HEMODYNAMICS IN INTRAHEPATIC VASCULAR SYSTEM OF THE DAMAGED LIVER, ESPECIALLY, LIVER CIRRHOSIS.*

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The liver is an organ of special structure composed of small unit called "lobules" consisting of basic framework of numerous sinusoids and liver cells that are laid between a capillary network. In consideration of the importance of intralobular circulation, moreover, it must be considered that slight changes of liver cell reflect to sinusoidal circulation; namely, liver cell is influenced by sinusoidal circulatory disturbances, and finally, liver cell damage may occur gradually in this way. So, the author has considered on the occurrence of liver cell damage from the above findings. Condition of the injured liver has been observed with vital microscopical examination and resin casting pattern of hepatic vascular system.

Vital microscopical observation of the liver has been performed dy KNISELY,[1)2)3)] WAKIM and MANN[4)], and other investigators[5)], and in Japan, by NAKATA[6)7)], NAGAI[8)], TASAKA et al[9)]., the author[10)11)] and his collaborators[12)13)14)15)16)17)18)19)20)]. However, it is yet disputable whether sphincteric action at the junction between sinusoid and central vein can be recognized as a regulatory mechanism of intralobular circulation.

From the intralobular circulation viewpoint, the occurrence of central necrosis of liver cell must be discussed again. On the vascular feature of the cirrhotic liver as a chronic disease must also be discussed furthermore. On investigation of hepatic vascular tree, resin casting pattern is the most suitable procedure. Such research was done by MCINDOE[21)], ELIAS[22)23)24)], POPPER[25)26)], HALES[27)], and Breedis and young[28)], while in Japan, by MIYAKE[29)], OKUDAIRA[30)], the author[31)41)] and his collaborators[32)33)34)35)36)37)38)39)40)] in the past. And so, the author's results obtained on the above subjects are summarized and reported as follows:

I. Intrahepatic circulation in the liver of normal mouse.

In vital microscopic observation with transillumination technique, the liver of mice and rats was used, especially, that of mice. In the peripheral zone, the sinusoid ramified to form a fine network, while in the midzone, the sinusoidal network is

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simplified; subsequently it is divided into some fine network again in the central zone. Blood flow in sinusoid is irregularly observed. Though sinusoidal sphincteric action had been pointed out by Knisely and other American investigators, such an action could not be observed in the experiment.

To observe intralobular circulation and damaged liver cell with accuracy in vital observation, dye-stuffs are infected intravenously. Usually, Evans Blue is injected to clarify degenerated liver cell, but in this experiment, Chromazurol S[42] was used by choice, because with this dye intralobular circulatory condition and bile ductule can be clarified more vividly.

II. Intralobular circulation in the damaged liver.

1. The liver of mice treated with small quality of carbon tetrachloride.

Swelling and fatty metamorphosis as liver cell damage is caused by CCl_4 in the peripheral zone. And then circulatory disturbances of sinusoidal flow are caused by narrowing of sinusoid due to compression of swollen liver cell, hypertrophy of the Kupffer's cell and moreover, blocking by mononuclear cell in circulation. Soon after, the sinusoidal flow is suspended, and in the central sinusoid, an ischemic condition is caused, thus finally, liver cell necrosis may occur.

2. The liver of mice treated with Parathion.

In peripheral zone, granular degeneration of the liver cell is gradually accentuated by injection of Parathion, and further, change as is stated above is observed in midzone, subsequently, sinusoidal narrowing is observed. Disturbance of midzonal sinusoidal flow is accentuated gradually, and finally obstruction of the sinusoid is so noticed that sinusoidal flow is suspended. Central necrosis and hemorrhage may be caused following such a condition in a long run. Thg above observation shows that sinusoidal blood flow is disturbed by the swollen liver cell, hypertrophy of the Kupffer's cell and blocking by the large mononuclear cell. These disturbances of sinusoidal flow are not only influenced by the above factors but, of course, by the medicament.

Finally, necrosis of the liver cell and hemorrhage are subsequently caused by ischemia due to the disturbed sinusoidal flow. The fact that the liver cell is influenced by poison can not be denied, and one must attach great importance the fact that blocking of intrasinusoidal flow may also be followed in a long time. It must newly be considered from the circulatory disturbance viewpoint that ischemic hypoxemia or anoxemia caused by blocking of the sinusoidal flow plays an important part on pathogenesis of the central necrosis.

