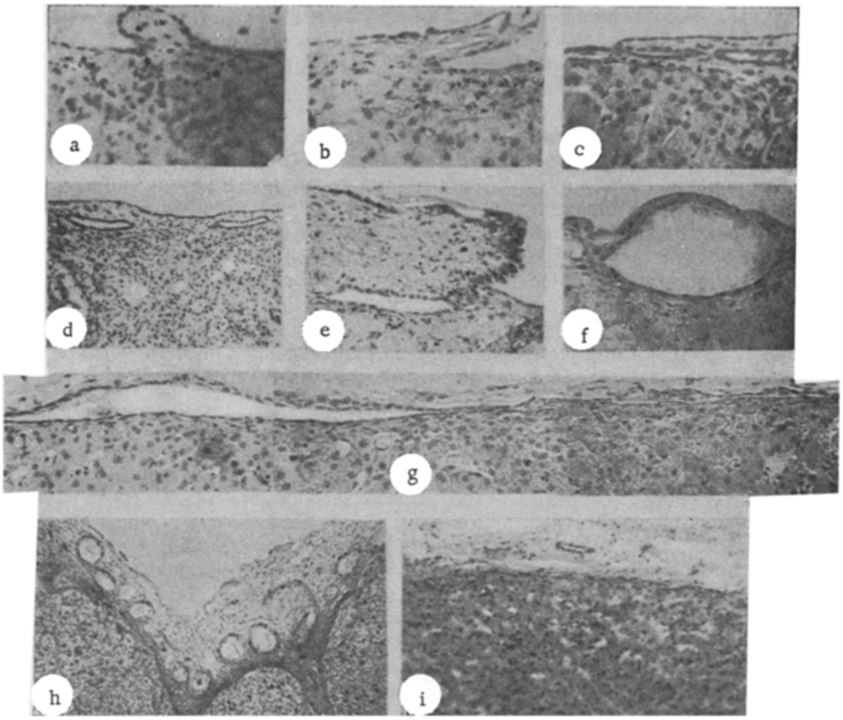

Fig. 2. Stages of formation and morphological properties of mesothelial channels: a, b) formation and growth of folds of serous membrane (frontal sections through the liver); c) closure of cavity lined with mesothelium between a horizontal fold and the liver surface; d) cavities cut off from the surface; e) formation of a mesothelial cavity with the participation of a thick horizontal fold; f) preservation of the angular outline of the cavity at places where it is cut off from the surface; g) mesothelial channel in a sagittal section through the liver; h, i) mesothelial channels in the connective tissue of the liver capsule of the same dog 2 and 2.5 years after the third interavenous injection of sodium salicylate. Frontal sections through the liver. Hematoxylin-eosin (a, b, c, d, e, g, h, i), Van Gieson (f). Biopsy, 280× (a, b, c, e, f, g); 140× (d, h, i).

for the appearance of tubular structures in liver pathology is interpreted in the literature as the "new formation of bile ducts" (one of the features of regeneration). It was only after the individual stages of formation of the corresponding structures had been discovered on the surface of the liver that it was concluded that their lining is mesothelial in origin.

This view regarding the method of formation of mesothelial cavities differs from hypotheses put forward earlier to the effect that tubular structures with a mesothelial wall are formed as a result of pathological changes in the reactive structures of the serous membranes [2], growth of the mesothelium in the same way as fibrin during its organization [7, 12], or invasion of the underlying tissue by the mesothelium followed by its separation from the main layer [6]. These conclusions were drawn from the results of investigation of the serous membranes of other organs: the heart, lungs, ovaries, etc.

The folds and cavities with their mesothelial lining described above were found mainly on the diaphragmatic surface of the liver; on the visceral surface changes in the mesothelium were more often restricted to swelling and infiltration with leukocytes. Mesothelial tubules, often sharply dilated, were most numerous during the development of hemodynamic and structural changes in the peritoneum covering the liver (Fig. 2h). In later biopsies, when the picture of well-defined pathological changes could be identified, or, on the contrary, there was evidence of normalization of the blood and lymph circulation and resolution of the fibrosis, they were rare, their lumen was collapsed, and they were difficult to distinguish (Fig. 2i).

The impression is gained from an analysis of these observations that with the development of liver pathology not only does the mesothelium remain intact, but it becomes activated so that its surface area is increased (folds, tubules with a mesothelial wall). The method of formation of the mesothelial tubules on the surface of the liver does not rule out the probability that they communicate with the peritoneal cavity even after they have burrowed into the underlying tissue. This assumes the possibility of an additional drainage of tissue fluid from the liver along the channels lined with excretory mesothelium. In other words, the morphological findings suggest that with the development of liver disease the excretory capacity of the mesothelium is increased, so that it becomes a significant drainage function. Evidence that this assumption may be valid is given not only by the active state (sharp dilation, appearance of acid mucopolysaccharides), but also by the closeness of the channels to the "suction holes" of the diaphragm. Indirect confirmation of the active drainage function of the mesothelium is given by the fact that the channels appear only at certain stages of development of the pathological process, and they evidently tend to disappear in the presence of marked decompensation or during restoration of the normal microscopic structure of the liver. It is therefore most likely that the mesothelial nature of certain structures known as "newly formed bile ducts" may account for the well-known fact of their reduction with the onset of repair processes in the liver [3, 8]. It is likewise not impossible that the drainage function of the mesothelium may be one factor responsible for the formation of ascites where marked dynamic disturbances are present in the liver.

However, the question of whether this function of the mesothelium of the liver is an essential factor in the pathogenesis of ascites requires special investigation.

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