CHANGES IN THE LIVER IN ANIMALS WITH EXPERIMENTALLY INDUCED SPLENIC DISEASE

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Numerous investigations of the development and therapy of various pathological conditions of the liver and spleen have been made. However, various forms of complex pathological conditions at these organs have been encountered, and take the form of the so-called hepato-lienal syndrome, about whose origin one can merely speculate. Present day opinions of the part played in this condition by thrombophlebitic processes in the spleen [5], congenital features of the development of the venous system [2, 6, 7], or by a combined reaction of liver and spleen [1, 3] in the various pathological processes have done nothing to indicate finally the mechanism of the development of the complex pathology and these organs.

We have made 89 experiments on rabbits weighing 2.5-3.5 kg, and five on dogs weighing 15-30 g. In addition we also investigated 15 spleens and 6 liver biopsy specimens taken from children during splenectomy performed on account of splenomegaly of unknown origin.

EXPERIMENTAL METHOD

Local anesthesia was induced with 1% morphine (1 ml/kg), and a laparotomy was performed. A vertical incision 4-6 cm long was made in the epigastric region 2 cm to the left of the middle line. The spleen was removed through the incision and the following procedures were carried out: I (10 experiments) the trunk of the lienal vein was ligated; II (8 experiments) the venae gastricae brevis as well as the lienal vein were ligatured; III (12 experiments) after ligation of the main trunk of the lienal vein 1 ml of a 1% standard solution of thromboplastin was injected; IV (10 experiments) extensive subcapsular trauma was inflicted on the spleen.

Similar sets of five experiments were made on 20 rabbits which had been sensitized by the injection of horse serum , as well as on 20 rabbits which in addition to being sensitized in this way also received three injections into the tonsils of two billion microbial cells of an attenuated 2-day culture of Streptococcus viridans.

Of the control rabbits, the spleen was removed from three, and in the remaining six splenectomy was performed three months after ligation of the lienal vein. This vein was ligated also in five of the dogs.

After the operations regular observations on the animals were maintained, and records were made of the weight, respiration of the pulse rates, and a further investigation of the blood was made.

To study the development of the pathological process the animals were killed at various times from 2 weeks to 12 months after the operation. The liver and spleen were weighed and measured, and their tissues were investigated histologically.

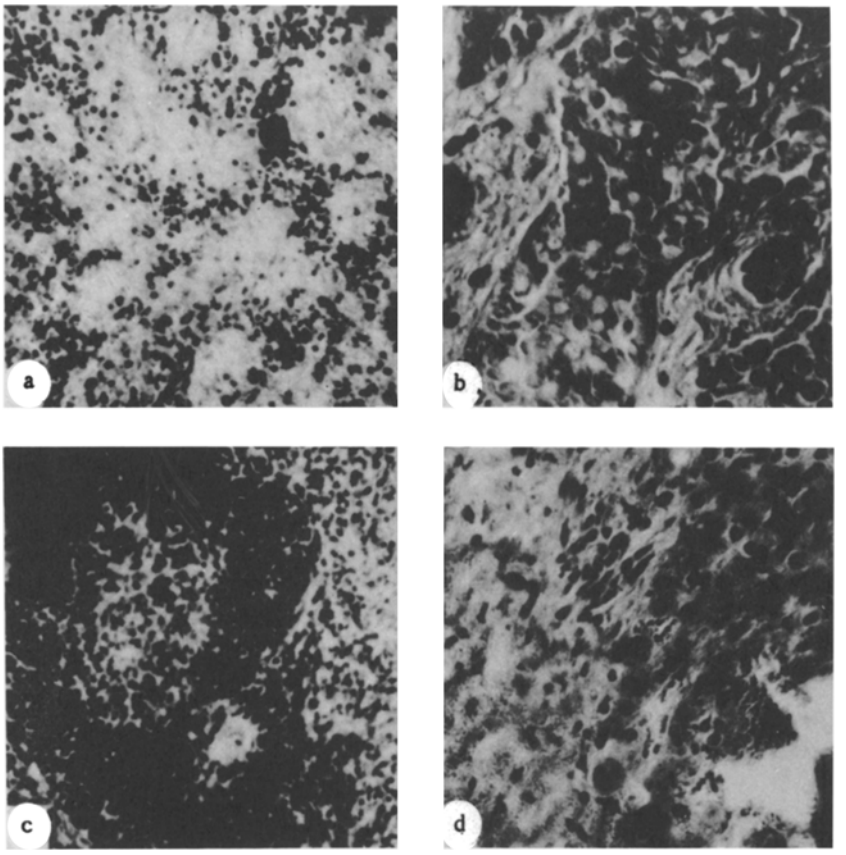

Fig. 1. a) Vessels of the spleen engorged with blood, stasis of the blood. Micrograph Reikh. Stain hematoxylin-eosin. Magnification 10 x 40; b) reticular hyperplasia of the pulp in the spleen. Micrograph Reikh. Stain hematoxylin-eosin. Magnification 10 x 20; c) focal albuminous dystrophy of the hepatic cells. Micrograph Reikh. Stain hematoxylin-eosin. Magnification 7 x 20.

