Virchows Arch. A Path. Anat. and Histol. 377, 97–110 (1978)

Virchows Archiv A

Three-Dimensional Morphology of the Liver in Cirrhosis and Related Disorders

Tohru Takahashi

First Department of Pathology, Tohoku University School of Medicine, Seiryomachi, Sendai, Japan

Summary. Cirrhotic livers of different types were subjected to three-dimensional graphic reconstruction of nodules, interstitial septa and blood vessels from serial histologic sections. It was found that in all cases adjacent cirrhotic nodules were connected to one another so as to form a nodular network, in spite of their apparent separation in histologic sections. The nodules were linked in the form of chains with abundant anastomoses, and the network was 'conjugate' with the intrahepatic vascular tree, as revealed by its close relationship to blood vessels. A parenchymal network of the same type was also found in livers with subacute or chronic hepatitis, suggesting that this type of structure was common to cirrhosis and its precursor lesions and represents the geometrical configuration of hepatic parenchyma surviving zonal hepatic necrosis. A re-examination of chronic liver disease in terms of its structural framework provided a new viewpoint from which to analyse the morphogenetic problems of these disorders.

Key words: Liver cirrhosis – Subacute hepatitis – Chronic hepatitis – Three dimensional structure.

Introduction

The three-dimensional structure of an organ is sometimes quite different from what appears in two-dimensional sections. Tissue inter-relationships are hard to interpret as three-dimensional structures, and whether seemingly discrete structures are really so is often beyond intuitive judgement. Stereological methods in their present state are not helpful (DeHoff et al., 1968). Although cirrhotic nodules appear to be separated by connective tissue septa in the majority of cases, the actual three-dimensional structure is not that of a dispersed system. In the present article the author intends to relate the histologic appearance of several types of chronic liver disease to the corresponding three-dimensional structure, with special reference to the connecting relation of parenchymal masses.

0340-1227/78/0377/0097/$02.80

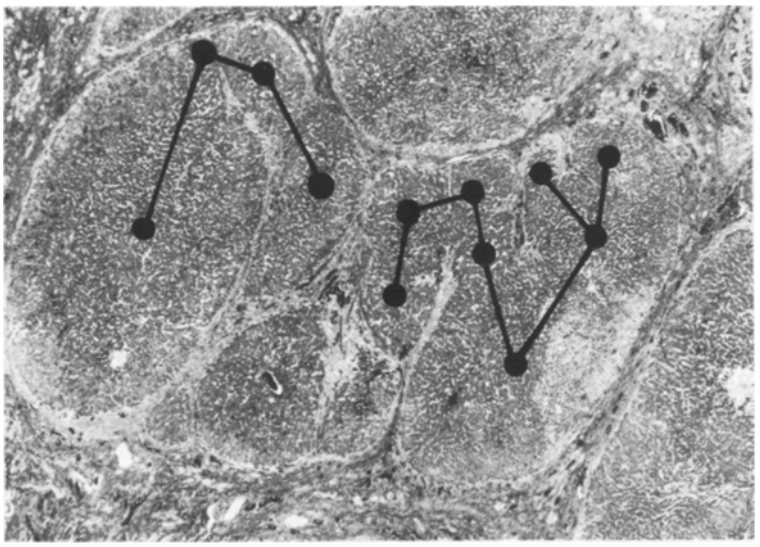

Fig. 1. Typical histological appearance of cirrhotic liver. Deep indentations of parenchymal islets by connective tissue septa cause complicated flexions of nodular chains. The dots and lines in the figure roughly indicate the centers of individual nodular sections and their internodular connections, respectively. Goldner's trichrome combined with Weigert's stain for elastic fibers. 15×

It seems pertinent to explain briefly the background of the present three-dimensional analysis of liver diseases. The author previously reported a morphometric analysis of cirrhosis in association with Suwa (1964). In that study, the cirrhotic liver was replaced by a geometrical model where nodules were assimilated by spherical bodies of different sizes, randomly dispersed in the space. Assuming some distribution function for the radius of the spheres, a stereological method was developed to estimate the variables of the assumed distribution function, from histometrical examination of circular sections of nodules on a microscopic slide. Recently, the method has been further extended into a more general form (Suwa et al., 1976).

In reality, however, its application to the histological picture has not always been successful, mainly because the shape of nodule sections deviates more or less from a circle. For example, they frequently present a lobulated appearance apparently due to partial coalescence of several nodule sections (Fig. 1). The histological appearance suggests a spatial structure which differs from a simple dispersion of separate nodules, and it seems more likely that the nodules are united so as to form a three-dimensional continuous system.

The same pattern is found, in an accentuated form, in precirrhotic lesions such as subacute hepatitis (Fig. 2). In this case the parenchymal belts which have survived zonal necrosis exhibit an irregular meandering form, and their gross netlike arrangement suggests interconnection of potential nodules. Thus, subacute hepatitis presents a structural pattern similar to that of cirrhosis, which is simply reproduced by plastering parenchymal coating on an isomorphic framework. The concept of a structural framework is of fundamental importance