3. The liver of rat sensitized with antihepatic serum of rat.

In the liver of rat sensitized with the antihepatic serum, balloon-like swelling of

the Kupffer's cell is caused and blocking of sinusoidal flow by increased mononuclear cells in circulation is subsequently observed at the narrowing portion of sinusoid. A remarkable liver cell damage occurs accordingly in the region of disturbed sinusoidal flow. Furthermore, there occurs at the junction between central vein and sublobular one remarkable contraction, while, at the other area, the vein dilates and sausage like pattern appears in the vein. In the above condition, so-called sphincteric action can not be observed in many sinusoids tying up between central veins, as being pointed out by Knisely and other American investigators. The regulation of sinusoidal flow, therefore, is not observed by this action. However, in the specific condition mentioned above such as sensitization contraction at the junction between central vein and sublobular one is only recognized.

III. Hepatic vascular system by resin casting pattern.

There are some differences in hepatic vascular pattern according to the specifies of the animal[39]. These characteristics of vascular pattern will be clear on reference to the appended figure.

1. Hepatic vascular pattern of the normal liver.

Portal vein (Vp): Trunk of the Vp divides into two branches with the angle of 160–170 degrees. Peripheral branches divide into several small branches at the right angle, and finally these small branches ramify into 3 tiny tributaries, and the lobule as a unit of liver structure is formed. Vascular pattern of lobule takes the form of an inverse umbrella.

Hepatic artery (Ah): Within the liver there is one artery, and sometimes 2 or 3 arteries accompanying with each Vp, but the diameter of the Ah is one third or one fifth that of the adjacent Vp. Diverged branch of hepatic artery is in the similar mode as that of Vp. Periductal plexus develops well and forms network in the portal space. Arterio-venous anastomosis is observed in the following portion:

(1) so-called Mall's "intercommunication"[43],
(2) arterio-venous connection (arterio-venous fistula) in interlobular region,
(3) arteriole connection with inlet venule in perilobular zone,
(4) anastomosis through periductal plexus.

No gross veno-venous anastomosis is found in the normal human liver.

2. Hepatic vascular pattern of the cirrhotic liver.

Pattern of hepatic vein and portal one in the cirrhotic liver shows various alterations, distortion of vessel and reduction of venous vascular bed. On the other hands the Ah shows dilatation and winding of branches, and tiny arterioles increased in number.

A. Laennec's liver cirrhosis.

The trunk of Vp dilates and the dividing angle of their branches which divides at a

right angle in the normal liver shows a sharp angle. Therefore, the spaces between branches become so narrow that branches accumulate as an aggregation. While, the partial branches assume an obtuse angle, so that the space between the branches becomes wide. The branch in the 7th order is as large as 0.65 mm and the inlet venule 0.02–0.03 mm in diameter; therefore, the branches become thinner, more flattening and winding. It sometimes happens that the interlobular vein shows 'beer cask like' expansion and ramifies into small fine branches suddenly. As above-mentioned, the venule becomes so fine that one may observe the appearance of coarse distribution. Peripheral ramifications show fine and marked alteration, and yet, in the extreme case, these fine venules disappear. The interlobular vein, inlet venules and sinusoids are compressed by the pressure of nodules of hepatic cells to such an extent that they become to show a coarse network-like distribution or are distributed as if they form the wall of the circular nodules. On resin casting pattern of the cirrhotic liver, round or irregular-shaped defects are often examined, but these are the nodule of hypertrophic liver cell, and into these area acryl resin can not injected in these area. These cavity-like defects are as large as 1.7 mm–1.0 mm in their diameter, the largest one being 4.0 mm, but they are all alike generally. Accordingly, running of the interlobular veins show a basket-like alteration by the compression of these round nodules. Namely, these branches accumulate in a bundle and envelop the nodule in a circle. These vessels forming circular vascular bed, however, are not so many as those in secondary liver cirrhosis in number. Another pattern is the alteration of 'parasol-like' curve of the ramification, which envelops the surface of the liver, accompanied with plexus-like increased venules. Such plexus-like increased venules extend as if they were creeping over the lobule.

