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*Review*

# The scarring of the liver acini (Cirrhosis)

## Tridimensional and microcirculatory considerations*

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**Summary.** 1) Cirrhosis is defined as the scarring of the liver acini in zone 3, zone 1 or in both; the resulting nodules are scarred and modified remnants of acini of various orders. The division of the nodules into "micronodules" and "macronodules" is difficult to justify as their two dimensional appearance changes at different planes of section.

2) Early scar formation precedes changes in the microcirculatory dynamics. Sprouting of vascular branches, especially of arterioles, takes the leading role in the development of mature scars, i.e. of *fibro-vascular membranes*. The fibrous repair is at the same time the road builder for collateral flow.

3) The pathophysiology of the collateral circulation is the basic determinant in the formation of the cirrhotic patterns. The three microcirculatory phases in the cirrhotic process are due to a changeover of the intrahepatic circulatory path from the normal trichotomy of the preterminal vascular branches to convoluted collateral channels. The three phases of the cirrhotic process are:

*a. The Triadal Nodule.* It receives blood from the TPV and THA *and* from the perinodular plexus. The nodular parenchyma may already be segregated from the ThV, a situation that leads to portal hypertension.

*b. The Para-triadal Nodule.* It is a conglomerate of nodules that often are not completely separated from each other; they are derived from neighbouring acini of various orders which receive blood from large triads contained in the perinodular scar. The blood arrives into the sinu-

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soids primarily via the perinodular plexus. Some sinusoids may receive additional blood through sclerosing remnants of terminal afferent branches and through irregular vascular twigs which, along with septa, enter the nodules at various sites.

*c. The A-triadal Nodule.* It is completely separated from neighbouring nodules by thick scars, its parenchyma totally segregated from afferent and efferent vascular branches. The nodules receive blood only from a dense perinodular plexus of wide capillaries.

**Key words:** Nodular microcirculation and morphology – Intrahepatic collaterals – Functions of liver scars, roadbuilders of collateral flow – Definition of cirrhosis

## Introduction

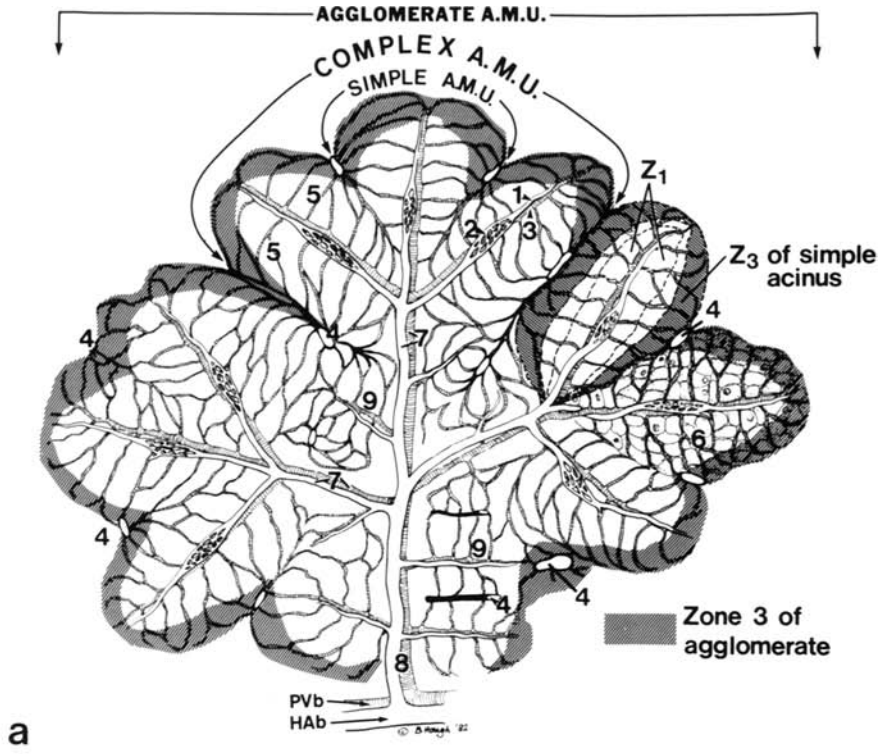
The *pathogenesis of cirrhosis* has had various explanations as different from each other as the manifold aspects of this pathologic entity. In an earlier paper (Rappaport and Hiraki 1958) the cirrhotic nodules were shown to be remnants of simple or complex acini, or of acinar agglomerates that have been damaged and scarred at their microcirculatory periphery. Significant contributions to the study of the pathogenesis of nodule formation have been made by many investigators. The path of transition of the parenchyma to nodules no longer having their afferent vascular supply and biliary drainage in the center has been traced by Moschcowitz 1948; Barone 1962; Caulet et al. 1964; Popper 1977; Gall 1960; Takahashi 1978. This paper formulates a new concept of the pathogenesis of cirrhosis based on the scarring of the liver acini (Fig. 1). The investigation is founded on circulatory and microcirculatory events as they became evident in our tridimensional studies of serially sectioned cirrhotic tissue blocks.

The last WHO definition of cirrhosis was formulated as "a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules" (Anthony et al. 1977). One is amazed in this definition of cirrhosis by the absence of mention of vascular changes, which, as we will see, play a leading role in scar and nodule formation.

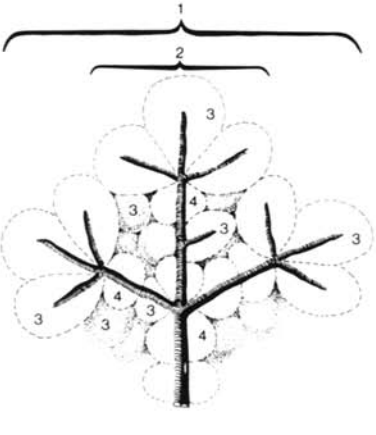
### *Definition of Concepts*

Our study is based on the acinar structure of the hepatic tissue and rests on the self-evident principle that the hepatic parenchyma is organized

**Fig. 1. a** Acinar Microcirculatory Unit (*A.M.U*): *1* = terminal hepatic arteriole, *2* = peribiliary arteriolar plexus, *3* = terminal portal venule, *4* = terminal hepatic venule, *5* = sinusoidal glomus of simple acinus, *6* = sinusoid, *7* = preterminal HA & PV branches, *8* = portal and arterial branches supplying *A.M.U* of agglomerate, *PVb* = portal venous branch, *HAb* = hepatic arterial branch, *9* = small triadal vessels originating from large PV & HA and supplying an acinulus. $Z_1$, $Z_3$ = microcirculatory zones *1* and *3*. **b** Bianchi's scheme of acinar agglomerate (slightly modified). *1* = acinar agglomerate, *2* = complex acinus, *3* = simple acinus, *4* = acinulus. **c** Human liver. Acinulus outlined by fibrosis in $Z_3$. *PV* = large portal branch, *tr* = small triad supplying acinulus


AGGLOMERATE A.M.U.
COMPLEX A.M.U.
SIMPLE A.M.U.
$Z_1$
$Z_3$ of simple acinus
Zone 3 of agglomerate
PVb
HAb

a


1
2
3
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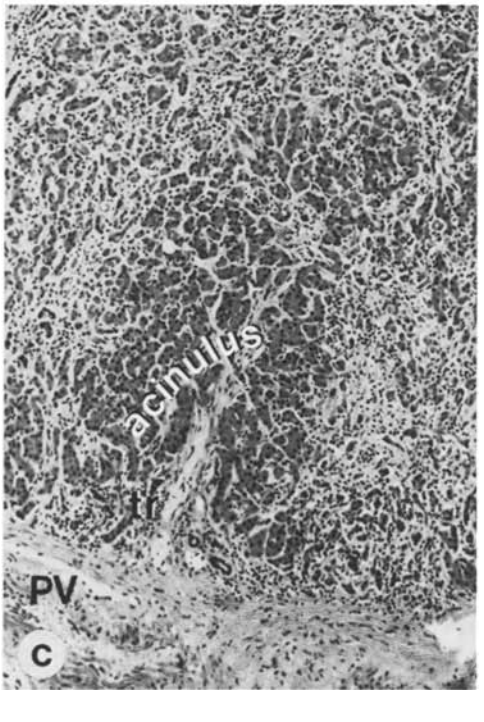

acinules
PV
C

b

around its nutrient vessels. Figure 1 b shows the acinar concept as designed for pathologists by Bianchi (1977).

Hepatic acinar microcirculatory units (AMU) are defined as simple, complex, and agglomerate (Fig. 1 a). They are composed of terminal hepatic arterioles (THA), portal venules (TPV), and sinusoidal pathways connecting them with hepatic venules (Rappaport 1983). These units are in the same order of magnitude as simple and complex acini and agglomerates. There are microcirculatory zones in each microvascular unit. Zone 1 ($Z_1$) is the area where the terminal afferent branches empty into the sinusoids; here the arterial and portal streams mix. Zone 3 ($Z_3$) represents the microcirculatory periphery of the simple acini (SA) as well as of the larger units. The acinar zones are heterogenous in their enzymic and metabolic activities. $Z_3$ is the site of drug metabolism and sensitive to ischemic and toxic damage including alcohol (Rappaport 1979). Note the acinuli, tiny parenchymal clumps (Fig. 1 b, 4) around portal and arterial branches that originate almost at a right angle from the preterminal afferent vessels. The acinuli help form the parenchymal sleeve surrounding vessels of higher order than the terminal ones. A human acinulus outlined by fibrosis in $Z_3$ is shown in Fig. 1 c; its vessels originate from a large vascular branch (PV, lower right corner of figure). The patterns of parenchymal damage (necrotic, fatty, fibrotic) are due to a combination of zonal injuries and are often followed by fibrosis (Fig. 2 a). *Perivenular* fibrosis results from damage of the most peripheral parts of $Z_3$ of SA that lie close to a terminal hepatic venule (ThV) (Mikkelsen et al. 1965). *Triangular fibrosis* occurs when damage has been limited to the $Z_3$ of three complex acini (CA) that surround a ThV. *A starfish-shaped scar* (Fig. 2 b) is the result of necrosis of the parts of the individual zones 3 of several acini that are adjacent to a ThV. Partial fibrosis of zone 3 of several acini may cause fibrous bands to link ThV to ThV and thereby occupy $Z_3$ of a CA (Fig. 2). If bands represent cross-sections of septa extending into the depth of the parenchyma, then the remnants of a complex acinus (Fig. 2, RCA) are transformed into a cirrhotic nodule of medium size. Should, however, injury and scarring affect the entire $Z_3$'s of several SA's, then the *periacinar* fibrous bands link ThV to TPV. Such fibrous bands may indicate the presence of tridimensional septa that transform the remnants of simple acini (RSA, Fig. 2) into small cirrhotic nodules. These may still show a fibrosing small portal space (PS) in their center. For the sake of clarity the simultaneously occurring fibrosis in zone 1 around the terminal afferent vessels and bile duct (Bd) has been deleted in Fig. 2 a. However, fibrosis also occurs in zone 1, either exclusively, as for instance in primary biliary cirrhosis, or in combination with zone 3 as commonly seen in various forms of cirrhosis.