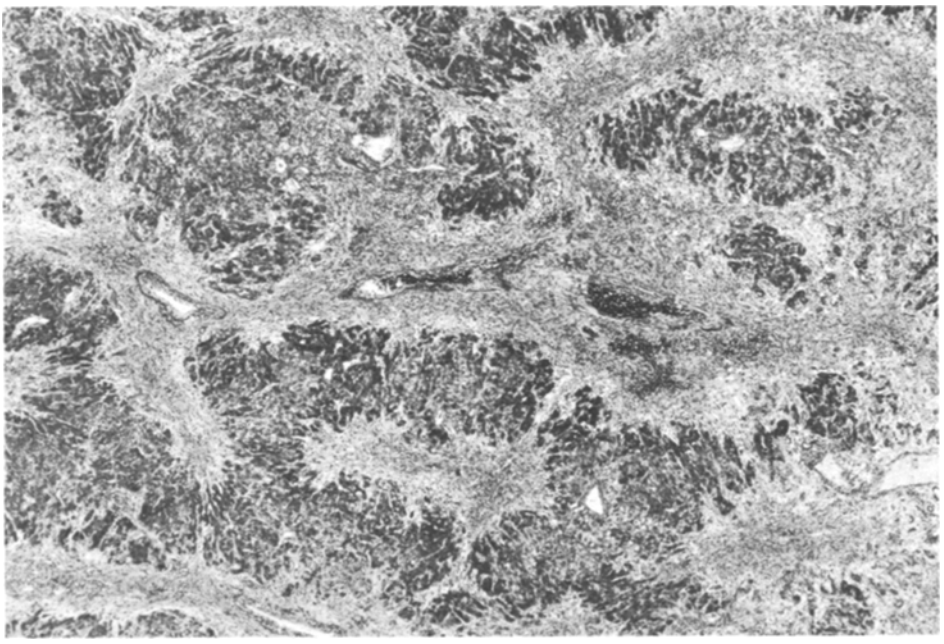

Fig. 2. Case 4. Subacute hepatitis with evidently zonal pattern. Goldner's trichrome combined with Weigert's stain for elastic fibers. 35×

in morphogenetic analysis of chronic liver disease, because it provides the basis for a classification of hepatic lesions according to isomorphism or heteromorphism of their geometry. In the present report, preliminary studies of hepatic structures in some chronic liver diseases are described following reconstruction from serial histological sections. The results are evaluated with a view to introducing a pertinent model into the analysis of hepatic structure, which is susceptible to topological treatments.

Materials and Methods

Five autopsy cases of different chronic liver diseases were selected for the present study. The cases are outlined in Table 1. The series includes three cases of cirrhosis, the histologic type being classified according to Popper and Schaffner (1957) and Gall (1960). Cirrhosis of specific etiology such as biliary or cardiac cirrhosis was not studied in the present series. Cases with primary hepatic neoplasm were also excluded. Precirrhotic lesions (subacute and chronic hepatitis) were studied and one case of each diagnosis was selected from autopsy specimens. A biopsy specimen of a lymph node with sarcoidosis was also examined, since the architecture of the granulomata was expected to be analogous to that of cirrhotic nodules.

All the liver specimens were excised within 2 h post mortem and fixed in Zenker-formalin solution. They were embedded in celloidin-paraffin, and semiserial histologic sections of 6 μ in thickness were prepared from each specimen at a proper interval of one to five sections. The required range of sectioning depended upon the dimension of the pathologic change. For instance, in the case of coarse-nodular cirrhosis a thickness of 8 mm was necessary to cover the diameter of the largest nodule, whereas a thickness of only 2 mm was sufficient for finely granulated liver

Table 1

Case No.	Age and sex	Weight of the liver (g)	Histologic appearance of the liver
Case 1	23 F	780	Cirrhosis, posthepatitic, coarse-nodular
Case 2	57 F	590	Cirrhosis, posthepatitic, coarse-nodular. Uncompleted nodulation
Case 3	3 M	1970	Cirrhosis, portal, related with a congenital metabolic error (lipodystrophic diabetes)
Case 4	36 F	580	Subacute hepatitis, 60 days after the onset. Death from hepatic insufficiency
Case 5	51 M	1660	Chronic persistent hepatitis, 2 years' duration. Suicide by leaping from the height

in chronic hepatitis. The sections were stained with Goldner's trichrome combined with Weigert's stain for elastic fibers.

Three-dimensional reconstruction was performed by a graphic method. An area of 30 to 200 mm^2 was arbitrarily selected on the first slide of the semiserial sections. By use of a profile projector (Nikon, Model V-16), the area was projected onto a sheet of tracing paper under a magnification of 20 to 50×, and the borderlines between the parenchymal and interstitial areas were carefully delineated. At the same time, sections of the blood vessels were drawn, so far as they were discernible under the magnification. The procedure was repeated with advancing steps of serial sections.

The spatial relation between the parenchymal, septal and vascular structures was examined by looking through the drawings after they were placed one upon another in series. The results were presented in stereograms in two different ways. In one of them, the septa were disregarded in order to visualize parenchymal masses. The other was the reverse image, made by the septa alone. The former was called the 'positive' stereogram and was useful in providing a perspective of the relationship between parenchymal regions and blood vessels. The latter, 'negative' stereogram, ensured a better view of the interconnections of the parenchymal structures in the space. A combined use of the two stereograms was effective in demonstrating the results of observation.

Results

Figure 4 shows a positive stereogram of nodules and blood vessels in Case 1 of coarse-nodular cirrhosis with apparently separate nodules on histology (Fig. 3). In the 'positive' stereogram a dense aggregate of nodules makes the visualization of a perspective of their spatial connectivity rather difficult. However, several internodular connections are seen as partial coalescence of nodules. This illustration alone affords convincing evidence for nodular interconnections in a cirrhotic liver. There are few, if any, isolated nodules; they do not exceed 2% of the total number. It is evident that the great majority of nodules are connected with one another and form a continuous system.