Hepatic vein (Vh): Small branches and sublobule veins become flat and tortuous in form; furthermore, they show reduction or disappearance of vascular bed. Sublobular vein shows conspicuous alteration as distortion, winding and 'parasol-like' transformation, but increase of small venules are not recognized. And clear basket-like circular pattern is also unseen.

Hepatic artery (Ah): In normal liver the diameter of the hepatic arteries averages approximately one third or one fifth to that of the adjacent portal veins. Because of the finding as was stated above, blood flow of Ah consists of only 20–30% of the whole blood flow through the liver. In the cirrhotic liver, however, arterial vessels from trunk to periphery expand remarkably; especially, the diameter of arterioles enlarges to two third or fully as large as the adjacent portal veins. These expanded arterioles show not only winding, but spiral-like tortuous in the severe case. Distribution of the arterioles with winding and creeping of the above mode resembles the creeping of an ivy. The round defects as mentioned above are enveloped with increased peripheral arterioles, but arterioles are not as numerous in the secondary cirrhosis. Such a pattern as the arterioles associated with the portal venules around a nodule was named as 'basked type'. Another pattern in

which the increased arterioles formed a network and plexus-like distribution or the arterioles associated with 'parasol-shaped' portal venules distributing in a form of creeping over the lobule, was designated as 'creeping type'. In general, in these vascular patterns of cirrhosis, complex and intermingled distribution of these 2 types is seen. Periductal plexus develops well and expands also, so that the increased tiny arterioles appear as 'moustache-like' form.

Anastomoses between periductal plexus and branches of Vp expand, that is, resin injected in the artery is readily introduced into the Vp easily, as if resin were easily flowing into the venule and sinusoid. Therefore, sinusoid seems to be the arterial sinusoid.

Gross anastomosis between separate portal veins is not usually found; however, in this condition, end to end anastomosis is recognized. Gross arterio-venous anastomosis does not only increase, but expands in this condition. And gross anastomosis between venule (0.08 mm) of Vp and that of Vh are also recognized.

B. Secondary liver cirrhosis.

Vp: Change of Vp is similar to the vascular pattern of Laennec's cirrhosis essentially; the defects corresponding to the nodule, however, are rich in variety, the size being from 0.3 mm to 5.0 mm. These defects are irregularly round or in fissure shaped form. The venules surrounding the defect show a basket-like curve; furthermore, a bundle of numerous venules is distributed around the defect. 'Parasol-like' alteration and plexus-like distribution of portal venules as well as Laennec's cirrhosis are recognized; increase of venule in number, moreover, is remarkable.

Vh: Reduction and disappearance of vascular bed, and winding, flattening and tapering off of the venule are recognized. The central vein becomes as fine as the sinusoid in width.

Ah: In the hepatic arterial system similar changes resembling to Laennec's cirrhosis are observed; viz., dilation and marked increase of arterioles. Basket-like pattern around the nodule and creeping pattern over the lobule are recognized more conspicuously than in Laennec's cirrhosis. Anastomosis among Vp, Vh and Ah is similar to that of Laennec's cirrhosis.

C. Biliary liver cirrhosis.

Conspicuous dilatation of bile duct is the characteristic pattern.

Vp: Dilatation and winding of the peripheral branches of Vp, and circular bending of the venules are recognized, but a tendency of basket formation is seen in a less degree and coarse network formation in venules around the nodule is recognized. While, 'parasol-like' alteration is not so striking as in Laennec's liver cirrhosis.

Ah: Dilatation and alteration of the artery are similar to the former and the arterioles are completely as large as the adjacent portal branches. Arterioles show more prominent winding than in Laennec's cirrhosis. The defect is surrounded by

a network of arterioles as the basket-like type; however, arterioles consist of a coarse network. And also the arteriole forming a creeping pattern is in a less degree than in Laennec's liver cirrhosis. It is a characteristic point that the arterioles in periductal plexus do not only increase remarkably in number and dilate in diameter, but are distorted more markedly than in the other cirrhosis.

D. Congestive liver cirrhosis.

Dilatation of hepatic vein is remarkable, while the portal system in whole is relatively thin; that is Vp sinister is as large as 8.0 mm in diameter. The appearance of this cast seems to be consisted of only hepatic venous bed mostly.