The formation of scars in the liver has a most deleterious effect on the hepatic microcirculation by impeding or obliterating some of its pathways. Collateral channels must be opened in order to permit 1/5 of the cardiac output to pass each minute through the liver. The same pathophysiological principles are operative here as they are in the bypass of an occluded vessel in any organ or limb. Studies of the extrahepatic collateral vessels

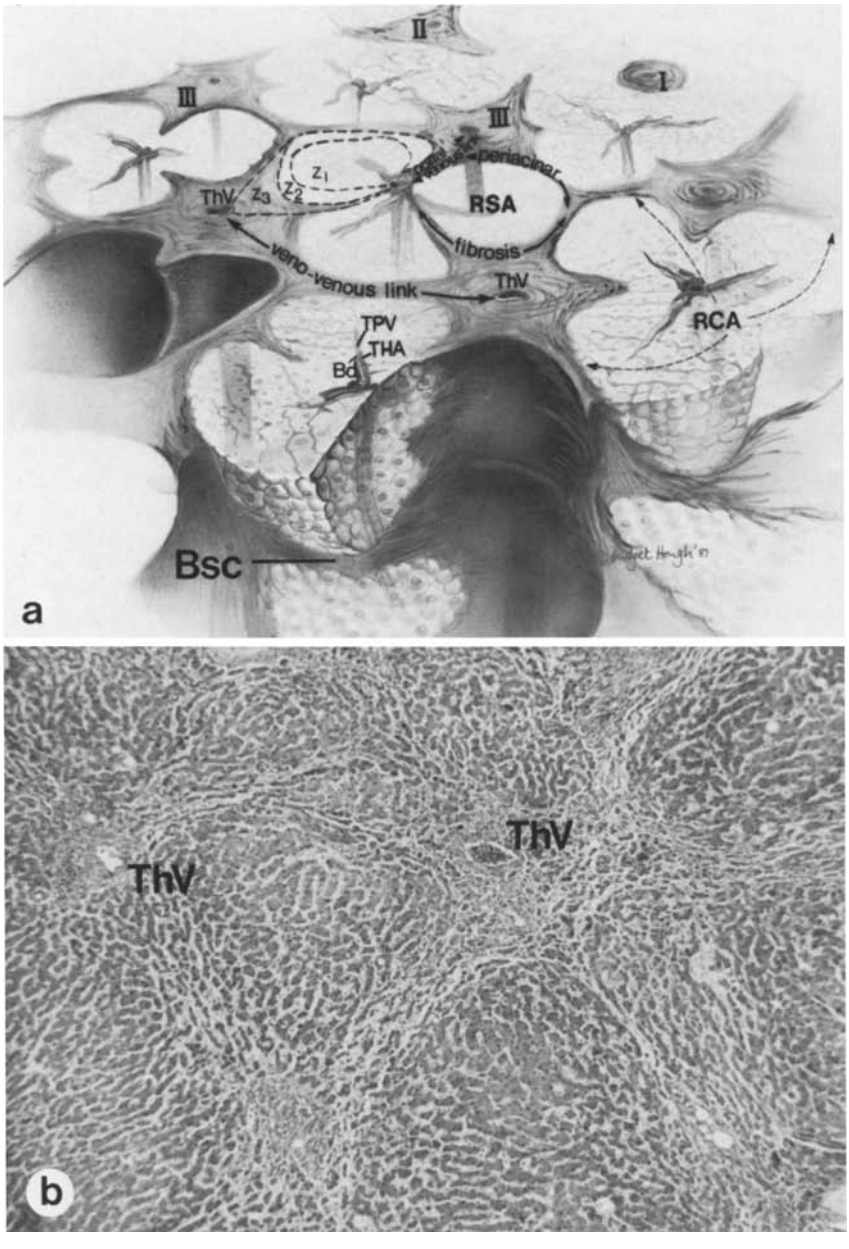



**Fig. 2. a** Tridimensional pattern of fibrosis in $Z_3$ of the acini. *I* = perivenular, *II* = triangular and *III* = starfish fibrosis. $Z_1$, $Z_2$, $Z_3$ = zones of simple acinus. *THA* = terminal hepatic arteriole, TPV = terminal portal venule, *ThV* = terminal hepatic venule, *Bd* = terminal bile duct. *RSA* = remnant of simple acinus, *RCA* = remnant of complex acinus, *Bsc* = bottom scar of nodule (remnant of *CA*). (**b**) Starfish-shaped fibrosis around a terminal hepatic venule (*ThV*) is due to veno-venous fibrous links. (× 68)

have been made since the beginning of our century (McIndoe 1928). We will deal in the section "Vascular Factors" with the development of *intrahepatic* collaterals and their relation to the formation of scar tissue.

## Materials and methods

Tissue blocks from cirrhotic livers (cardiac, alcoholic, posthepatitic, biliary, and due to alpha-1-antitrypsin deficiency) were obtained from the Liver Pathology Reference Centre of the Canadian Liver Foundation and from the Departments of Pathology, Toronto General Hospital, Toronto Western Hospital, Sick Children's Hospital, and Sunnybrook Medical Centre. They were sectioned stepwise and stained with hematoxylin and eosin, hematoxylin/phloxin/saffranine or Masson's trichrome stain. From each block at least 150 sections 6 μm in thickness were cut to ensure that entire acini could be serially sectioned and studied. In each case at least 3–5 nodules were followed from top to bottom. Care was taken not to select a nodule close to one of the surfaces of the tissue block since the nodules are not stacked like bricks; rather they deviate from the vertical direction. Moreover nodules vary greatly in size and shape at different levels of section. To facilitate their study we selected, when possible, nodules located near an easily recognizable structure such as a large vessel, bile duct, scar or neighbouring characteristic acinar configuration; these were used as landmarks in orienting the sections. Photomicrographs (black & white, and colour) were frequently taken at low and high magnifications. Sketches were often made of interesting microscopic fields in order to underline the relationship of the nodule under observation with a neighbouring area. These sketches as well as the microphotos were the materials on which the drawings were based.

## Results

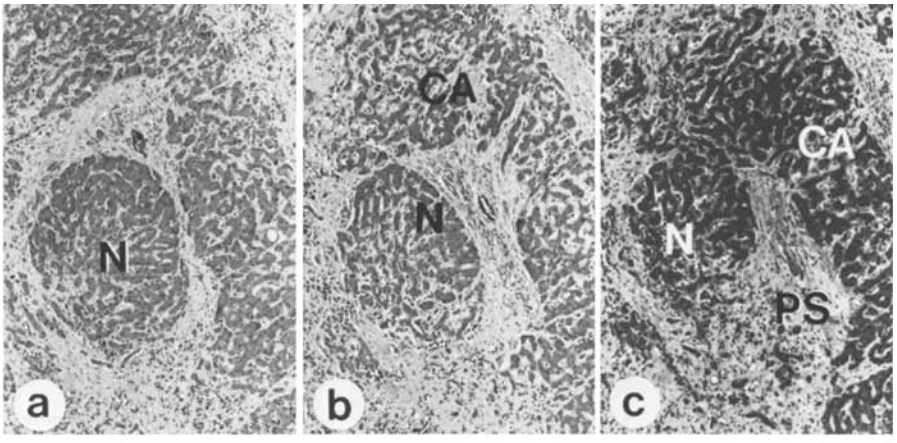
All forms of cirrhosis, though etiologically different, are characterized by similar patho-anatomical features. We will deal first with the tridimensional study of the *nodules,* continue with our observations on *fibrosis* and *scars* and close with the *vascular factors* operative in cirrhosis.

### *Nodules*

The common classification of the nodules into micro- and macro-nodules became questionable in a tridimensional study. "Micronodules" completely surrounded by scar became at a deeper level "macronodules" (Fig. 3); the reverse situation was also common. In the following we are classifying the observations made in our 3-dimensional study of the cirrhotic nodules. *We do not intend to introduce a new terminology in cirrhosis.* We hope to demonstrate that the diagnosis derived from a routine study of histological sections does not clarify the distortion of structure in the cirrhotic liver, and the microvascular changes remain obscure.

It is an accepted viewpoint, that blood flow is a major factor in the survival and functions including the regenerative one, of the nodular parenchyma; it is therefore useful to classify the nodules according to their vascularization:

*Triadal nodules* (Fig. 4) contain one or more terminal portal triads within their parenchyma, i.e. the remnants of SA, CA or acinar agglomerates (see RSA and RCA in Fig. 2a). In the large nodules hepatic venules may also be present.



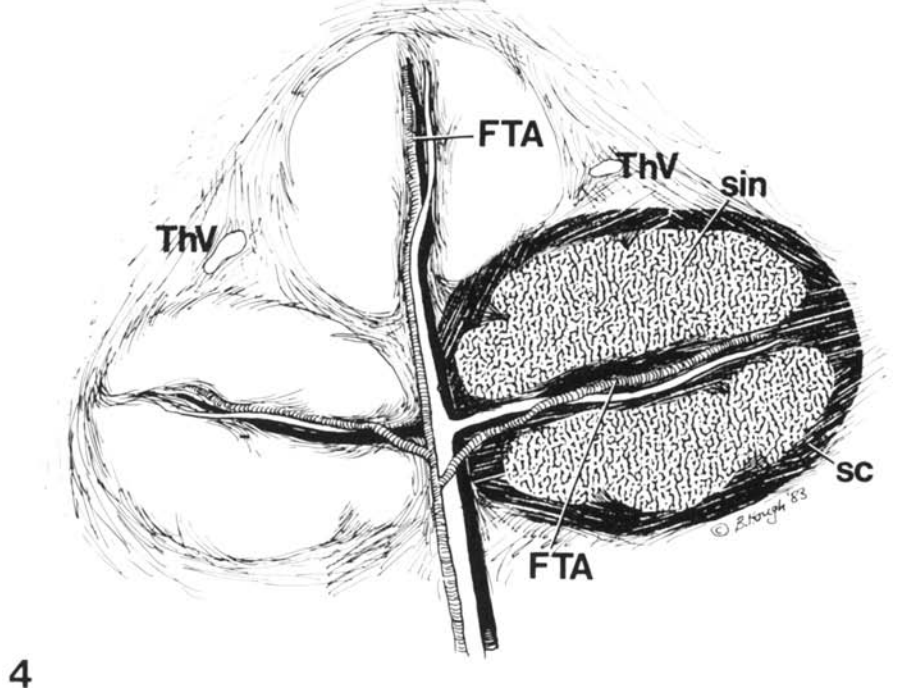




**Fig. 3a–c.** Completely separated "micronodule" becomes 200 μ deeper, a "macronodule". *N* = nodule, *CA* = complex acinar remnant, *PS* = portal space; **a–c** = 200 μ. (×85)

**Fig. 4.** *Triadal* nodule part of complex acinus. A simple acinus with Zone 3 scarred and partial peritriadal fibrosis forms the triadal nodule. *FTA* = fibrosing terminal arteriole, *ThV* = terminal hepatic venule, *sin* = sinusoids, *Sc*-scar

*Para-triadal nodules* (Fig. 7) are a conglomerate of nodules that contain no normal portal triads and are supplied by sclerosing branches from one or two large triads situated outside their parenchyma, i.e. within the perinodular scar.

*Atriadal nodules* (Fig. 15) are small and embedded in large scars that contain few and distant triads and hepatic venules. The scars are rich in thin-walled vessels, many the size of large capillaries. The nodules have no triads, or any afferent or efferent vascular twigs.

*Triadal nodules* are formed as necrotic tissue is being removed from simple acini damaged at their microcirculatory periphery, i.e. $Z_3$. Therefore the scars laid down in the previously necrotic areas encircle the remnants of the acini and generate rounded shapes (Fig. 5a–c). Nodules containing a triad are separated from each other by fibrous septa or by hepatoportal sclerosis (Mikkelsen et al. 1965) which hinder the flow of sinusoidal blood from $Z_3$ into the ThV's situated within the scars. However, triadal nodules also have their terminal afferent vessels surrounded by fibrous tissue (Fig. 5a). The sinusoids originating from the portal vessels have to pass through the scars in zones 1 and 3 and still be patent in order to irrigate the parenchyma. Serial sectioning of such a nodule (Fig. 5a–d) reveals that the surrounding fibrous bands are in fact a cross section of a complete scar, enveloping the entire nodular parenchyma like a membrane. The hepatic venules are segregated from the parenchyma by the scars, causing the rise of portal pressure. Triadal nodules often contain a cross-section of a triangular portal space (Fig. 6, PS), indicating thereby that the nodular parenchyma is the remnant of a complex acinus with fibrosis in $Z_3$.

The *paratriadal nodule* (Fig. 7) results from a grouping of nodules that may or may not be completely separated from each other, receiving blood supply from large triads now functioning as collaterals and situated in the scars of the nodular conglomerate (Fig. 7 and 8). Blood enters the nodules via a few remnants of sclerosing THA and TPV (Fig. 7, FTr), and by septal vessels (Fig. 7, SV) that penetrate the parenchyma to join the irregular sinusoidal network.