A 'negative' stereogram shows the connections more directly. An example is Figure 6, which was prepared from Case 2 of coarse-nodular cirrhosis in which nodulation was less advanced than in the previous case (Fig. 5). The reconstruction illustrates the skeleton of the interstitial septa, while the round spaces correspond to nodules. There are broad openings in the septa, which

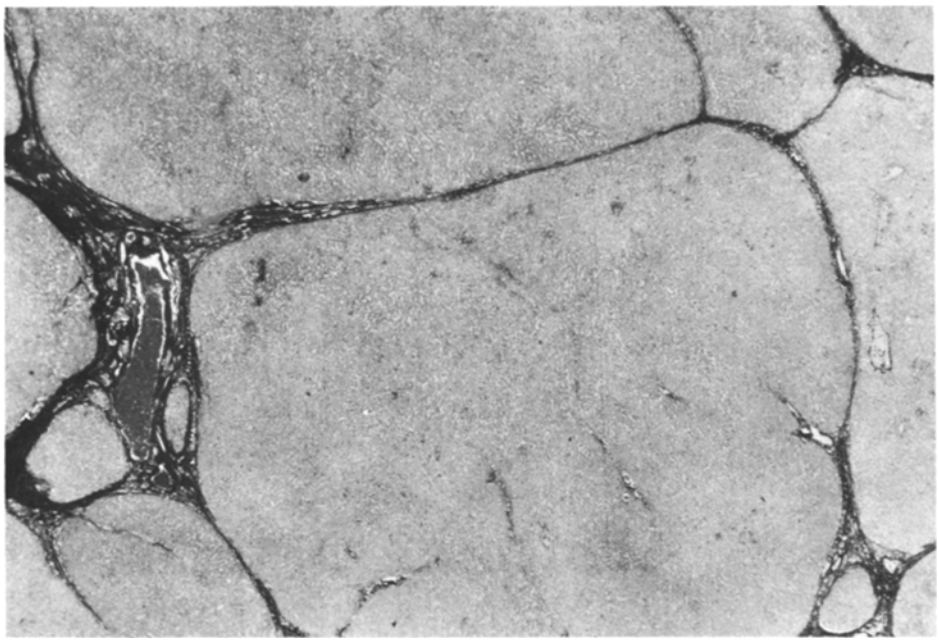

Fig. 3. Case 1. Coarse-nodular cirrhosis with apparently separated nodules. Azan stain. 13×

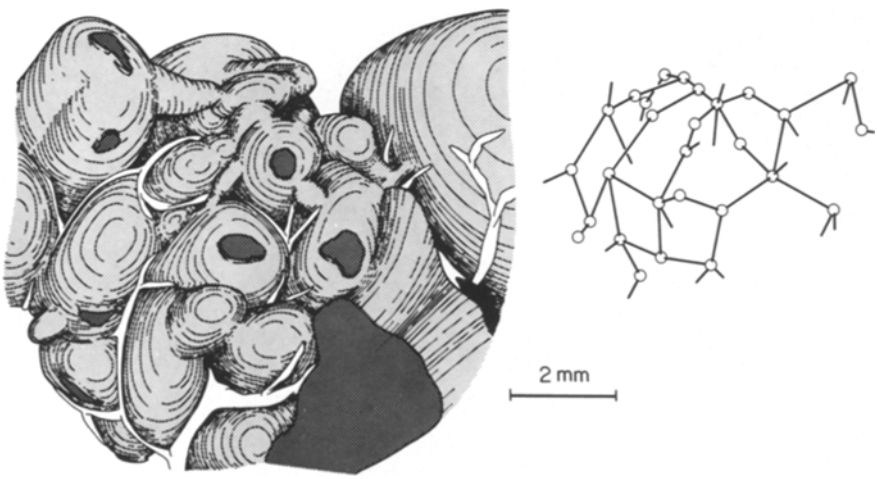

Fig. 4. (Left) Graphic reconstruction of the nodules and blood vessels of Case 1, showing a number of connections between the nodules. (Right) Linear model visualizing the connectivity of nodules. It reveals a three-dimensional network system. The nodules are expressed by nodes, the internodular connections by branches

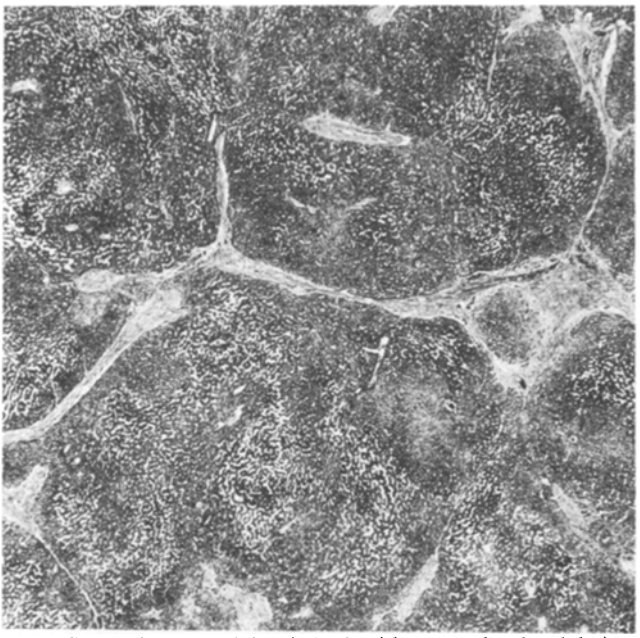

Fig. 5. Case 2. Coarse-nodular cirrhosis with uncompleted nodulation. Goldner's trichrome combined with Weigert's stain for elastic fibers. 20×