Vp: The portal system is comparatively thin in general, and dilatation of trunk is not recognized in other liver cirrhosis. Peripheral branches become thin, of course, wind slightly and distribute in a network-like fashion. Reduction of the portal bed and small defect are recognized. The venules packing the defect are deficient. It is characteristic that the 'parasol-like' alteration of interlobular vein is not observed.

Vh: In the hepatic venous system marked dilatation of venule and expansion of vascular bed are recognized. The diameter of the defects is as large as approximately 0.2–1.1 mm. The condition of the sinusoid sometimes shows a coarse ramified network. These defects of the venous bed are permeated by several arterioles. Flattening and winding of sublobular vein and central one are recognized; furthermore, a basket-like curve of venules is noted. It is a characteristic pattern that conspicuous parasol-like variation of interlobular and central vein is recognized.

Ah: A trunk shows slight dilatation, but the diameter of the peripheral arterioles is approximately two thirds that of the adjacent portal venule. Furthermore, increase in number and extension of the arterioles are conspicuous. It is a striking feature that several increased and enlarged arterioles permeate through the defect of the venous bed. The difference from other types of the cirrhosis is that a deficient tendency of basket-like alteration is noted. While, in another creeping pattern several arterioles in a crowds distribute in coarse network. Such a pattern is a particular mode. Periductal plexus enlarges slightly and forms coarse network. Venovenous anastomose as well as other types of the cirrhotic liver are recognized. And such anastomose which consists of portal, arterial and venous resin are sometimes found. It is a notorious feature that abundant arterio-venous anastomosis is recognized.

DISCUSSION

It has been pointed out that the occurrence of central necrosis in the lobule is caused by poison, bacteria and its toxin, and virus. Glynn and HIMSWORTH[44] also, claimed that in carbon tetrachloride poisoning, disturbances of intralobular inflow was caused by the compression of the swollen liver cell. The author and his as-

sociators have stated the following opinions: Narrowing of sinusoid is caused by the hypertrophied granular degeneration and fatty degeneration of the liver cells, and moreover, the hypertrophied Kupffer's cells; whereas, the narrower portion of sinusoid is easily obstructed accidentally by mononuclear cell in circulation. It may, therefore, be considered that hypoxemic or anoxemic condition must easily occur in the central zone, and liver cell necrosis in the central zone must subsequently occur. Central necrosis and hemorrhage in parathion poisoning occur later than in CCl_4 poisoning, but in this case, of course, blocking of the sinusoidal flow is caused by the same factors as the former. It follows from this phenomenon that liver cell necrosis in the central zone may occur. It will be thought that on occurrence of central necrosis, liver cell degeneration is caused by the primary change of the poison, and circulatory disturbance following the phenomenon: namely, necrosis, moreover, is completed by anoxemia or hypoxemia. The author and associators performed studies on intrahepatic vascular changes in the liver cirrhosis with corrosion preparat. In this study the author obtained the following results: Alteration in the intrahepatic vascular system as enlargement and alteration of the trunk in Vp, and decrease in number of venule and portal venous bed were recognized, while, in the hepatic artery marked expansion, increase in number and distortion of arterioles were observed. In the hepatic venous system, alteration of branch and reduction of venous bed were noted. On the other hand, respective characteristics were observed according to the sort of liver cirrhosis. The author pointed out that the vascular pattern of the cirrhotic liver might be classified into 2 types, namely, basket type and creeping one. The former shows a basket-like distribution of the curved blood vessels surrounding the nodule in circular. Such a basket pattern was caused by venules and arterioles, increasing around the nodule curved by the compression of the nodule. In such a condition, arterial inflow increased as compared with portal venous flow around the nodule. So, circulatory condition in the cirrhotic liver was in contrast with normal circulation. Creeping type of the latter was a pattern shown by parasol-like alteration of the interlobular venule, and additionally by plexus-like increase in number of the arterioles accompanying with each portal vein. These changes may be originated from marked fibrosis. In biliary cirrhotic liver, characteristically typical pattern was not found, but arterioles increased remarkably forming a loose basket pattern, and expansion and winding of the periductal plexus were also observed. In congestive cirrhotic liver, the 'parasol-like' alteration of the sublobular venule was the conspicuous pattern. Such vascular reaction as several arterioles permeating into the defect around the central venule, furthermore, was specific finding. It may be claimed that in cirrhotic liver, the hepatic arterial system shows an active attitude. These facts may, therefore, be understood as teleological change to inflow blood into the liver in larger quantities. Whether or not regeneration and hyperplasia of the liver cell were stimulated by intralobular inflow of a large quantity of arterial blood through abundant arterioles around a nodule, or