The paratriadal nodule evolves as the blood supply via the terminal triads, originating by a trichotomy of the preterminal branches of the hepatic artery (HA) and portal vein (PV), is progressively lost; thus the parenchyma forfeits its normal spatial organization. The straight route of blood flow from THA and TPV via the sinusoids is no longer the sole path. Most of the blood reaching the parenchyma arrives via the arterial plexus that is also associated with plexiform portal and hepatic venous branches, lymph vessels, and bile ducts within the $Z_3$ scar. There is no longer uniformity in the microcirculation of the nodules; inflow and outflow patterns change at various sites and levels. The parenchyma at the nodular periphery close to the supplying perinodular vascular plexus is well supplied and the hepatocytes look normal (Fig. 9a). In the center of the nodule, which at this plane of section represents the microcirculatory periphery, there is sinusoidal con-

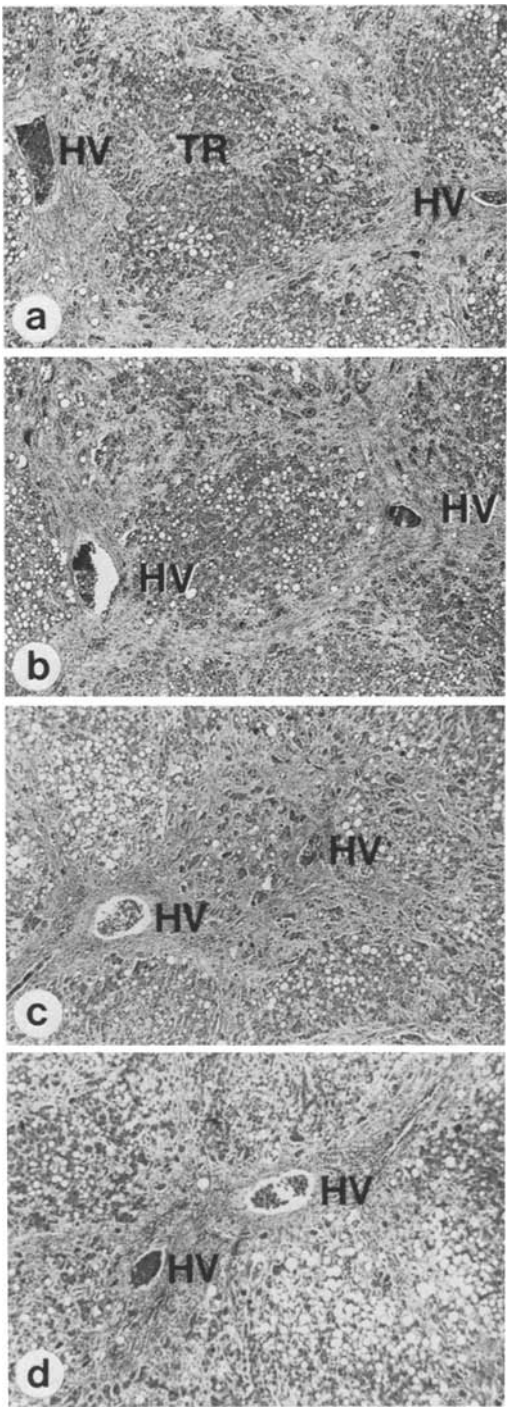
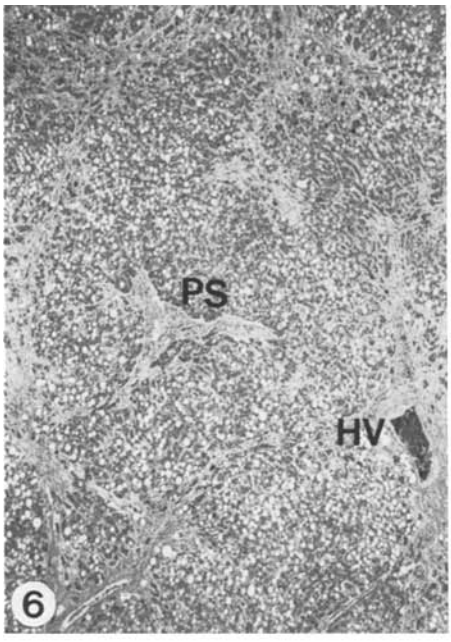
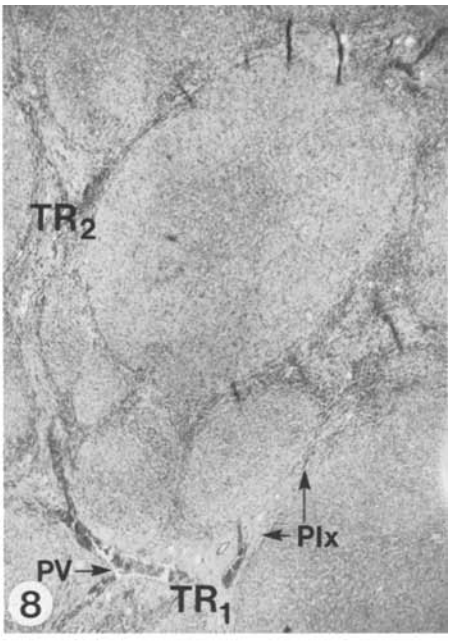



**Fig. 5a–d.** Serial sections through *triadal* nodule situated between two hepatic venules. **a** There is fibrosis around and inside the partially fatty nodule. *TR* = triad with fibrosis, *HV* = hepatic venule (× 68). **b** Step section 156 μ beyound the triad: the nodule is now smaller, the hepatic venules (*HV*) are close to each other (× 68). **c** Step section, 80 μ deeper than (**b**), reveals the bottom scar of the nodule; the venules are closer to each other (× 68). **d** In the section 24 μ deeper, the venules (*HV*) are connected by a fibrous band. Thus the triadal nodule was located in a V-shaped space between two *HV's* (× 68)



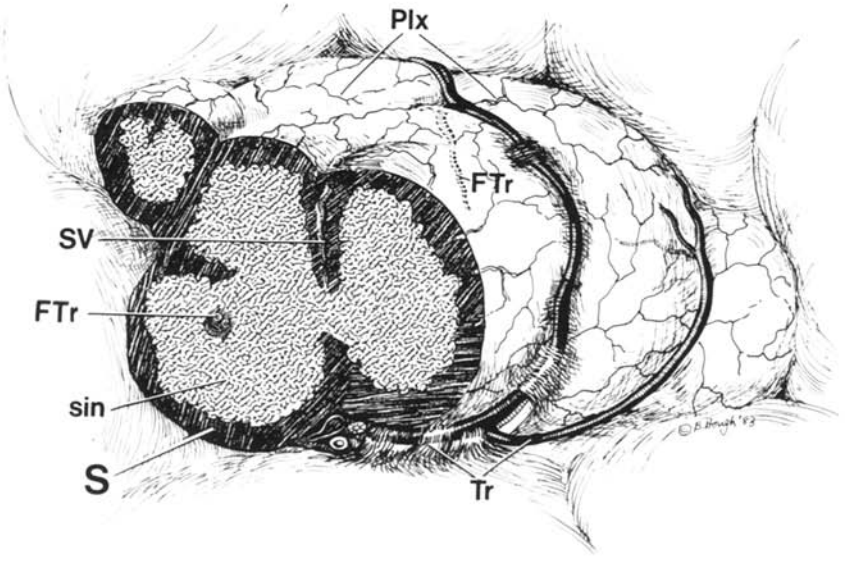




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**Fig. 6.** Nodule, remnant of complex acinus. The nodule has a three cornered shape and is outlined by a narrow scar; it contains a partially fibrosed triangular portal space from which terminal vessels branch out into the fatty acinar parenchyma. *PS* = portal space, *HV* = hepatic venule. (× 90)

**Fig. 7.** Diagram of para-triadal nodule. The entire conglomerate of nodules is englobed in a large scar containing a perinodular vascular and biliary plexus (*Plx*). The vascular plexus is fed by 1–2 large triads situated outside the nodule. Few triadal branches (*FTr*) still reach directly the sinusoids of some nodules. Other small vascular branches enter the conglomerate with the septa. *SV* = septal vessels, *Tr* = sclerosing triad, *S* = scar, *sin* = sinusoids

gestion and necrosis of the liver cells. Serial sectioning, however, reveals that at a deeper level the hepatocytes are well maintained around a vascular twig (Fig. 9b, c.Tw). The clumps of normal parenchyma around the tiny vessel are surrounded by widened sinusoids. This area of congestion extends toward the perinodular vascular plexus that also contains hepatic venules. Thus the assumption that the center of the nodule represents the microcirculatory periphery and the perinodular area corresponds to $Z_1$ should not be considered a rule. The scars may occupy partially or totally $Z_1$ and $Z_3$ and join similar scars to form an irregular and incomplete membranous meshwork. The nodular parenchyma within this meshwork represents degenerating or regenerating remnants of acini of various orders (Fig. 10). A section through such tissue displays nodules that are either completely surrounded by fibrous bands or show gaps in their circular scars because of internodular communication of the parenchyma (Fig. 11).

Nodules can also be formed by fibrous bands in $Z_1$ linking portal triads to each other, as for instance in biliary cirrhosis. These nodules resemble 'hexagonal lobules' and may contain one or more ThV's that are not fibrosed (Fig. 12). The width of the 'lobules' can vary from that of a simple acinus to that of a complex acinus, acinar agglomerate or group of agglomerates. Serial sectioning of such nodules reveals that the fibrous bands are cross-sections of dense connective tissue septa enveloping the nodular parenchyma. They extend to a depth of 1–2 mm and contain an arterioportal plexus, lymph vessels and fewer bile ducts than found in $Z_3$ scars. The membranes at the top or bottom of such a 'lobular' nodule are formed by the junction of several $Z_1$ septa (Fig. 13a, b).

Zone 1 septal scars can also become linked to $Z_3$ fibrous membranes, a process that leads to 'nodule-splitting' and generation of atriadal nodules. Figure 14 illustrates the process by which a triadal nodule, remnant of a simple acinus, becomes divided into two nodules having the supplying triad outside their parenchyma. A paratriadal group of nodules may contain small atriadal nodules supplied exclusively by their perinodular plexus; the majority of paratriadal nodules, however, still show small triads surrounded by fibrous tissue. The vascular twigs in the small triads may be branches of triadal vessels outside the nodule or of vessels entering the parenchyma with fibrous septa. Paratriadal nodules are the most common nodules seen in a liver with advanced cirrhosis.

### *Atriadal nodule*

The histological aspect of the atriadal nodule (Fig. 15a, b) is characterized by large fibrous scars surrounding small nodules that contain no afferent

**Fig. 8.** Human cirrhosis. The paratriadal nodule consists of a conglomerate of four nodules as shown in this plane of section. The nodule is flanked on the bottom by a large triad ($TR_1$), the branches of which feed the perinodular plexus. Some vascular branches enter the nodule via the septa. There is an indication of a second triad ($TR_2$) being present at the left upper portion of the conglomerate (×56). *Plx* = perinodular plexus, PV = portal vein branches