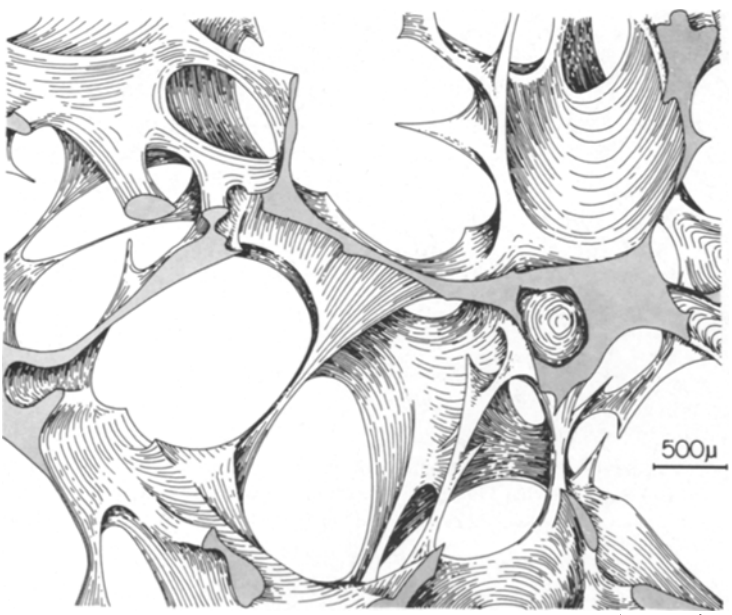

Fig. 6. Reconstruction of the interstitial septa of Case 2. The void spaces between the septa correspond to the nodules. Note abundant connections between the nodules

afford free communication between the spaces, demonstrating the continuity of the nodular structure. Popper et al. (1955) once pointed out incomplete nodular separation in a case of fatty cirrhosis.

The inter-connections between nodules can be clearly visualized using a linear diagram. It is constructed as a node-branch system, in which the nodules are replaced by nodes and the internodular connections by branches. As an example, the principle is applied to Case 1 and the result is demonstrated in the right part of Figure 4. It is a three-dimensional network, in which the nodules are linked to the adjacent ones to form multiple loops in the space. The structure is properly described as a 'nodular network'. Such an abundant multiple inter-connection readily accounts for the frequent lobulation of nodular sections (Fig. 1).

The architectural relationships of the intrahepatic blood vessels to the nodular network are examined in Figure 4. Portal and hepatic vein branches cannot always be discriminated, but it is clearly demonstrated that branches of the vascular trees penetrate the meshes of the nodular network and produce elaborate mixing of the two systems in the space. The configuration of the vascular tree depends so closely on that of the nodular network, that the former may be expressed as being geometrically 'conjugate' with the latter. Intrahepatic blood vessels are arranged along internodular grooves and constrict hepatic parenchymal mass. This anatomical pattern of cirrhotic livers results primarily from the orientation of the vascular tree, which restricts the expansive growth of hepatic parenchymal tissue as a pre-existing structure.

A conjugation of the nodular network and vascular tree is characteristic of all cirrhotic livers. Another example is demonstrated in Figure 8, a positive reconstruction of Case 3 of portal cirrhosis with diffuse fatty metamorphosis as shown in the photomicrograph Figure 7. Close interlacement of portal and hepatic venous trees with the nodular chains is clearly seen.

The characteristic three-dimensional framework of cirrhotic livers is already established in some precirrhotic lesions. The histological appearance of Case 4 (subacute hepatitis) is shown in Figure 2. The areas of liver cell injury have undergone almost complete collapse and the histology is that of so-called subacute yellow atrophy. A 'zonal' pattern prevails in the figure, illustrated by the regular centrilobular extension of the collapsed areas and consequently the surviving parenchyma demonstrates the acinar structure of Rappaport (1958) in an emphasized form. There are also bridgings of injured areas.

The reconstruction of this case is presented in Figure 9 in a positive form. Collapsed regions spread around the branches of the hepatic vein as clefts with a trabecular shape. The surviving parenchyma is united to form a network which is interlaced with the hepatic venous tree. Relatively large portal tracts are exposed in the collapsed region and may be seen to interdigitate with the parenchymal network. In every respect the gross framework is similar to that of cirrhosis.

The figure also shows how the network structure develops following zonal necrosis, since the parenchymal network is the three-dimensional remnant of viable parenchymal tissue. 'Bridging necrosis', the importance of which in the prognosis of liver disease was emphasized by Boyer et al. (1970), is in fact