whether or not basket-pattern of the arterioles was simply caused by following obstruction of venule due to the compression of nodule, could not be clarified. It seems, however, that the different circumstance from normal circulatory condition will be a factor which promotes regeneration of the liver cell. As mentioned above, the liver cell enveloped by basket-like vascular network will further be under the striking influence of abnormal circulatory circumstance. A study on DAB hepatoma of rat was biochemically compared with turn-over of phosphorus metabolism in the author's laboratory[45]. From such results obtained, it may be asserted that the change of P turn-over in the liver may be caused by the change in a long duration of circulatory dynamics. However, further study in detail shall be reported at the next chance to come.

CONCLUSION

1. With the occurrence of central necrosis, the importance of disturbance of sinusoidal circulation was pointed out.
2. Sphincteric action in sinusoidal end as a regulatory mechanism was unrecognized. In such specific conditions as the liver sensitized with antihepatic serum, however, contractile reaction in the junction between central and sublobular vein was clearly observed.
3. In liver disease such as cirrhosis, specific morphological changes in hepatic cirrhotic liver 2 patterns of the blood vessel were observed, one was basket type, and the other creeping type. In Laennec's cirrhotic liver, the size of defect of vascular bed was uniform and its region showed typical basket-formation. In the secondary cirrhotic liver, the size and the form of defect were variable, and small hepatic vessel forming vessel bed of the basket type was abundant, but showed irregular arrangement. Small vessels in creeping type increased more in number than in the primary case. In biliary cirrhotic liver deficient tendency of basket-formation and loose network formation of arteriole were noticed, but the increase of periductal plexus was conspicuous. In congestive cirrhotic liver, large hepatic venous bed and irregular defect around central vein were recognized. The remarkable permeating tendency of several arterioles was clearly observed, and more numerous arterio-hepatic venous bed and irregular defect around central vein were recognized. The remarkable permeating tendency of several arterioles was clearly observed, and more numerous arteriohepatic venous anastomoses were observed than in the other cirrhotic liver.

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LEGENDS FOR FIGURES

Fig. 1. Balloon-like swelling of Kupffer's cell in the liver of sensitized mouse is noted after provocative injection. VC···Vena centralis, K···Kupffer's cell, L···Leucocyte
Fig. 2. As a result of balloon-like or spindle shaped swelling of Kupffer's cell after the provocative injection, narrowing of sinsoids is noted. VI···Vena interlobularis
Fig. 3. Disturbances of sinusoidal blood flow are caused by blocking of large monocyte (LM) at narrower portion where Kupffer's cell projected as balloon cell into the lumen of sinusoid.
Fig. 4. Funnel-shaped contraction at the junction between VC and vena sublobularis after 10 minutes of the provocative injection in the sensitized mouse.
Fig. 5. After 15 minutes of the injection, the above mentioned contraction is continuously noted.
Fig. 6. After 20 minutes of the injection, contraction of the venule is relieved gradually.
Fig. 7. After 25 minutes, contraction of the venule returned to the condition before the injection.
Fig. 8. Changes of venules of the liver after the provocative injection in the sensitized mouse with R. H..
Fig. 9. Schema showing changes of the venules and blood flow in the liver after the provocative injection.
Fig. 10. Schema showing hepatic vascular pattern of the liver with resin cast.
Fig. 11. Hepatic vascular pattern of the normal liver by resin casting. No. 504 (A boy, 3 years of age)
Fig. 12. No. 504. Arrow shows interlobular vein surrounding sinusoid.
Fig. 13. No. 631. Hepatic vascular pattern of the Laennec cirrhotic liver.
Fig. 14. No. 631. Distortion of branches of Vp and proliferation are observed.
Fig. 15. Creeping type pattern of the hepatic vascular tree. Marked proliferation of arterioles is noted.
Fig. 16. Hepatic venule shows distortion and flattening.
Fig. 17. No. 218. Resin cast of hepatic vascular tree of the secondary cirrhotic liver. Defect of small branshes of Vp and proliferation of hepatic arterioles are noted.
Fig. 18. Basket type patter consists of coarse network of arterioles.
Fig. 19. Creeping type pattern. Proliferation of hepatic vascular tree, espicially, arterioles is observed.
Fig. 20. Enlargement and winding of hepatic arterioles is remarkable.
Fig. 21. No. 619. Hepatic vascular pattern of the cirrhotic liver. Anastomosis among branches of Vp each other.
Fig. 22. Anastomosis between branches of periductal plexus and portal venules.
Fig. 23. No. 496. Hepatic vascular pattern of the biliary cirrhotic liver. Defect of hepatic vascular tree is noticed, but no typical basket type pattern is observed.
Fig. 24. Proliferation of arterioles is remarkable.
Fig. 25. No. 635. Cardiac cirrhosis of the liver.
Fig. 26. Arrow (↑) shows decrease of branches of Vp. Arrow (↟) shows proliferation of hepatic arterioles. Sinusoid is drained with resin injecting into hepatic venule.
Fig. 27. Arrow shows network of proliferated hepatic arterioles.
Fig. 28. Dilatation an winding of branches of hepatic venules (↑) and hepatic arterioles (↟) are