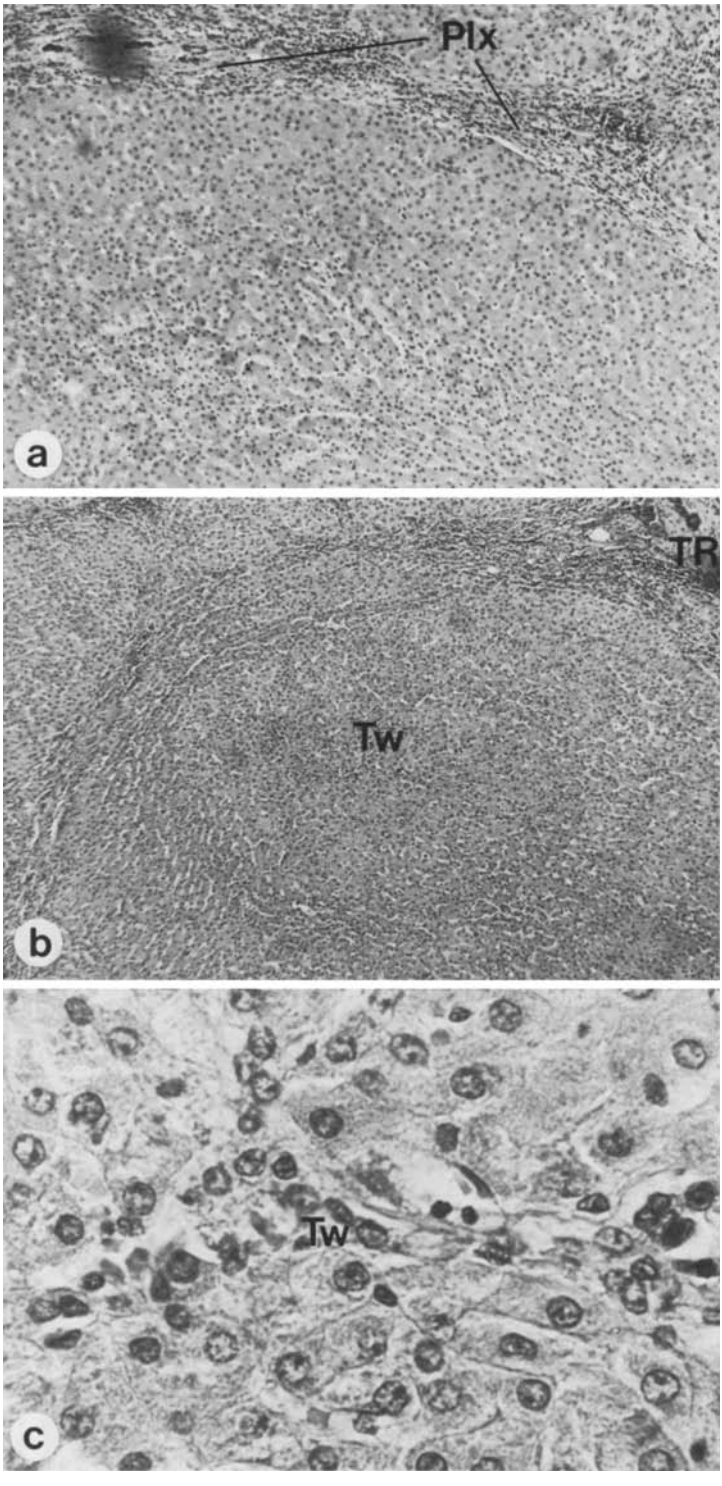



**Fig. 9a–c.** The microcirculation in the nodules changes at various sites and levels. **a** There is sinusoidal congestion and necrosis within the centre of a paratriadal nodule; the parenchyma in the nodular periphery close to the perinodular plexus (*Plx*), looks normal (×90). **b** Step section, 246 μ deeper than the congested and necrotic area. The parenchyma is well maintained around a vascular twig (Tw) in its centre that is surrounded by dilated sinusoids. *TR* = triad (×56). **c** The parenchyma around the vascular twig (*Tw*) shows, under higher magnification, normal hepatocytes (×1,013)

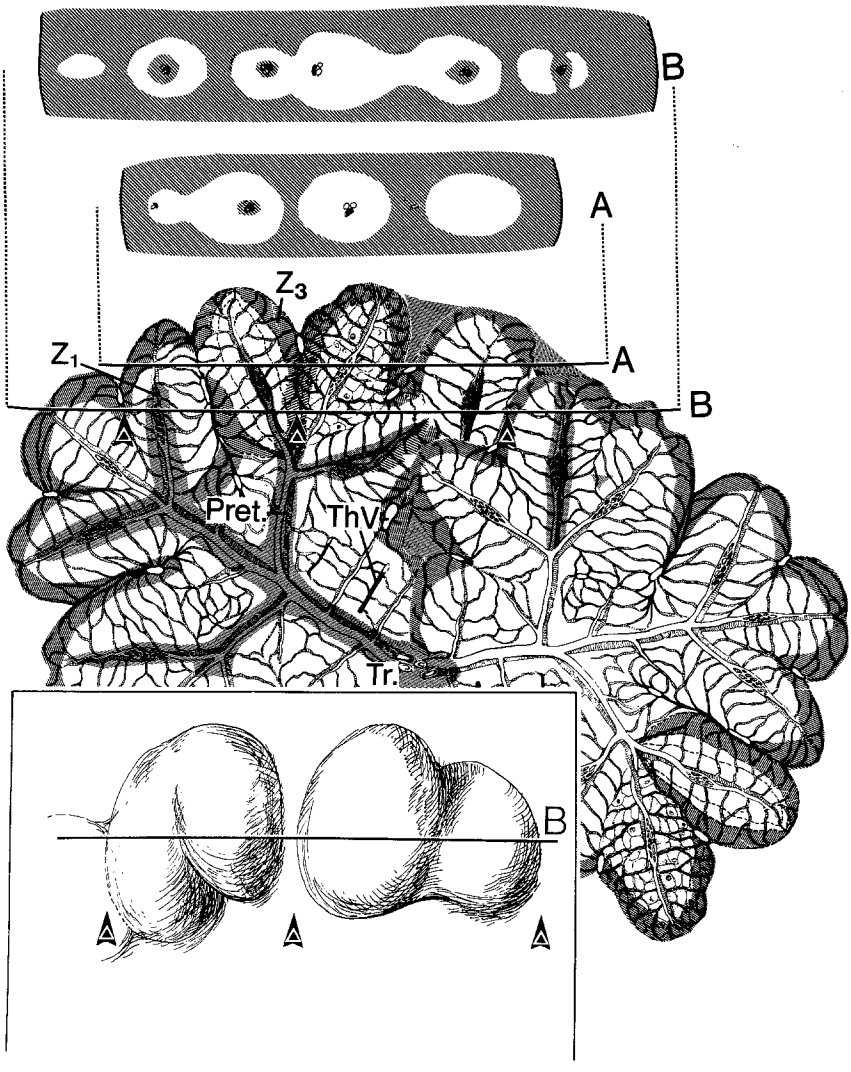



**Fig. 10.** Diagram of paratriadal nodules. Paratriadal nodules result from the maintained interconnection of parenchymal remnants of acini sclerosed at $Z_1$ and $Z_3$. The cross-hatched areas indicate fibrosed zonal portions of the structural and microcirculatory hepatic units. Cross-sections at a superficial (*A*) and a deeper (*B*) level of the same scarred acini show nodules of different size and shape. The tridimensional aspect of the nodules situated between the arrows is shown in the lower inset. $Z_1$ = Zone *1*, $Z_3$ = Zone *3* (microcirculatory periphery), *Pret* = preterminal arterial and portal branches, Tr = Triad feeding acinar agglomerates, *ThV* = terminal hepatic venule

or efferent vascular branches. Also, there are no small or medium sized triads close to the nodules. The scar tissue, though appearing avascular under low magnification displays plexiform thin-walled vessels mainly of large capillary size (30–35 μ in width) under high magnification. Serial sectioning of the atriadal nodules (Fig. 16a–c) demonstrates that each of them

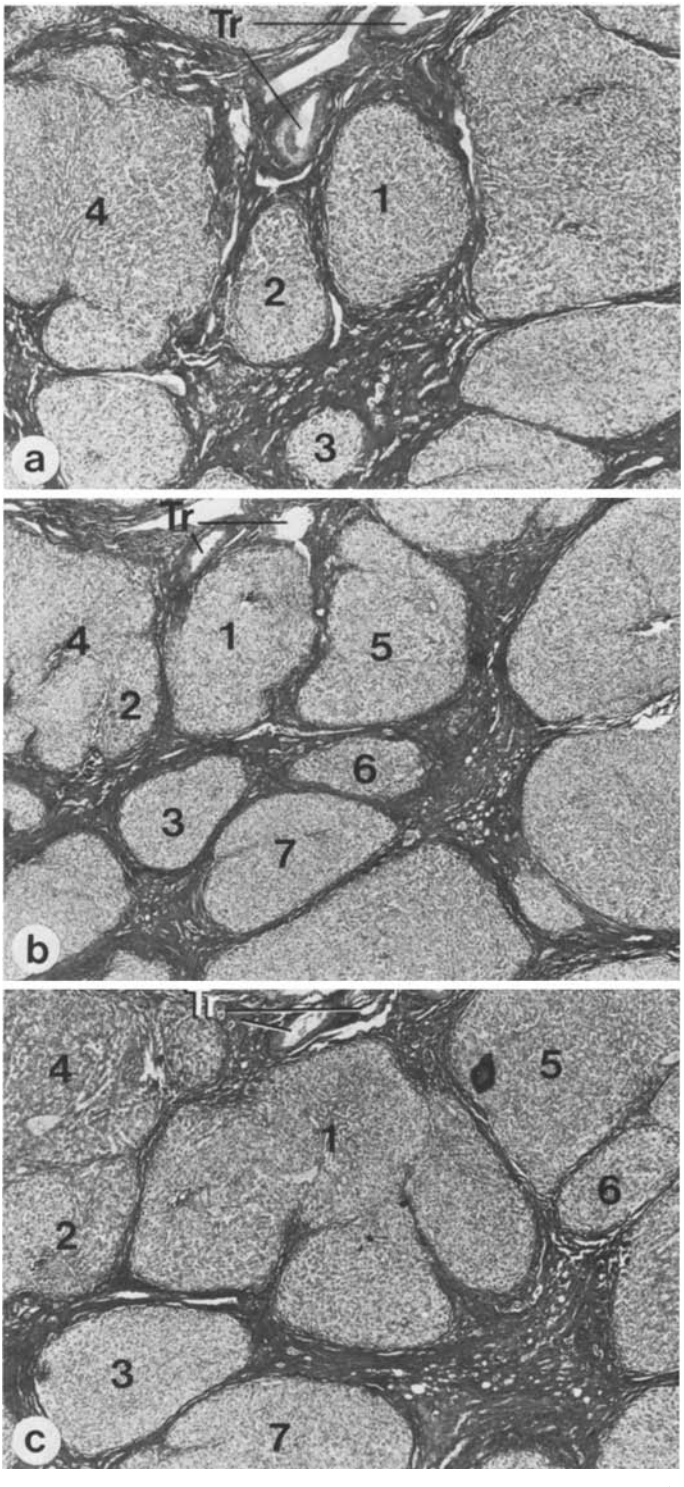
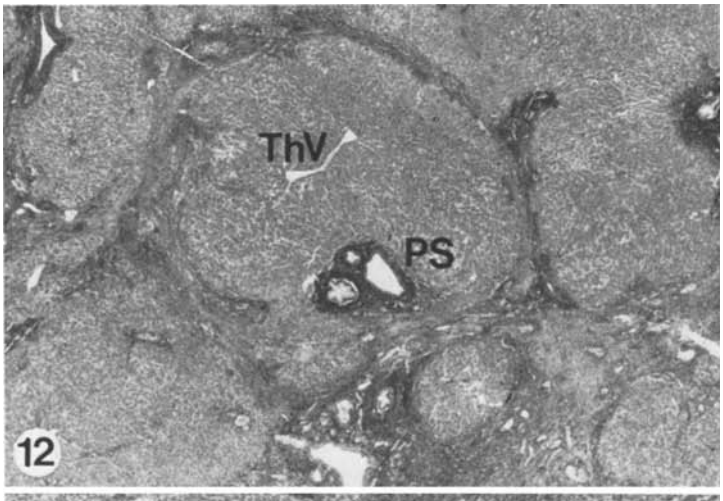
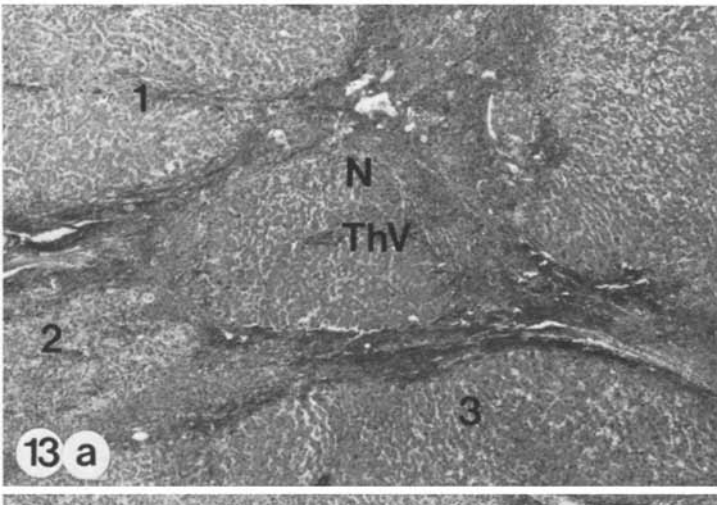