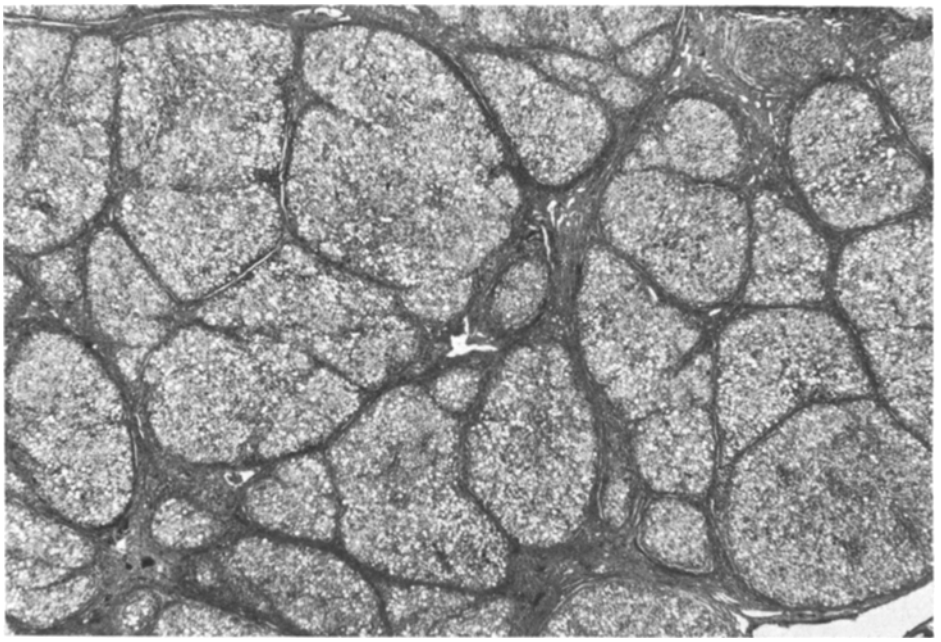

Fig. 7. Case 3. Cirrhosis of portal type with marked fatty metamorphosis of the intranodular parenchyma. Goldner's trichrome combined with Weigert's stain for elastic fibers. 15×

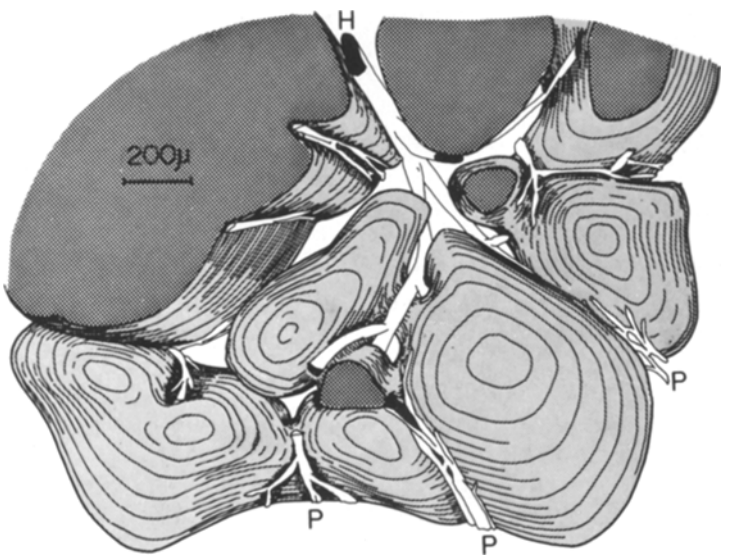

Fig. 8. Reconstruction of the nodules and blood vessels of Case 3. Intertwinement of the nodular network with blood vessels. *P*: portal vein. *H*: hepatic vein

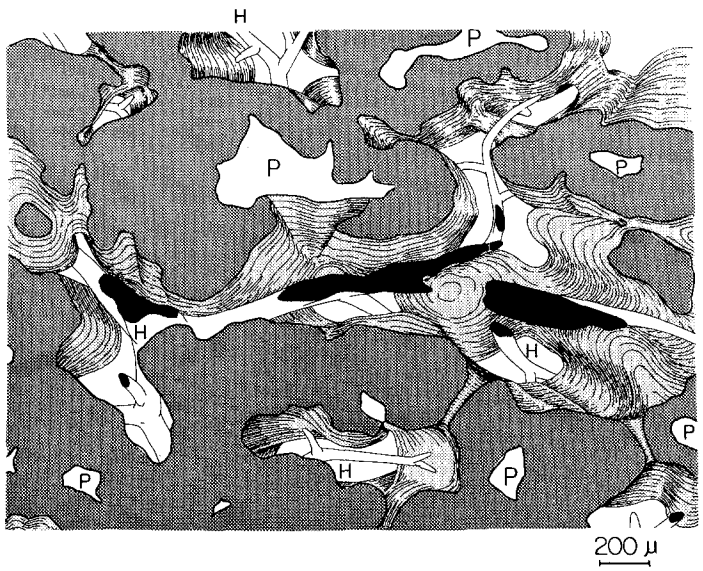

Fig. 9. Case 4. Reconstruction of the hepatic parenchymal tissue which survived massive necrosis. The same area as in Figure 2 was presented. The parenchymal tissue constitutes a three-dimensional network intertwined with the hepatic vein branches. *P*: portal tract. *H*: hepatic vein

a sectional picture of the interconnected necrotic foci which form a three-dimensional network.

A second precirrhotic lesion is chronic hepatitis (Case 5). The histopathological appearance of the liver at autopsy is characterized by chronic inflammatory infiltration in the enlarged portal tracts with partial formation of intralobular septa (Fig. 10). Inconspicuous piecemeal necrosis suggests little activity in the hepatitic process (DeGroote et al., 1968).

The three-dimensional structure of this case is exhibited in a negative stereogram (Fig. 11). There are abundant sail-like membranous septa extending between the blood vessels, dividing the parenchymal tissue into small regions. The parenchymal units roughly corresponds to the hepatic lobules in the sense of Pfuhl (1932), as indicated by small hepatic veins running along their axes. The portal or periportal localization of the main pathologic processes also indicates the fundamentally zonal character of the lesion. Larger hepatic veins are entirely enclosed in the septa.