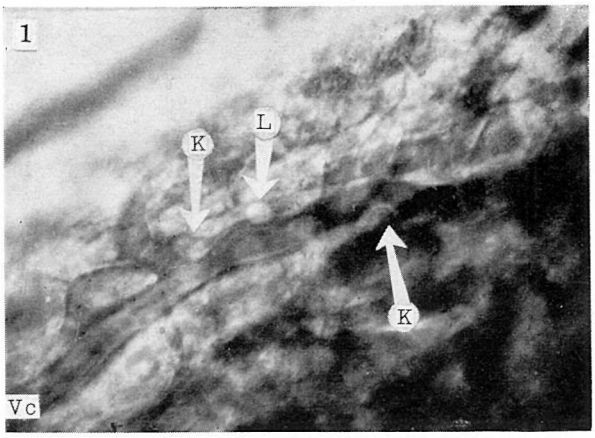
observed.

Diagram 1. Schema of hepatic pattern in verious hepatic injuries, especially, liver cirrhosis.

Table 1. Difference of vascular morphology in various liver cirrhosis. – No findings, + Sometimes changes is noted, +, ++, +++, Degree of changes.

Diagram 2. On occurrences of central necrosis of the lobule in the liver, correlation between circulatory disturbances of intrasinusoidal blood flow and swelling of the liver cell, and in addition to blocking of large mononuclear cell is shown.

Diagram 3. Relation between injuries of the liver cells and intrasinusoidal circulation in process of various liver cirrhosis is shown.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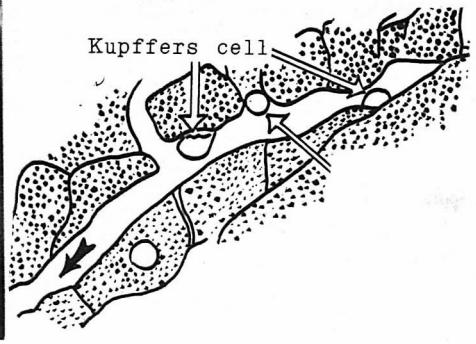
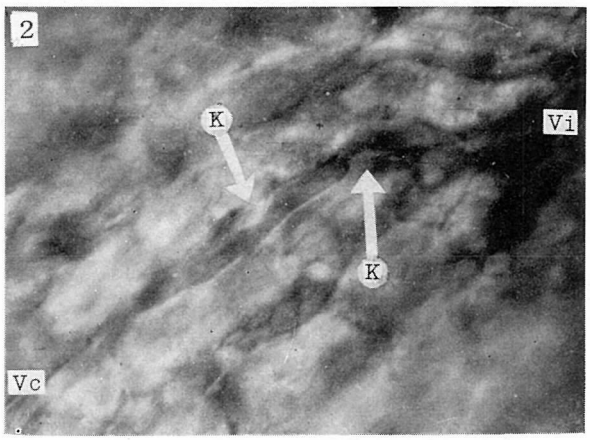
K
L
K
Vc