**Fig. 11a–c.** Incomplete septa in a paratriadal nodule allow the nodules to merge. **a** Three nodules (*1, 2, 3*) are surrounded by a heavy scar that in its upper portion is flanked by a large triad (x14). *Tr* = triad. **b** Sixty micra further the septum of nodule *2* has become incomplete and the nodule merges with an adjacent paratriadal nodule (*4*). Three nodules (*5, 6, 7*) have appeared in the heavy scar ( × 14). **c** At a section 84 μ further from (**b**), nodule (*1*) that was completely surrounded by a heavy scar is now part of the remnant of a complex acinus *Tr* = triad ( × 14)



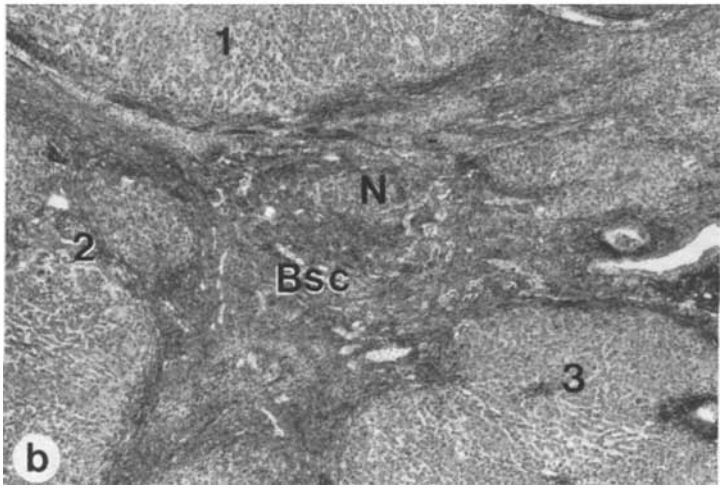




**Fig. 12.** Biliary cirrhosis. The nodule is delimited by fibrous membranes in Zone *1*. The terminal hepatic venule (*ThV*) and Zone *3* around it are not scarred. *PS*=portal space. (×90)

**Fig. 13a, b. a** Bottom of nodule surrounded by wide $Z_1$ scars, *N*=nodular parenchyma, *ThV*=sclerosing venular branch, *1, 2, 3*=surrounding nodules (×90). **b** Section 12 μ deeper; there are only a few hepatocytes left in the bottom scar of a nodule. *Bsc*=bottom scar of sectioned nodule (*N*) (×142)

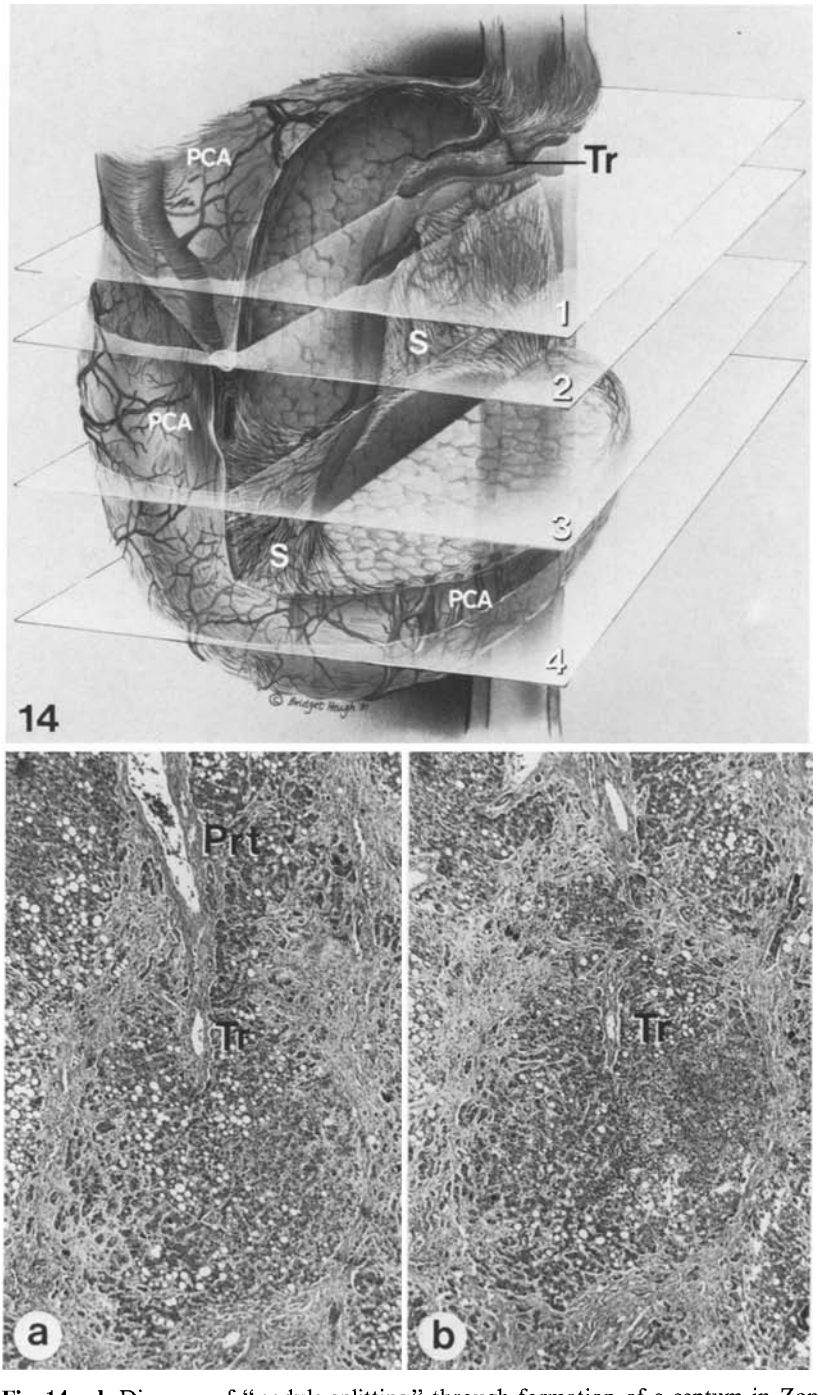



**Fig. 14a–d.** Diagram of "nodule-splitting" through formation of a septum in Zone 1 of the acinar remnant. The drawing is reconstructed from 4 planes of section of a triadal nodule. *S*=septum, *PCA*=portacaval anastomsis, *Tr*=Triad. **a** *Plane 1* shows the branches in the nodular triad (*Tr*) arriving from a preterminal triad (*Prt*); both triads are surrounded by fibrous tissue (×81). **b** *Plane 2* a step section 60 μ deeper: the terminal triad (*Tr*) is in an incomplete septum within the nodule ×81). **c** *Plane 3*, a step section 150 μ deeper than plane 2. The septum (*S*) containing the triad almost completely divides the nodule in two halves; it joins the perinodular scar (*Sc*). *Tr*=triad (×81). **d** *Plane 4*, a step section 120 μ deeper than plane *3*, shows the fibrosing triad in an incomplete septum that joins the perinodular scar (*Sc*) at the periphery of the nodule. The incomplete septum is in *Zone 1* of a simple acinus with fully scarred *Zone 3* and Triad (*Tr*) (×81)

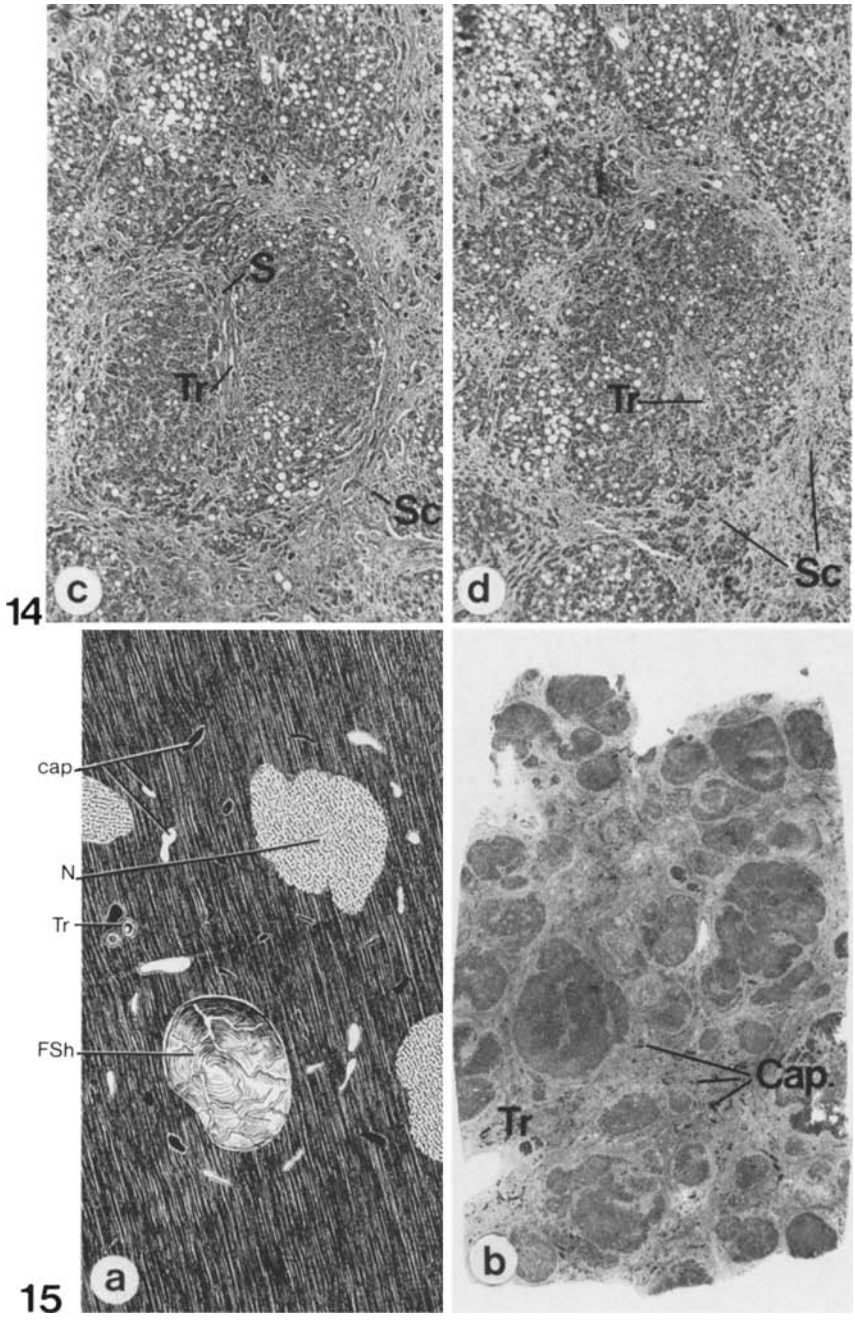



**Fig. 15. a** Diagram of atriadal nodules in a large dense scar. *N* = nodule, *Tr* = triad, *Cap* = capillaries, *Fsh* = fibrous shell and perinodular capillary plexus. **b** Atriadal nodules, view of entire slide, *Tr* = triad, *Cap* = some of the large capillaries within the scar ( × 4.5)