The three-dimensional structure in chronic hepatitis closely simulates that in Case 2, which justifies Gall's concept of 'posthepatitic' cirrhosis. The resemblance also shows that the structural basis of a parenchymal network is also established in chronic hepatitis, though the framework may be less apparent than in Case 2 due to imperfect separation of nodules. The network in this case is of course conjugate with portal tracts and proximal hepatic veins.

Figure 12 is the photomicrograph and Figure 13 the positive stereogram of a lymph node with sarcoid granulomata. The granulomata are entirely connected in the space to form a network conjugate with the terminal vascular tree, a structure which represents an exact counterpart of the nodular network in

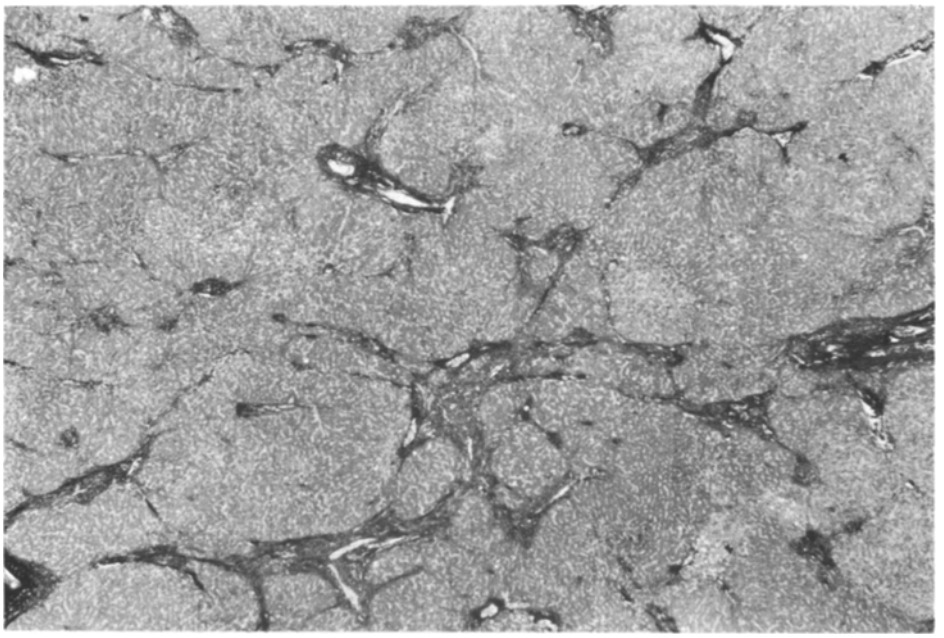

Fig. 10. Case 5. Chronic hepatitis with widening of portal tracts due to inflammatory infiltration. Formation of several membranous septa. Nodular regeneration is inconspicuous. Azan stain. 25×

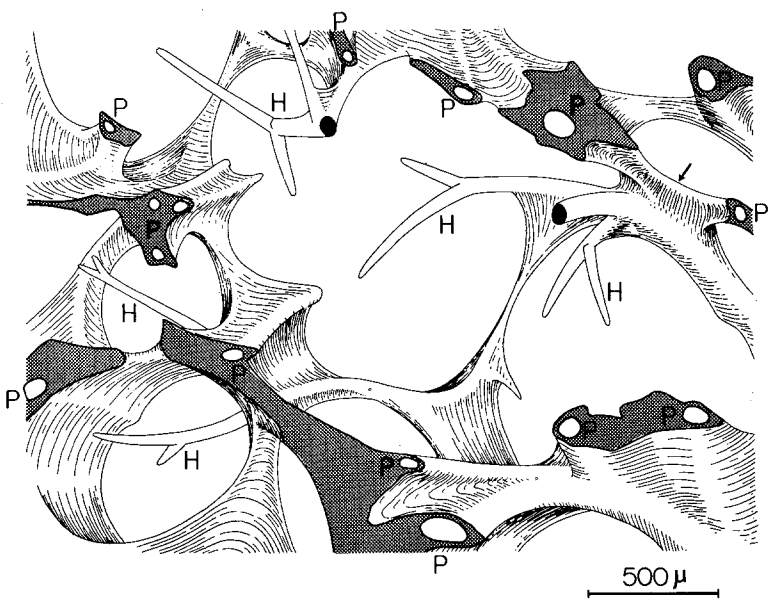

Fig. 11. Reconstruction of the septal tissue and blood vessels in Case 5. *P*: portal vein. *H*: hepatic vein

