In all cases the filterability test must include analysis of the type of structure of the membranes used and of the shape and size of the pores in the chosen microfilters. An essential condition for a correct interpretation of the results obtained during development of the filterability test and of the change from the phenomenologic level of analysis to the study of its mechanisms is the concurrent study of erythrocytes and polymer filters. Introduction of the concept of morphometric correlation between parameters of cell structure and porosity of the polymer film during passage of cells through it provides a basis for the methodology of membrane screening for the filterability test and also enables parameters of the periodic structure of membranes to be estimated from data of the joint morphometry of the membrane and cells immobilized by it.

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ULTRASTRUCTURAL BASIS OF INTRAVASCULAR THROMBOSIS IN THE LIVER IN OBSTRUCTIVE JAUNDICE

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KEY WORDS: liver, biliary cirrhosis, intravascular blood clotting, ultrastructure, thrombus.

Numerous investigations have shown that a syndrome of disseminated intravascular clotting (DIC) develops in a number of pathological states, and is frequently regarded as a component of terminal states [3, 5, 7]. The liver is known to synthesize several blood clotting factors, and development of the DIC syndrome accordingly assumes particular importance. On the basis of the study of the coagulation properties of blood in vitro in liver diseases, development of a DIC syndrome has been postulated [1, 6, 8, 11], and confirmed at autopsy [5]. However, the morphological features of intravascular blood clotting in the vascular bed of the liver have not been fully explained.

It was decided to study the vascular bed of the liver and particular features of the ultrastructure of platelet thrombi in experimental cholestasis.

EXPERIMENTAL METHOD

Liver tissue from 28 rats with a model of obstructive jaundice was investigated by the method described previously [4]. The experimental animals were decapitated on the 10th, 15th, and 20th days of the experiment (five rats acted as the control, eight died from complications of secondary biliary cirrhosis on the 18th and 20th days). Pieces of liver tissue were pro-

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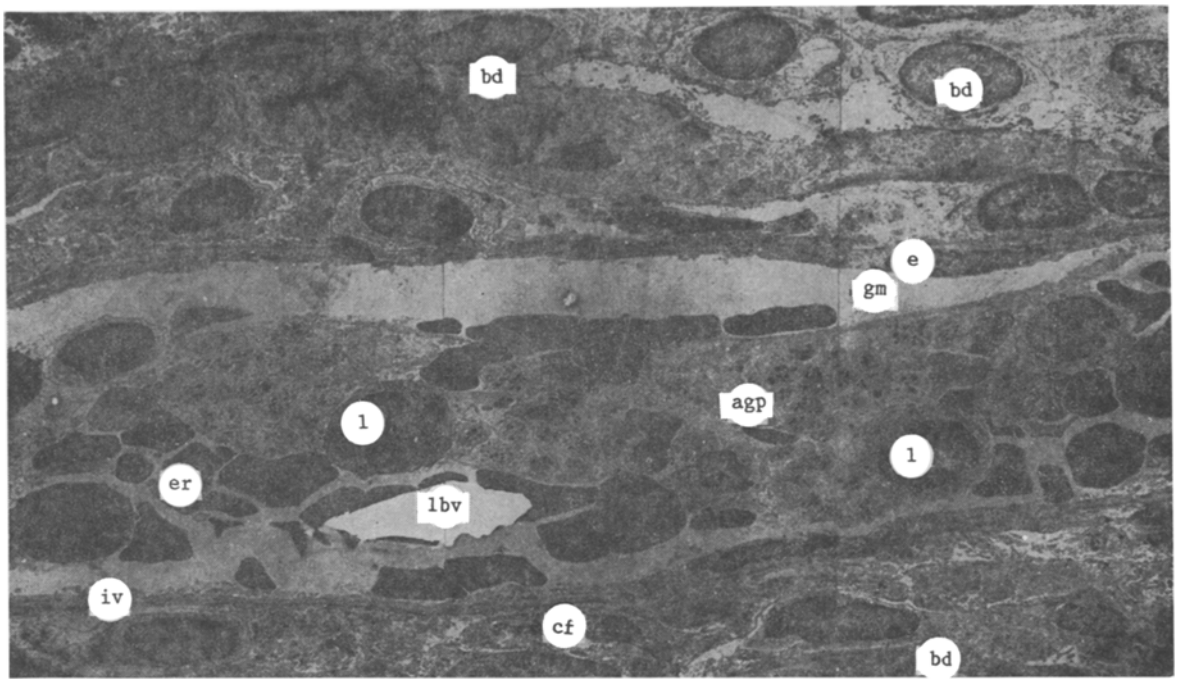