The material was fixed in a 10-12% formalin solution and embedded in celloidin; some of the material was cut on a freezing microtome. The sections were stained in hematoxylin-eosin, or in picrofuchsin, and they were tested for iron and for argyrophilia of the fibers by Foot's method.

EXPERIMENTAL RESULTS

In the postoperational period the animals which had not been sensitized or infected showed no appreciable disorder of their general condition, and by the end of the 2-4h week they could scarcely be distinguished from healthy animals.

The only prolonged change was in the white cells: for 1-2 weeks there was a leucocytosis and a neutrophilia; by the end of the first month there was a change to a lymphocytosis which was maintained for a 4-month period of observation.

However when the animals were sensitized and infected, for the first few days after the operation they lost weight rapidly, refused food, and became very weak; seven of them died. However after one month the 33 surviving rabbits could scarcely be distinguished from healthy rabbits.

The morphological changes in the spleen and liver depended upon the influence brought to bear upon them.

In animals which had not been sensitized or infected ligation of the lienal vein and its collaterals, and the injection of thromboplastin evoked some increase in the size of the spleen during the first month. By the beginning of the 3-4th month of the experiment the size of the spleen had returned to normal. For the first month histological

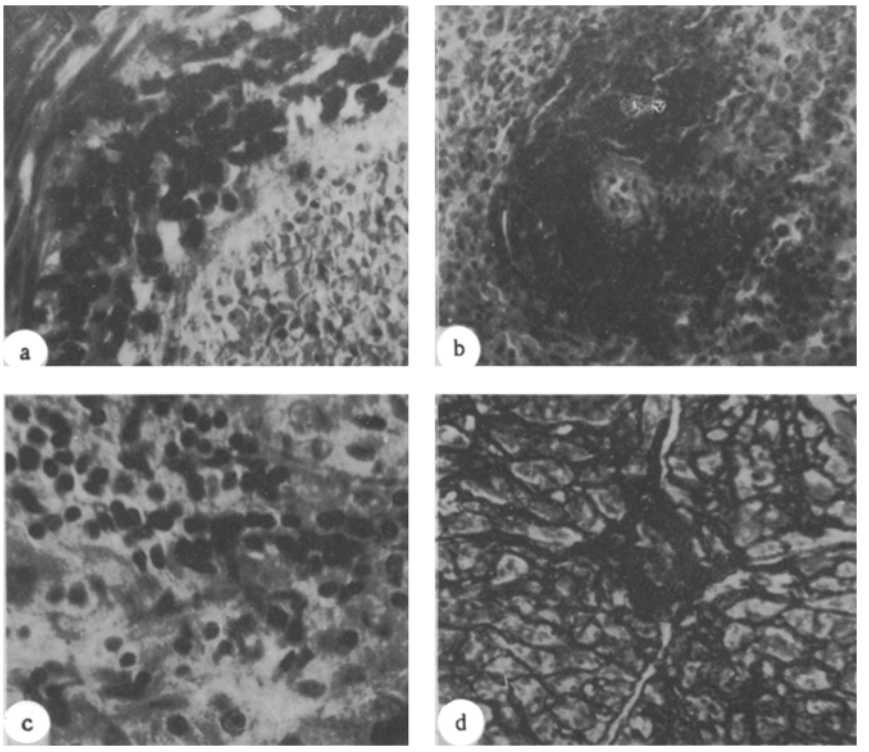

Fig. 2. a) Stasis in splenic vessels. Micrograph Reikh. Stain hematoxylin-eosin. Magnification 10 x 40; b) sclerosis of walls of vessel in spleen. Micrograph Reikh. Stain hematoxylin-eosin. Magnification 7 x 20. c) extensive lymphoid infiltration in stroma of liver. Micrograph Reikh. Stain hematoxylin-eosin. Magnification 10 x 40. d) sclerosis of intertrabecular stroma of liver. Micrograph Reikh. Foot's stain. Magnification 10 x 20.

abnormalities could be observed in the circulation, there was stasis, and initial signs of thrombosis (Fig. 1a), and there were also numerous hemorrhagic zones, most of them showing diapedesis. Staining by Foot's method showed the presence of coarse argyrophil fibers of the red pulp, most of them subscapula and following the course of the trabecubeculae. The follicles of the white pulp were somewhat atrophic. There was a focal proliferation of the cells of the reticuloendothelium system (Fig. 1b).