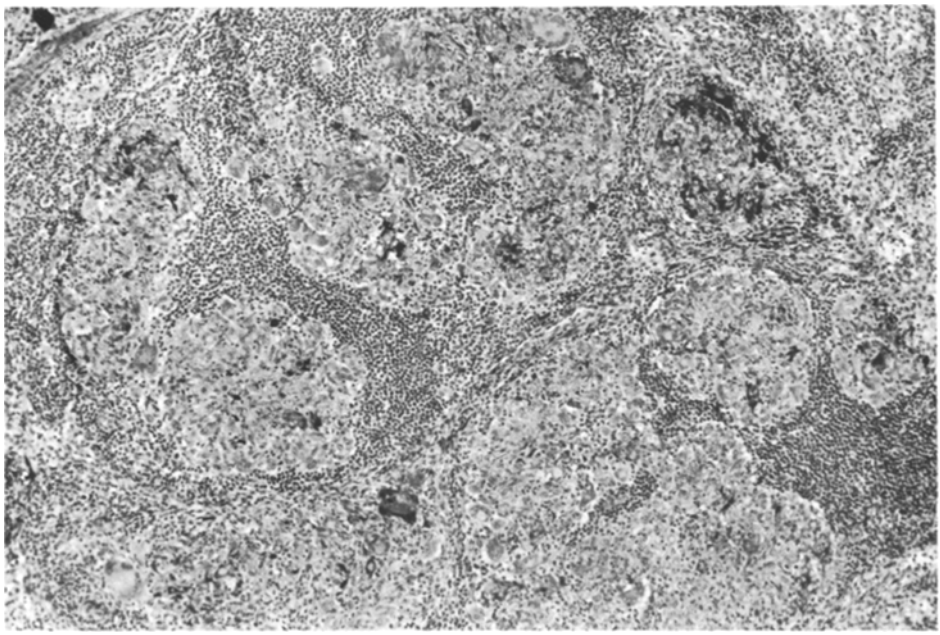

Fig. 12. Sarcoidosis of lymph node with multinodular granulomas. Goldner's trichrome combined with Weigert's stain for elastic fibers. 80 ×

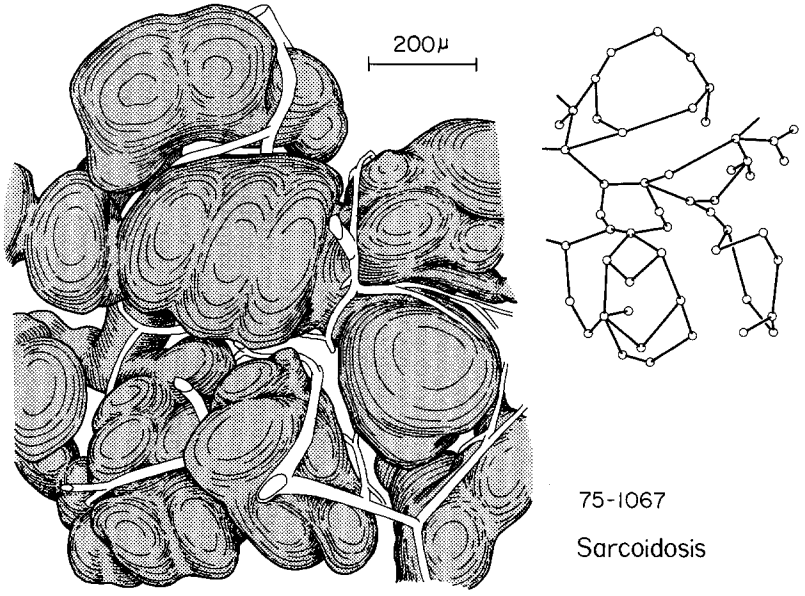

Fig. 13. (Left) Graphic reconstruction of sarcoid granulomas. Network formation of individual granulomas with intertwining blood vessels. (Right) Linear model showing connections between the granulomas

cirrhotic livers. An apparent explanation for network formation in sarcoid granulomas is that the vascular trees are not directly involved in expansive granulomatous growth in this disease, and the network structure is a common anatomical expression of tissues that grow expansively preserving pre-existing vascular trees.

Discussion

Liver cirrhosis, subacute and chronic hepatitis are three closely allied disorders. Their morphological similarity lies in a common structural framework, as demonstrated by the present reconstruction studies. Transformation from hepatitis to cirrhosis can occur without changing the common structural framework of the parenchymal or nodular network system.

The development of the network structure after zonal hepatic lesions is illustrated in Figure 14, taking the hepatic vasculature into consideration. Takahashi (1970) demonstrated that the blood vessels of the normal liver are characterized by regular interdigitation of the terminal portal and hepatic venous branches. A 'zonal' necrosis involves a trabecular region either around the portal or hepatic venous ramifications, and when this extends to a certain width, multiple anastomoses inevitably develop among neighboring necrotic belts, forming a network. This simultaneously molds the surviving parenchyma into a network which is closely interdigitated with the necrotic region. Consequently, the two 'conjugate' networks are topologically similar to each other (Kronsbein et al., 1965).

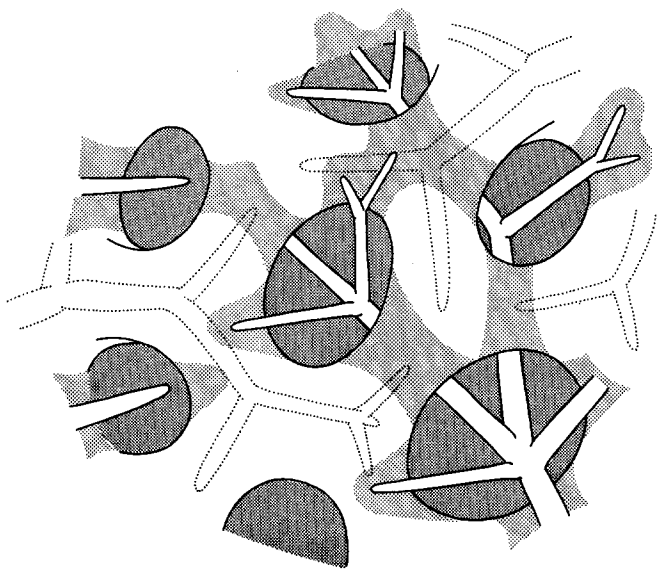

Fig. 14. Extension of 'zonal' necrosis depending on the interdigitating vascular arrangement in the space. The shadowed areas denote the extent of zonal necrosis surrounding the efferent (or afferent) vessels. There are connections of the necrotic areas, which produce a network structure