Fig. 1. Platelet thrombus in lumen of longitudinally divided interlobular vein (here and in Fig. 2, liver of a rat with obstructive jaundice for 20 days). iv) Interlobular vein; lbv) lumen of blood vessel; agp) aggregated platelets; bd) bile ducts; e) endothelium; l) leukocytes; er) erythrocytes; cf) collagen fibers; gm) granular material.

cessed by the usual histological and electron-microscopic methods. Ultrathin sections were stained with uranyl acetate and lead citrate and examined in JEM-100B and 100S electron microscopes.

EXPERIMENTAL RESULTS

On the 10th day of experimental cholestasis the liver of the experimental animals was enlarged and, on morphological examination, platelet thrombi were discovered in isolated observations in the lumen of the interlobular veins, and these were interpreted as incidental cases. Signs of portal hypertension were not found at these times of investigation. On the 20th day of cholestasis the liver was yellowish green in color, and twice its normal weight, or 7.18 ± 0.23 g/100 g body weight. The stump of the ligated and divided duct was greatly dilated and contained from 2.0 to 6.0 ml of bile. The portal vein and mesenteric vessels were greatly dilated, stretched, and filled with blood, and frequently venous collaterals were formed with vessel of the anterior abdominal wall. In some cases ascites fluid was found in the peritoneal cavity. By this time of cholestasis (the 20th day) biliary cirrhosis of the liver had developed [4].

Morphological investigation at this time revealed not only characteristic changes in the structure of the liver cells and biliary system, but also the development of intravascular blood clotting in some interlobular veins. Under these circumstances thrombi almost completely occluded the lumen of the vessel. No definite subdivision of the thrombus into head, body, and tail could be detected, and it was a uniform, aggregated mass extending over a long length of the vessel.

Stasis in the portal system due to the thrombus was the main cause of the portal hypertension. According to some workers, portal hypertenion is associated, not with thrombosis of the interlobular veins, but with changes in the structural and functional parameters of the vascular wall.

Electron-microscopically the intravascular thrombus was a large mass of aggregated blood cells, predominantly platelets. Over a wide area of the longitudinal section of the interlobular vein (Fig. 1) and also in transverse section (Fig. 2a) platelet thrombi with only a few erythrocytes and single leukocytes, with no particular structural changes, mixed with them.