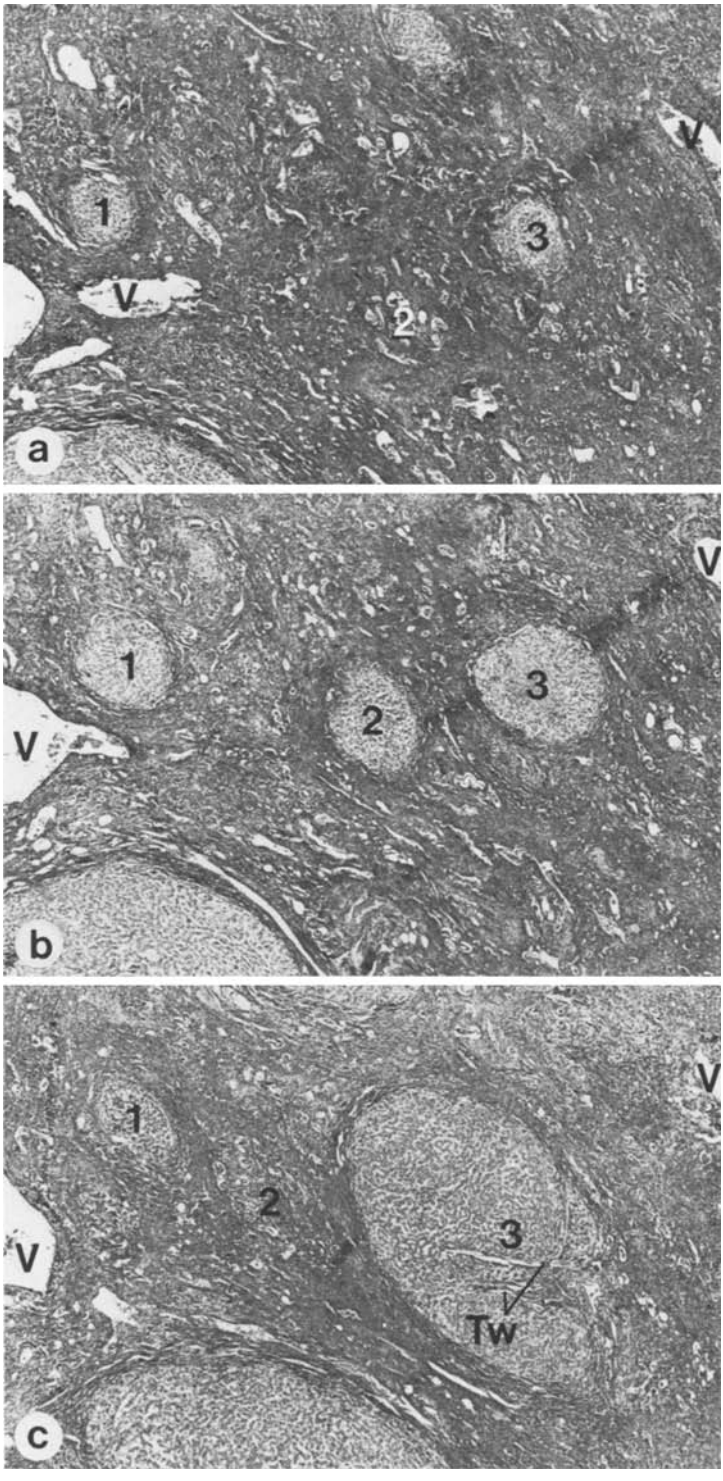



**Fig. 16a–c.** Three nodules without triads in a heavy scar. **a** Nodules *1* and *3* were not visible at a step section 24 μ above this plane; nodule 2 is barely visible. Note the orienting points: the vascular lumina (*V*) right and left (×11). **b** Nodules *1, 2, 3* are of larger size at a plane of section 12 μ deeper than above (×11). **c** Triadal nodules *1* and *2* are disappearing at the step section 24 μ deeper than above. *Nodule 3,* still increasing in size, shows small vascular twigs (*Tw*) in its parenchyma (×11)

is totally encased in a thick fibrous shell. The hepatocytes are packed tightly and the sinusoids are barely visible. There are no parenchymal interconnections between the nodules. Rarely one encounters an isolated large triad in the midst of a broad scar. A cirrhotic liver displaying exclusively atriadal nodules is rarely seen, even at autopsy, as most patients have succumbed during the stage of paratriadal nodularity.

*Scars*

Scars of various shapes and orientation are present in the cirrhotic liver. They range from the smallest accumulation of collagen fibres arranged concentrically around the vessels in zone 1 and/or zone 3 of SA to large scars enveloping SA and acinar structures of higher order. Scars in $Z_1$ contain inflammatory infiltrates more often than those in $Z_3$. The shape of the scars, perivenular, triangular, starfish, periacinar and large patch, are illustrated in Fig. 2a. The tridimensional study of the scars demonstrates their membranous nature, i.e. they envelop the parenchymal clumps, the remnants of acini that have undergone zonal damage. Scars may act as septa that separate the acinar units partially or completely (Fig. 10). When one step-sections a nodule in its entirety one may first meet a horizontal fibrous patch in which, after further sectioning, a small group of cells will appear. These cells represent the upper (or lower) tip of the nodule (Fig. 16). In the following step-sections the scar may now appear as a circular band; it gradually widens at the expense of the parenchyma in its center to again become a fibrous patch at the other pole of the sectioned nodule. The thickness of the scars can be as great as 200–300 μ, and averages 180 μ. The scar tissue pervades the liver in a manner similar to that seen in multiloculated cysts; the parenchymal nodules rest within the cavities of the scar (Fig. 15a, FSh). This meshwork of fibrous membranes carries a rich arterial, portal, hepatic venous, lymphatic and bile ductal network that supplies, drains or may bypass the acinar remnants of the parenchyma. The lymph vessels in the scars form a plexiform network that at some level communicates with the hepatic vein branches and with veins outside the liver. There is further the connection of lymphatic plexuses with similar periportal and subcapsular networks (Fig. 17) permitting the plasma fluid of the impeded hepatic microcirculation to be drained into the abdominal cavity (ascites).

Reliable light microscopic evidence of the connection between the septal afferent and efferent vessels of the perinodular plexus and the inlets and outlets of the sinusoids in the nodules is rarely seen. It is to be hoped that electron microscopic studies will demonstrate structural continuity and fill this gap in our understanding of how supply and drainage of the nodular parenchyma across the scars are brought about by the plexuses. The morphologic complexity of the perinodular plexuses can best be seen in the horizontal scar patches covering the top or bottom of nodules. The biggest horizontal patches are in the vicinity of large triads. These patches are often considered as signs of a healed massive loss of parenchyma and tissue collapse. However, they are of the same thickness as other scars enveloping

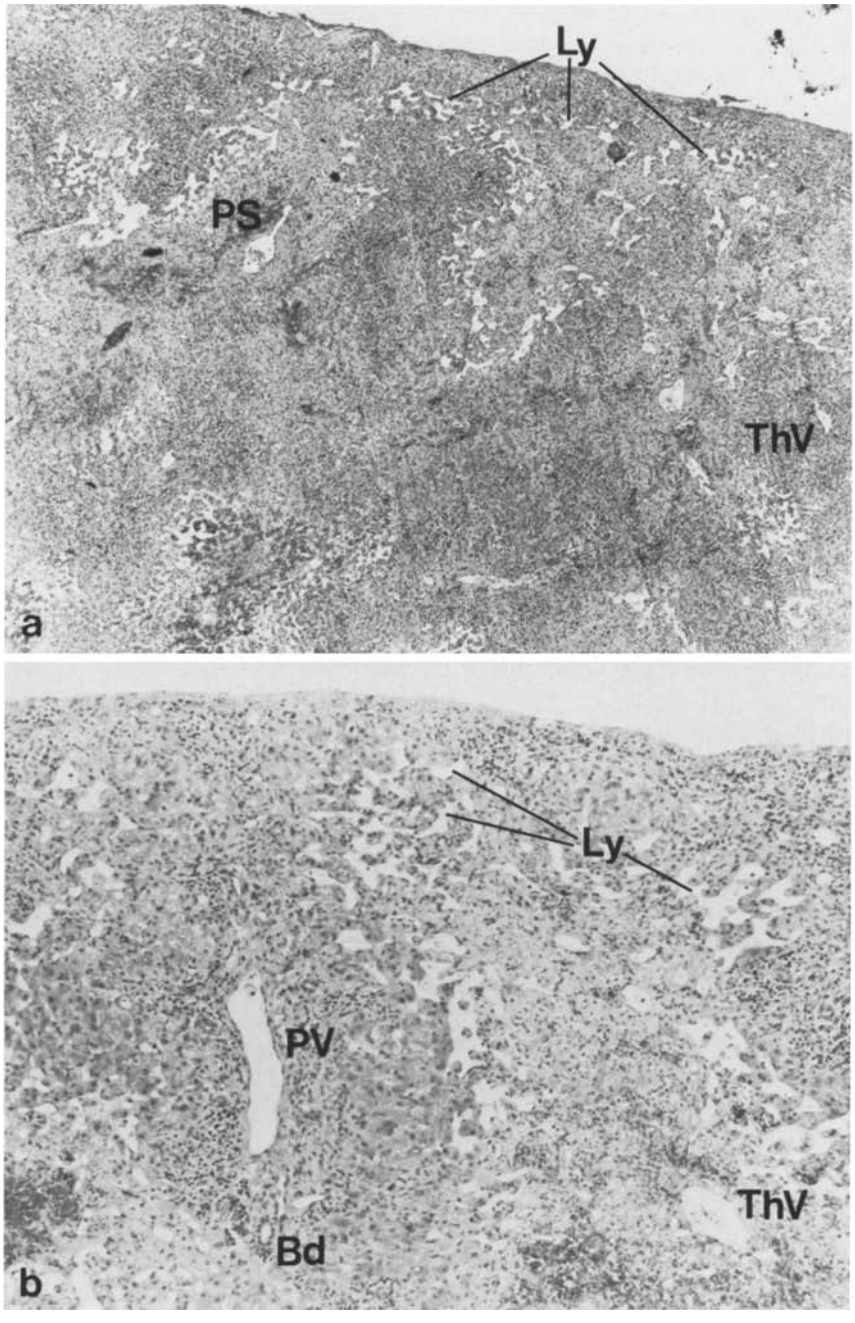



**Fig. 17. a** Dilated lymphatic network linking periportal, perivenous and subcapsular lymphatic clefts (*Ly*) in liver of patient with Budd Chiari syndrome. *PS* = portal space, *ThV* = hepatic venule ( × 37). **b** Periportal and perivenular areas are shown under higher magnification. Triad with portal venule (*PV*) and small bile duct (*Bd*), *Ly* = lymphatic clefts, *ThV* = Terminal hepatic venule. ( × 110)

the nodules. Serial sections of such scars demonstrate their close relationship to nodules either above or below.

*Vascular factors*

Important vascular changes in flow and topography affecting the terminal and preterminal portal veins, hepatic arteries and hepatic venules take place during the process of removal of the necrotic tissue and its replacement by scars. In acute injury granulation tissue originating from the connective tissue in the portal spaces and from scant similar tissue around the terminal hepatic venules is active in the removal of the necrotic material by scavengers and in the laying down of collagen by the fibroblasts. In chronic injury, such as in alcoholic liver disease, collagen can be produced by other cell types. The arterioles, their capillaries and the PV's are essential for repair of liver injury. Arteriolar and capillary budding begins in zone 1, together with sprouting of the bile ductules, because the arterioles of the peri-ductal plexus are part and parcel of the ductal wall (Rappaport 1982). Collagen formation around the ThV, i.e. the peri-venular portion of $Z_3$, may precede or parallel that in the PS. The latter become replete with inflammatory cells that have migrated from arterial capillaries and portal venules. A fibrous web with sprouting capillaries is woven from the triangular PS and from around the hepatic venules (HV). Arterioles and proliferating bile ductules from $Z_1$ invade the necrotic areas in and around parenchymal remnants of the acini; they enmesh the TPV and the ThV's with fibrous septa. The septa grow into membranes that envelop the acinar remnants. The vascular net in these fibrovascular membranes (Fig. 18) includes the normal arteriolar-portal connections and sinusoidal pathways that have been transformed by neoangiogenesis (Moschcowitz 1948; MacDonald 1952) into collaterals that bypass the collagenous dams (Rappaport 1976). The latter have been erected around the ThV as perivenular sclerosis, and elsewhere in $Z_3$. The effects of hemodynamic laws governing collateral circulation (Learmonth 1950) are evident here and are illustrated in Fig. 19. The raised portal pressure, as measured by a balloon catheter wedged in a macroscopic hepatic venous branch, is around 20 mm Hg while the free pressure in the perinodular hepatic venous branches fluctuates with respirations around 2 mm Hg. It is obvious that the pressure gradient from the portal and arterial stream is steeper toward the perinodular venules than towards the sinusoids (see Fig. 19). The formation of intrahepatic portohepatic, arterioportal, and HA to HV shunts is therefore a common finding. The flow in each of the immense number of collateral rivulets (Fig. 18), when added up, results in a stream that bypasses the TPV's and the THA's and 'steals' blood from these channels (Fig. 18, inset). Vessels completely deprived of flow collapse and become obliterated (Thoma 1920). The myocytes of the media of vessels with diminished blood flow may undergo degenerative changes that lead to obliterative angiopathy as has been observed in the stroma of cirrhotic liver (Straubesand and Riede 1979). Sometimes the vessels may thrombose and become occluded with or without

an attempt at recanalization. This is followed either by death of the nodular parenchyma or by complete transfer of the vascular supply of the nodule to the perinodular plexus. Such events establish the dominant supply of the nodules via the triads and the angiomatous vessels within the perinodular scar (Fig. 18). These perinodular vessels are best demonstrated in a scanning electromicrograph of their microdissected cast (Fig. 20a, b).