Network formation as the result of zonal hepatic lesion is an essential prerequisite for the development of liver cirrhosis. Zonal character is confirmed in most precirrhotic lesions such as toxic hepatic injuries, alcoholic injury (Gerber and Popper, 1972) or chronic hepatitis of portal or periportal type. Although in viral hepatitis the pattern of necrosis is sometimes regarded as focal, because of its spotty character (Smetana, 1963), the author thinks in agreement with several others (Lucké, 1944; Thaler, 1952) that it should also be classified with the zonal group. In this condition 'spotty' necrotic foci are often accentuated in the centrilobular region and effectively result in a zonal distribution (see Case 4). Liver cirrhosis does not develop on purely focal lesions such as hepatic abscesses, since they do not lead to the formation of a network system.

One can propose the following hypothesis for the genesis of liver cirrhosis. A parenchymal network as the basic framework for a cirrhotic liver is established at the time of initial hepatic injury. After this, progressive and expansive parenchymal hyperplasia transforms this pattern into a nodular network, which is the basic structure of liver cirrhosis. The final results may be modified by several additional factors, for example secondary parenchymal necrosis.

The relationship between the diverse appearances of cirrhotic livers and different types of precursor lesions will be better visualized if they are reexamined in terms of the structural framework. This analysis is based on the following principle; if a cirrhotic and a precirrhotic liver both have an isomorphic network in spite of their apparently different histologic pictures, it is reasonable to assume that the latter can develop into the former through a continuous transformation. Mere distortion of the network due to parenchymal hyperplasia will never cause a change in its inter-relationships. A transition from one condition to another requires different interactions and must be suspected when pronounced heteromorphism is demonstrated in the networks of two diseased livers. Here radical transformation of the framework is necessary, and may be brought about by episodic hepatocellular injury such as the multilobular necrosis described by Baggenstoss et al. (1972) in some cases of chronic hepatitis.

The results of the present study have demonstrated the importance of a framework in the analysis of the structure of cirrhotic livers. This framework is in the form of a nodular network geometrically replaced by an interconnected three-dimensional mesh. A further analysis requires a topological approach which will be discussed in a forthcoming report.

References

Baggenstoss, A.H., Soloway, R.D., Summerskill, W.H.J., Elveback, L.R., Schoenfield, L.J.: Chronic active liver disease. Hum. Path. **3**, 183–198 (1972)

Boyer, J.L., Klatskin, G.: Pattern of necrosis in acute viral hepatitis. Prognostic value of bridging (subacute hepatic necrosis). New Engl. J. Med. **283**, 1063–1071 (1970)

DeGroote, J., Desmet, V.J., Gedigk, P., Korb, G., Popper, H., Poulsen, H., Scheuer, P.J., Schmid, M., Thaler, H., Uehlinger, E., Wepler, W.: A classification of chronic hepatitis. Lancet **II**, 626–628 (1968)

DeHoff, R.T.: Curvature and the topological properties of interconnected phases. In: Quantitative microscopy (eds. DeHoff, R.T., Rhines, F.N.). New York: McGraw-Hill 1968

Gall, E.A.: Posthepatic, postnecrotic, and nutritional cirrhosis. Amer. J. Path. **36**, 241–271 (1960)
Gerber, M.A., Popper, H.: Relation between central canals and portal tracts in alcoholic hepatitis. Hum. Path. **3**, 199–207 (1972)
Kronsbein, J., Buteau, L.J., DeHoff, R.T.: Measurement of topological parameters for description of two-phase structures with special reference to sintering. Trans. Met. Soc. AIME **233**, 1961–1969 (1965)
Lucké, B.: The pathology of fatal epidemic hepatitis. Amer. J. Path. **20**, 471–593 (1944)
Pfuhl, W.: Die Leber. In: Hdb. d. mikroskop. Anat. d. Menschen. V/2. Berlin: Springer 1932
Popper, H., Elias, H.: Histogenesis of hepatic cirrhosis studied by the three-dimensional approach. Amer. J. Path. **31**, 405–441 (1955)
Popper, H., Schaffner, F.: Liver: Structure and function. New York: McGraw-Hill 1957
Rappaport, A.M.: The structural and functional unit in the human liver (liver acinus). Anat. Rec. **130**, 673–690 (1958)
Smetana, H.F.: Pathology of hepatitis. In: Diseases of the liver (ed. Schiff, L.). 2nd ed. Philadelphia: Lippincott 1964
Suwa, N., Takahashi, T., Sasaki, Y.: Histometrical studies of liver cirrhosis by mathematical treatments of linear intercepts on a small number of random histological sections. Tohoku J. exp. Med. **84**, 1–36 (1964)
Suwa, N., Takahashi, T., Saito, K., Sawai, T.: Morphometrical method to estimate the parameters of distribution functions assumed for spherical bodies from measurements on a random section. Tohoku J. exp. Med. **118**, 101–111 (1976)
Takahashi, T.: Lobular architecture of the human liver from the viewpoint of hepatic vascular architecture. Tohoku J. exp. Med. **101**, 119–140 (1970)
Thaler, H.: Über die formale Pathogenese der posthepatitischen Lebercirrhose. Beitr. path. Anat. **112**, 173–186 (1952)

Received September 3, 1977