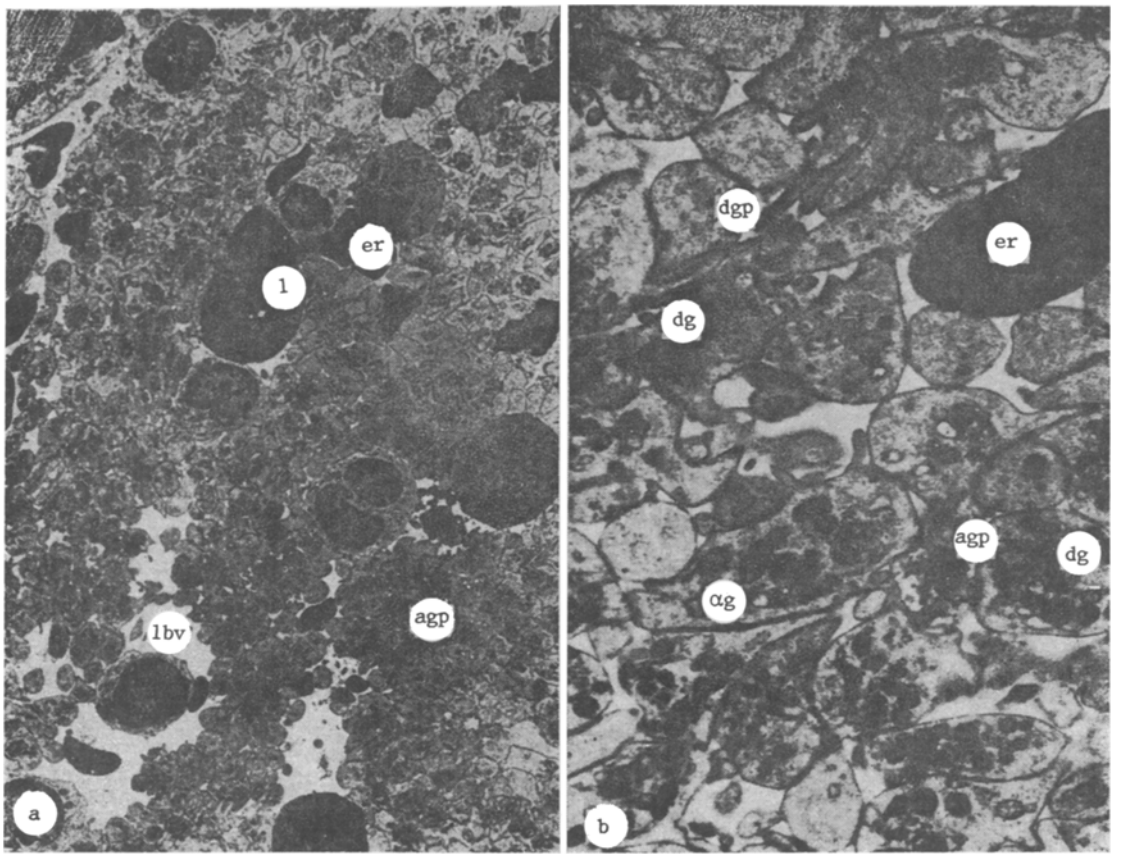

Fig. 2. Platelet thrombus in lumen of transversely divided interlobular vein. b) Fragment of Fig. 2a. dgp) Degranulated platelets; dg) dense granules; αg) alpha granules; m) mitochondria. Remainder of legend as to Fig. 1.

The thrombus occupied the central part of the lumen, and a small space was left between it and the endothelium, through which blood plasma probably circulates. In regions of intravascular blood clotting no changes were found in the endothelium, basement membrane, or other components of the vessel.

The structure of the firmly aggregated platelets varied considerably. Most platelets were irregular in shape, with a distinct limiting membrane, and two zones were distinguishable in them: central, containing granules and small vacuoles (the granulomere zone), and peripheral, homogeneous and not containing granules (hyalomere zone). The granulomere contained granules of varied structure, differing morphologically from one another (Fig. 2b). The ratio of granulomere to hyalomere varied greatly in different platelets: in some cells granules were numerous, in others they were scarce, and in a third group they were absent completely. The same pattern also was observed in a study of dense and less dense granules, known as "a-granules." The dense granules were round or oval in shape, with high electron density, and as some workers have stated [2], they contain serotonin, ADP, ATP, and catecholamines. In a few platelets lysis and translucency of the matrix of the granules were observed, evidently due to secretion of their contents into the lumen of the vessel. According to one opinion [9], degranulation is a sign of activation of platelets. Release of labeled serotonin from them, on average by 49.5%, was found 5 min after aggregation of the platelets, and this itself induced further aggregation of new batches of platelets.

The number of granules with low electron density and with a nonuniform matrix was somewhat smaller, except in some platelets which contained mainly granules of this kind. According to data in the literature [10], "a-granules" contain lysosomal enzymes, secretion of which leads to lysis of the platelets. However, in the present investigation, lysis and destruction of platelets in the composition of the thrombus were not found.

Besides granules, the platelets contained single mitochondria, tubular structures, and a few ribosomes. The tubular structures are purported to contain Ca^{++} (relaxation factor), secretion of which facilitates condensation of the thrombus.

Under high power of the microscope, granular material was found on the surface of the platelets; it filled the spaces between the platelets and also formed a granular layer around the platelet thrombus, probably consisting of glycoproteins and glycolipids [10]. It is important to note that in these investigations the platelet thrombus contained no fibrin threads, probably due to reduction if fibrinogen synthesis by the pathologically changed liver, or increased fibrinolytic activity of the blood. Experimental studies [7] showed that injection of threshold doses of thromboplastin into the blood stream led to a fall in the fibrinogen concentration and a simultaneous rise in fibrinolytic activity of the blood. No platelet thrombi were discovered in arteries, sinusoids, or central and sublobular veins. This fact is in agreement with results obtained by other workers, who found no changes in the vascular resistance of the hepatic veins in cirrhosis.