## Discussion

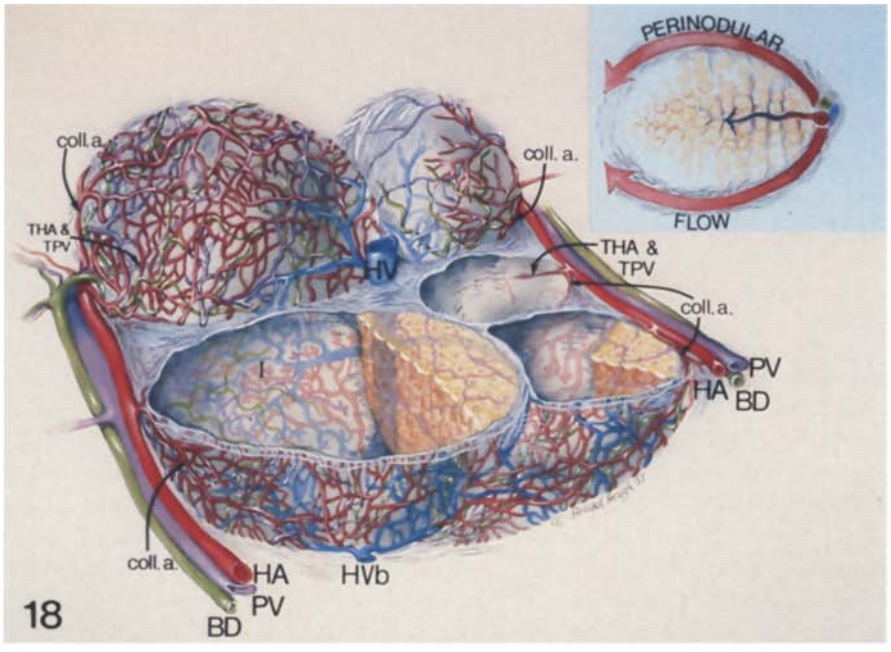
From a morphologic viewpoint it appears that the size and shape of the nodules are determined by the configuration of the scars. Nodules, however, are remnants of acini of various orders that had their zonal damage replaced by scar tissue. There are many combinations of zonal patterns possible that will yield a variety of nodular sizes and shapes in the cirrhotic liver (Fig. 10). However, neither size nor shape of the nodules determines the survival of the parenchyma in a scarred liver. As with any other tissue, survival depends on adequate microcirculatory supply and drainage.

In cirrhosis the principle of parenchymal organization around the *terminal* arterial and portal branches is no longer completely valid. In the triadal, paratriadal and atriadal nodules one observes a gradual shift from exclusive supply by the terminal trichotomy of the supplying vessels and their interdigitation with the ThV's, to a collateral circulation.

The nodules have been classified here according to the changes in their microcirculation. The triadal, and to a lesser degree the paratriadal nodules, are still attached to trichotomizing branches of the afferent vascular tree. The parenchymal berries continue to hang on the same branches of the portal and arterial tree. They receive part of their blood, in spite of the ongoing pathological tissue changes, through the same route as before. The nodules have a terminal or preterminal triad from which blood flows into the sinusoids, and bile is collected from the canals of Hering (1866). But the outflow of blood from the sinusoids into the ThV's is hampered by sclerosing and fibrosing perivenular barriers. Thus the nodules, so called "pseudo-lobules" that have formed, maintain a spatial continuity that ensures synchronized metabolic function of some vascular areas. These fibrous septa in $Z_3$ of the triadal nodules render the acinar structures conspicuous,

**Fig. 18.** The scars surrounding the nodules are fibro-vascular membranes. They contain angiomatous networks. These collateral pathways develop because the portal and arterial end branches normally distributed in trichotomy become fibrosed and obliterated (*see inset*). *HA* = hepatic arterial branch, *PV* = portal branch, *BD* = bile duct branch, *HVb* = hepatic venous branches, *THA* and *TPV* = fibrosing terminal arterial & portal branches, *Coll a* = collateral arterial branches

**Fig. 19.** The pressure gradient between afferent and efferent vessels is much steeper in the perinodular plexus than in the sinusoidal path. *HA* = hepatic artery, *PV* = portal venule. Note in the squared areas the junction of *HA*, *PV* and *HV* branches, the porto-caval and arterio-hepatic venous anastomoses; the portal branch in the arterio-portal shunt empties into the hepatic venule


PERINODULAR
FLOW
coll. a.
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THA & TPV
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HVb
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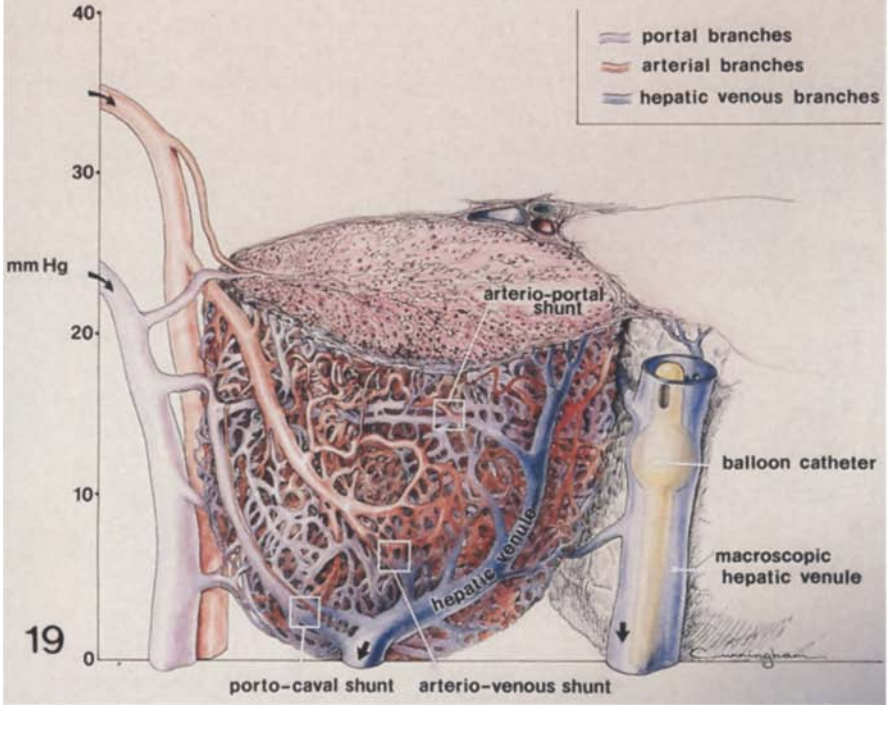
40
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portal branches
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balloon catheter
macroscopic hepatic venule
hepatic venule
porto-caval shunt
arterio-venous shunt
19

demonstrating that it is hard to maintain the "hexagonal lobule" as a model for functionally oriented hepatic tissue. It is interesting to note that the average values of *l*ength (1,430 μm), *w*idth (935 μm) and *th*ickness (676 μm) of the parenchyma in the micronodules containing a portal triad are only slightly smaller than those of the normal simple acini (*l*:1,480 μm, *w*:1,070 μm, *th*:797 μm). As to the size of nodules that histologically are commonly considered as "macronodules", out of 88 such microscopic nodules measured, only 3 had one dimension greater than 3 mm. This again proves that classifying nodules according to their size is a fallacy. Macronodules that still have a triangular triad in their center contain the surviving parenchymal remnant of a CA. It has been explained that the development of collateral arterial and portal routes, bypassing the barriers to the outflow of blood from the sinusoids, follows the steepness of the pressure gradient (see Fig. 19). After a period of interregnum, while blood is flowing into the sinusoids via the triad *and* through the collateral perinodular plexus, the normal microvascular framework of the acini becomes gradually obsolete. It is difficult to imagine how, during the period of transition, two streams opposing each other still manage to distribute their blood into the sinusoids unless some alternating distribution occurs. However, the progress in perivenular scarring and the 'steal' of portal and arterial blood from the TPV and THA by the collateral arterial networks (see Fig. 18, inset) and the intrahepatic portocaval shunts seal the fate of the intranodular triad. Along with the increased arterial supply via the perinodular arterioles there is the formation of a new unit, the nodule. It is built of tightly packed double cell plates, yielding the so-called 'regenerating nodule', in which the sinusoids can barely be distinguished. Their width is hard to judge with ×10 objective lens but their average length (651 μm) represents the diameter of small round nodules and equals almost twice the average radial length of a sinusoid (332 μm) in a normal acinus. These dimensional data bring additional proof of the evolution of 'micronodules' from SA.

'Macronodules' without a triad are very rarely noted in the stepwise sections of a tissue block. Sooner or later vascular branches are seen within the nodules. Frequently in deeper sections of the *apparently* atriadal 'macronodule' there is sometimes a partially scarred triangular PS sending 1 or 2 terminal branches into different parts of the nodule. Such a nodule hardly bears a resemblance to a CA; however, in deeper sections one uncovers the ruins of its initial architecture. The cirrhotic liver composed of such 'macronodules' is in a precarious position as the collateral flow is still insufficiently developed to assure survival and function of regenerating cells. When new and old routes of supply and drainage have to be used concomitantly the unfortunate microcirculatory disorder persists.

Nodules are surely metabolically active and one wonders whether zones of functional heterogeneity (Rappaport 1973) are detectable. It is obvious that in the nodule without a triad all blood is delivered by the perinodular plexus, therefore the rows of cells adjacent to the scar would correspond to $Z_1$. Indeed, the iron (Grace and Powell 1974), copper (Hunt et al. 1963), alpha-1-antitrypsin granules (Clausen 1980) and fat transported from the