With increase in the spleen of phenomena associated with hemodynamic disturbances (3-4h month) and with fibro-ademia, and with the organization of thrombin in the vessels and the appearance of reactive infiltration seen through the walls of the vessels there was an increased proliferation of the reticuloendothelial cells of the splenic sinuses. These changes were the more marked the more extensive the impairment of the flow of blood away from this organ. The most marked vascular changes, which were associated with reactive phlebitis, developed after the injection of thromboplastin.

In the liver as a consequence of these measures various degrees of disturbance of the circulation both in the peripheral and central portions of the lobules were observed. The changes showed up as engorgement of the capillaries and arterioles with blood, prestasis, stasis, and focal hemorrhages which subsequently became organized. In the hepatic cells there were signs of necrobiosis, and focal albuminous and fatty dystrophy (Fig. 1c). There was a marked proliferation of the cells of the reticuloendothelium system and coarse argyrophil fibers were formed. These changes were particularly marked in areas where there was the greatest disturbance to the circulation. Similar results were also obtained in experiments on dogs.

As our control experiments showed, in animals which had been sensitized but which had suffered no operative interference, there were marked changes in the spleen and liver; they took the form of stasis, mucoid and fibrinoid swellings and a fibrinoid necrosis of the wall of the vessel (in the first 2-3 weeks after sensitization).

The effect of the experimental measures we have described was to induce in the spleen the development of a marked engorgement, of stasis (Fig. 2a), and of diapeditic hemorrhages, phlebitis, hyalinosis, and sclerosis of the vascular walls (Fig. 2b). These changes occurred $1\frac{1}{2}$-2 times more rapidly than they did in nonsensitized animals.

During these changes, in the liver there was not only an engorgement of the vessels, and hemorrhages associated with a marked destruction of the vessels, but there were also considerable dystrophic changes of cells in the form of an albuminous dystrophy and fatty degeneration.

In regions where there were extensive hemorrhages associated with necrosed hepatic cells there was an extensive lymphocytic infiltration (Fig. 2c), a proliferation of the Kupfer cells, and the formation of coarse argyrophil fibers with extensive cicatricial areas (Fig. 2d).

In experiments where after sensitization the animals had been infected the changes were similar to those which had occurred after preliminary sensitization, but more marked. There was a specific increase in the dystrophic processes in the liver, in the appearance of zones of necrosis, and in the necrosis of hepatic cells followed by organization of the dystrophic and necrosed areas.

Whereas splenectomy in the control animals did not cause such marked changes in the liver, removal of the spleen from sensitized and infected animals three months after ligation of the lienal vein led to inhibition of the pathological process developing in the liver. Thus, in experiments in which five months elapsed after splenectomy, the only remaining changes in the liver where a marked dystrophy of the hepatic cells, a hemosiderosis, and a reactive outgrowth of connective tissue (replacing the previous hemorrhages and dystrophic hepatic cells).

In our studies of the spleens removed from children on account of splenomegaly, developed in the so-called hepatolienal syndrome of unknown origin, we found the morphological picture of the changes was very close to the situation in the experiment. There was a resemblance between the changes in the biopsy specimens of the liver taken from children operated for splenomegaly occurring in the hepatolienal syndrome. There was a dystrophy of the hepatic cells, coarse argyrophil fibers were diffusely present, and there was a varying degree of lymphocytic infiltration, which is also characteristic of the initial forms of hepatic sclerosis.

The results of the experiments indicate that the development of the pathological process in the spleen leads to the development to similar changes in the liver. However splenectomy produced no such effect in the liver. Previous sensitization and infection with streptococcus increase the severity of the vascular hepatic disturbances, the dystrophy of the hepatic cells, and focal cirrhotic changes.

The alterations we have described in the liver of the experimental animals are evidently related to the presence of some influence derived from the pathological changes in the spleen. The nature of these influences requires further investigation.

SUMMARY

It was shown in experiments on rabbits that development of a pathological process in the spleen related to impaired circulation in the lienal vein led to the development of annular cirrhosis of the liver. The cirrhotic process was found to be more marked when the splenic injuries occurred in association with previous sensitization of the animals with horse serum and their infection with an attenuated culture of Streptococcus viridans.

Mechanisms governing these effects require further study.

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