The investigations showed that intravascular blood clotting can take place in the liver in biliary cirrhosis, and is confirmed morphologically by the formation of platelet thrombi in the lumen of branches of the portal veins. Thrombus formation, moreover, is not always accompanied by a change in structure of the vessel walls, and fibrin is not one of their components, which is evidently a characteristic feature of liver pathology. Consequently, the mechanism of thrombus formation in obstructive jaundice is rather different and is most probably associated with disturbance of the systems regulating blood clotting. In patients with various types of liver pathology several disturbances of the clotting system (hyper- or hypocoagulation), linked with depression or activation of blood clotting factors – thrombin, thromboxane (TX), proconvertin, antithrombin III, prekallikrein, plasminogen, A_2-antiplasmin, etc., have been found in [7, 8].

An important role in the pathogenesis of intravascular blood clotting in cirrhosis of the liver is evidently played by slowing of the blood flow in branches of the portal vein, due to congestion in the biliary system. However, the causes of increased platelet aggregation are not sufficiently clear. It can be tentatively suggested that increased entry of tissue activators of clotting into the bloodstream from the damaged liver cells (thromboplastin) causes stimulation of platelet aggregation. Later, activated platelets secrete ADP and serotonin which, in turn, stimulate further platelet aggregation, which leads to the formation of "pure" platelet thrombi. However, because of the disturbance of fibrinogen synthesis or of activation of the anticlotting system, by the formation of heparin complexes [7], thrombus formation is incomplete. As a result of loss of functionally active platelets from the vascular bed, and also of the changes described above in the hemostasis system, the characteristic hypocoagulation of cirrhosis of the liver develops.

Prolonged experimental cholestasis, leading to the development of biliary cirrhosis of the liver, is thus accompanied in some cases by a disturbance of the anticlotting properties of the blood. The morphological manifestation of this process in the liver is platelet thrombi, localized in the interlobular veins, which are one possible cause of portal hypertension. Ultrastructural features of the thrombi are evidence in support of the increased aggregating power of the platelets, and together with disturbance of the hemostasis system, they are evidently among the factors responsible for hemorrhage in liver pathology.

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MORPHOLOGICAL EVIDENCE FOR USE OF RADIOOPAQUE EMBOLI BASED ON POLYHYDROXYETHYL METHACRYLATE FOR VASCULAR OCCLUSION

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Endovascular occlusion of blood vessels to arrest bleeding and as a measure reducing blood loss during surgical operations has been extensively used in recent years in surgery. The requirements for embolizing materials are satisfied most closely by the sponge-like hydrogel based on poly-2-hydroxyethyl methacrylate [1]. Emboli of this material do not cause damage or induce an inflammatory reaction of the vascular wall, but by intensifying thrombus formation and with the ability to swell in the lumen of blood vessels, they have a good and immediate obturating effect. Made of biologically inert material, hydrogel emboli are virtually not resorbed, and the obturating effect due to their use is thus stable and long-lasting. In medical practice visual control of the location of the emboli is often essential, and is possible only if the emboli have radioopaque qualities.

The aim of the present investigation was to develop a technology of radioopaque hydrogel emboli, to determine their compatibility with the tissues with which they come into contact, and to test their radioopaque properties.

EXPERIMENTAL METHOD

Hydrogel emboli can be made radioopaque by modifying the chemical composition of the polymer material or by addition of radiooopaque substances to the composition of the material of the emboli, without any chemical bond between the hydrogen and these substances. In the latter case, we are dealing with a dispersed system. We tested two methods of contrasting. The emboli which are being examined in this paper were rendered radioopaque by the addition of iodides, bromides, and polyiodides of silver, and also of α-(3-amino,2,4,6-triiodobenzyl)-butyric acid (Iopagnost) to the hydrogen. Emboli containing silver halides were prepared by successive swelling in aqueous solutions of silver nitrate and potassium iodide. Under these circumstances, silver iodides, insoluble in water and liquid media [2], are deposited in the mass of the hydrogel. When Iopagnost was used it was dissolved in a mixture of monomers from which the embolizing material (hydrogel) was used. During subsequent washing of the emboli

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