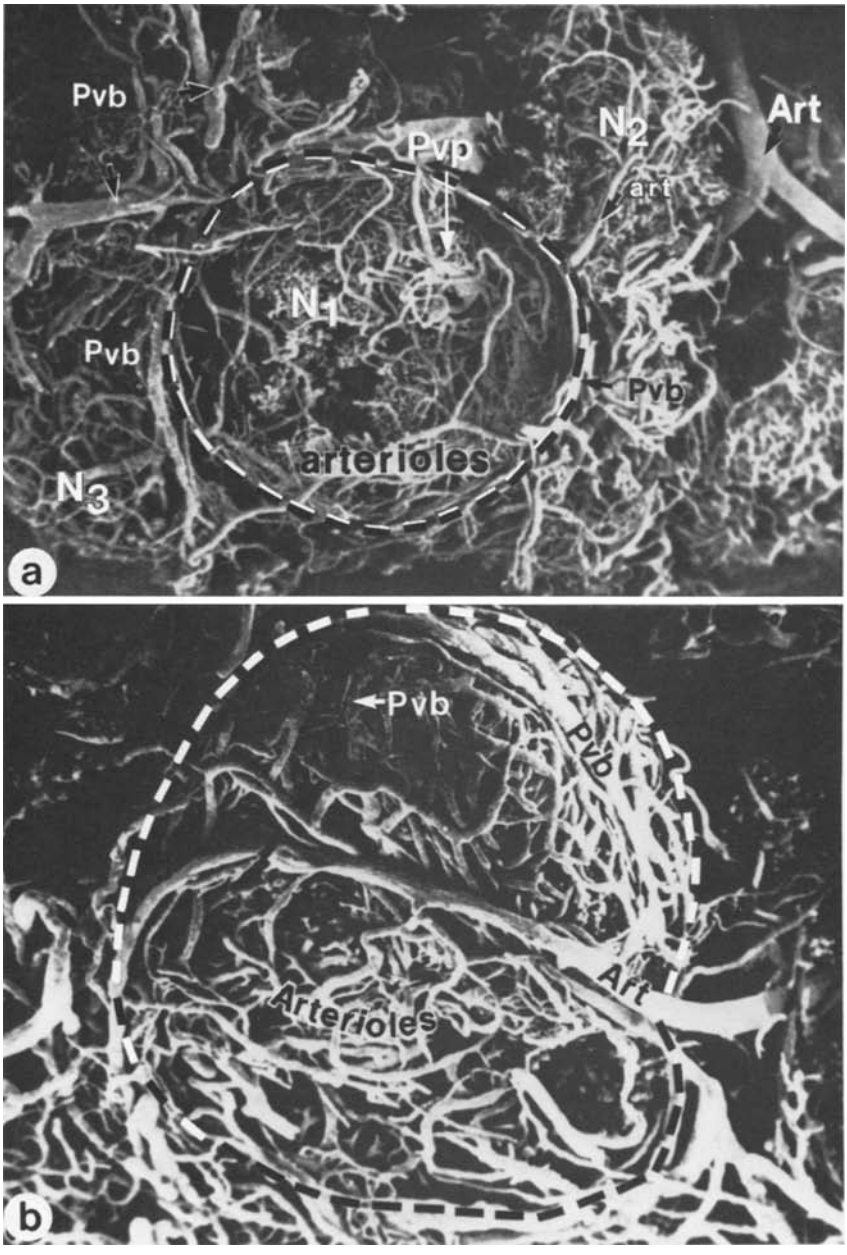


**Fig. 20a, b.** Scanning electron micrograph of perinodular plexuses in a cirrhotic liver (methylmetacrylate cast). **a** The dense thickets of microdissected arteriolar and portal venules surrounding three nodules ($N_1$, $N_2$ and $N_3$) are shown; they are part of the perinodular fibrovascular membranes. Art = collateral arterial branches, art = arterioles, Pvp = portal venous plexus, Pvb = collateral portal venous branches. Broken line outlines nodule $N_1$ (×32). **b** An arterial branch curves around a nodule (outlined by a broken line) and supplies the arterioles of the arteriolar plexus located in the perinodular scar. *Pvb* = collateral portal branches, *Art* = collateral arterial branch. (×81) (courtesy Dr. K. Yamamoto, Yokahama University)

fat depots (Rappaport 1960 and 1963) are mostly found near the scar. Nuber et al. (1980), in their study of metabolic zonation in thio-acetamide induced liver cirrhosis, found that in nodules containing a portal triad the heterogeneity of liver functions is preserved. They noted that the cells close to the portal field have high glycogen content as well as high G-6P-ase and phosphorylase, and show moderate SDH activities, while the cells at the nodular margin, close to the scars, exhibit very active SDH and elevated G-6PDH activity. The latter is interpreted here as the key enzyme at the beginning of the pentose-phosphate shunt where not only NADPH but also pentoses are produced. These pentoses are prerequisites for nucleic acid synthesis, important for the regenerating areas of the cirrhotic nodule. Shikata and coworkers (Uchida et al. 1981) found G-6P-ase activity irregularly distributed in the nodule while gamma-glutamyl transpeptidase activity was high only in the perinodular fibrous strands of the human cirrhotic liver.

The location of $Z_3$ in triadal nodules without ThV's inside them differs from nodule to nodule depending on the haphazard location of the hepatic venules near or within the perinodular plexus. Unfortunately there are too few histochemical studies enabling us to map out the pattern of enzymic activities within cirrhotic nodules. One is amazed at the neglect of this field though *fresh* hepatic tissue is available in the hundreds of liver biopsies done daily.

The tridimensional study of stepwise sectioned cirrhotic tissue provided evidence that the many nodular variations in size, shape, topography and microcirculation are explainable as pathological deviations from the normal architecture and microcirculation of the hepatic structural and functional units – the acini.

*Scar formation* is usually considered as the main culprit of liver dysfunction and failure. In recent years much effort has been made to understand the biochemistry of scar tissue (Rojkind et al. 1979) in order to prevent early fibroplasia or to reduce the fiber mass in the already scarred liver. From our observations we have to conclude that the scars are also the road builders for the collateral circulation. No vessel runs freely in the liver; they are all sheathed by connective or fibrous tissue. It is difficult to imagine how substantial necrotic areas could have been cleared of dead material without the activity of the granulation tissue. Besides depositing fibroblasts, it also prepares the way for the circulatory bypass of obstacles since the arterioles and arterial capillaries continue to bud within the granulation tissue to be transformed into the collateral vascular network (Jennings and Florey 1970). Thus septa, i.e. "divisions", are scars actually *joining* the areas where there is good afferent flow to those where blood flow is diminished. At the same time venules in the scars take care of the egress of blood from the nodules into the efferent vascular system. Consequently, scars are living membranes consisting to a great degree of channels (mainly arterial branches, arterioles and bile ductules) that are not compressed either by the fibrous tissue or by the expanding regenerating nodules (Caulet et al. 1964). Liver scars if ever observed in vivo may show strong pulsations.

In the scars one has difficulty in discerning a portal from a hepatic venule. The rule to look for a triad, i.e. for the association of PV, HA and Bd, does not hold, especially at the crossroads or at the dovetailing of fibrous bands forming a large scar. An arterial branch can be situated near two venous branches, both seemingly not in a triad. However, this does not exclude the diagnosis of 'triad' as the division of a PV branch may be cross-sectioned, all this occurring in the proximity of a Bd. A false impression of a triad can be created when a *hepatic venule* lies close to arterial branches and proliferating Bd's, since it is difficult to distinguish in the plexus an HV from a PV.

We are still lacking understanding of bilio-vascular relationships (Murakami et al. 1974) in the scar; the topography of the bile ductules is jumbled to our eyes. Investigations of microcasts of the biliary ductules (Itoshima et al. 1978) and pseudo-ductules in the scars with scanning E/M might bring more understanding of their structural and functional roles.

In conclusion, it is time to free ourselves of the pejorative ideas one forms when talking about the liver scars. More research on the biology of these *fibrovascular membranes* is necessary to find the *benefits* which the hepatic parenchyma may derive from them.

*Vascular Factor*

The primary importance of the obstruction of intrahepatic blood flow in cirrhosis has been considered by Connor (1939) and by R. MacDonald (1962). Today the vascular factor in cirrhosis is commonly discussed as the clinical syndrome of portal hypertension with all its repercussions, among them the increased cardiac output. Though hepatic blood flow may thereby be increased, the blood bypasses the nodular parenchyma and may not improve liver function.

Changes in the intrahepatic circulatory and microcirculatory pathways have a leading role in establishing the morphological abnormalities occurring in cirrhosis; this thesis is supported by our observations of step sections of tissue taken from several types of cirrhotic livers. Basically the rules of collateral circulation (Learmonth 1950) are valid in all forms of this disease. The development of collaterals evolves *gradually* in cirrhosis, because the obstruction of the terminal afferent branches occurs slowly. The collaterals can keep pace with the needs of surviving parenchyma provided the flow in them is adequate. Collateral flow ($F$) is determined by the formula $\frac{P_1 - P_2 \cdot r^4}{L} = F$ where $P_1$ and $P_2$ are the pressures at the arterial and venous ends of the capillaries respectively, $r$ the radius and $L$ the length of the collaterals. For good collateral flow adequate blood pressure (Derrick 1962) and a fair pressure gradient are essential. Good pressure is provided by an increased cardiac output due to the many vascular fistulae (HA → PV, HA → HV, PV → HV) present in the perinodular plexuses. Anastomoses between afferent and efferent vessels, at the level of terminal portal branches or arterioles, yield a steep pressure gradient. Flow is further enhanced if

the radius ($r$) of these collaterals is greater than the diameter of capillaries. However, $L$, the length of the circuitous collaterals, is in general much greater than that of the straight sinusoidal route and this would tend to diminish collateral flow ($F$). The velocity of flow is determined by the cross-sectional area of the vasculature. Normally the total arteriolar cross-sectional area is $25\times$ that of the arterial branches; velocity of flow is thus sufficiently decreased to allow metabolic exchange with the tissues. In the dense network of the perinodular plexus (see Fig. 20) the cross-sectional area is very wide and this will diminish the high velocity generated by the steep pressure gradient present in the A–V fistulae. Thus one may expect that the decreased velocity of the meandering collateral flow will facilitate the exchange of nutrients with the nodular parenchyma.

Morphogenesis in the various forms of cirrhosis differs according to the primary locus of the injury. The response to injury in $Z_1$, such as that associated with infections spread by the blood stream or lymphatics or with bile duct damage, is different than that response to injury which occurs in $Z_3$. In $Z_1$ damage the scarring will primarily be of the 'portal' type as the PS with its connective tissue is prone to immuno-reactions, acute and chronic inflammations. Therefore it is to be expected that the arteriolar – TPV junctions will lose their fine tuning role in regulating the acinar microcirculation (Rappaport 1973) and that the adjacent structures (bile ductules, lymphatics) will also become affected. Afferent *collateral* circulatory pathways must necessarily develop when inlet venules into the sinusoids become narrowed or obliterated. From the portal spaces the inflammation can invade the acinar parenchyma along $Z_1$ and include $Z_2$. On the other hand, $Z_3$ may be rendered partially ischemic because of the fibrosis around the terminal afferent vessels; ischemic injury can thus extend towards the ThV and be replaced by scars with newly developing collateral routes that may form intrahepatic portocaval anastomoses. Arterial branches situated proximal to the site of injury are the main site of origin of such collaterals (see Fig. 18).

The relationship between abnormal microcirculation and fibrosis deserves some comments. It has been established that fibroplasia requires the presence of rough surfaces, basement membranes and capillaries (Popper and Orr 1970), of fibroblasts or some other cells [Itolipocytes (Ito and Nemoto 1952), myofibroblasts] capable of forming connective tissue fibers. Such cells are present close to the site of parenchymal injury that causes rough surfaces (Popper and Udenfriend 1970). It is an even older finding that fibroblasts originate in loose connective tissue around the blood vessels; it is further known that blind ending capillaries sprout from arterioles and form granulations that, besides their mantle of macrophages and other cells, *contain fibroblasts*. All these elements are found along the microcirculatory pathways, which are in contact with each liver cell. Finally, the presence of the myofibroblasts in hepatic scars (Rudolph et al. 1979) is an indication of their derivation from the granulation tissue that brought them into the fibrous bands.

Arterioles and capillaries can be found in fibrous tissue up to its finest ramifications. It is difficult to discern in a fully matured scar whether the capillaries have been instrumental in depositing fibroblasts or whether the capillaries have invaded the young scars formed by fibroplasia. This question can only be answered experimentally. It is beyond doubt that scar and microvessels are densely interwoven, and this has been best illustrated by scanning E/M pictures of the microvascular casts (see Fig. 20). Thus the process of *fibrous repair is the road builder for collateral flow*. The microvessels sprouting with scar formation originate from those intrahepatic vascular branches that still have good flow and even raised pressure. The microvessels in the scars together with the scar tissue bypass the obstructed normal route, i.e. terminal afferent vessels → sinusoids → ThV. As flow increases in the microvessels they enlarge and become the tortuous channels of the perinodular plexus. Angioma-like tortuosity is the hallmark of collateral vasculature. However, in the plexus, *afferent and efferent* vessels *are not separated by parenchyma;* they are intermingled. Any change of the pressure gradient in a portion of the perinodular plexus may lead to a reversal of flow. The portal venules delivering blood may become draining channels and drain sinusoidal blood through porto-hepatic venous anastomoses into the hepatic veins. If the shift in the collateral circulation continues, then reversal in the intranodular microcirculation occurs and formerly well oxygenated areas of parenchyma become prone to ischemic insults so common in cirrhosis. Follow-up of the sinusoidal pattern by step-sections showed that only portions of nodules may be affected. Pooling of blood in certain sinusoids may indicate the location of efferent flow. Complicated dynamics in the sinusoidal flow of the nodules are caused by sclerosed terminal vascular branches and by septal vessels penetrating the nodules and feeding the sinusoids. Lasting alterations of the nodular microcirculation lead to further breaking up of the parenchymal clumps into smaller microcirculatory areas with newly formed microcirculatory peripheries that are easily damaged.

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**Note from the Editor**

It is very difficult to be original. The team under the leadership of A.M. Rappaport has submitted a new conception of the formal pathogenesis of cirrhosis of the liver. After careful consideration, the editorial board has decided to accept the paper, although not all co-editors were of the same opinion. We greatly appreciate, however, the heuristic stimulus of Rappaport's study and hope that the work receives the considerable attention it most surely deserves.