Kupffers cell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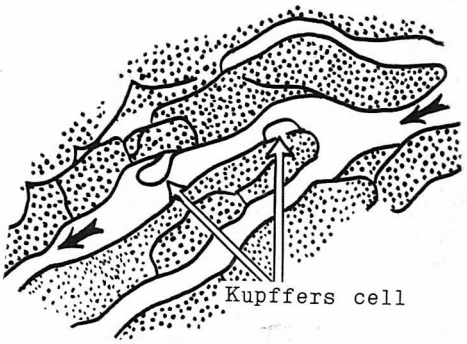
Vi
K
Vc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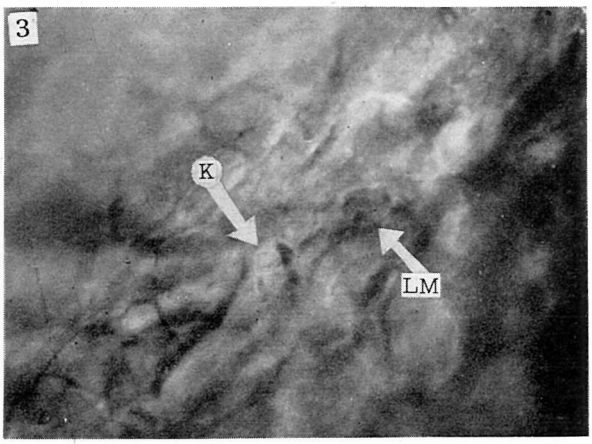
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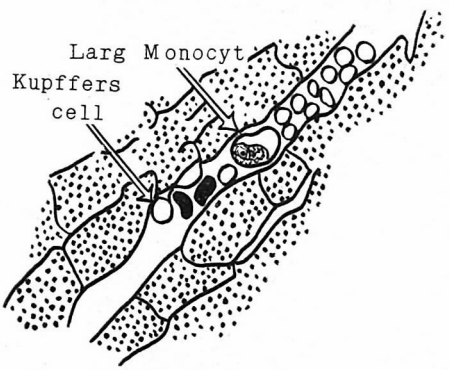
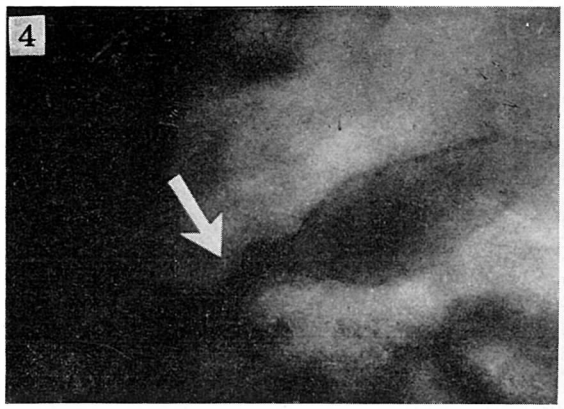
K
LM


Larg Monocyt
Kupffers
cell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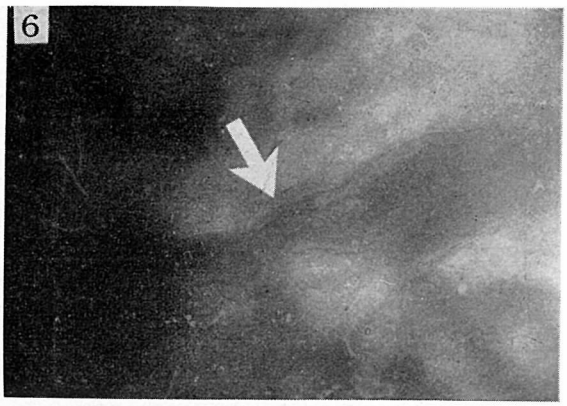
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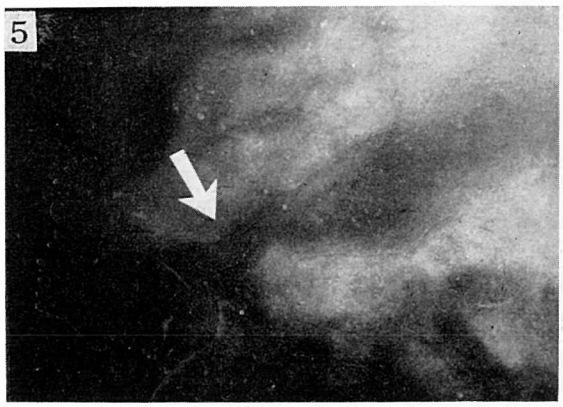
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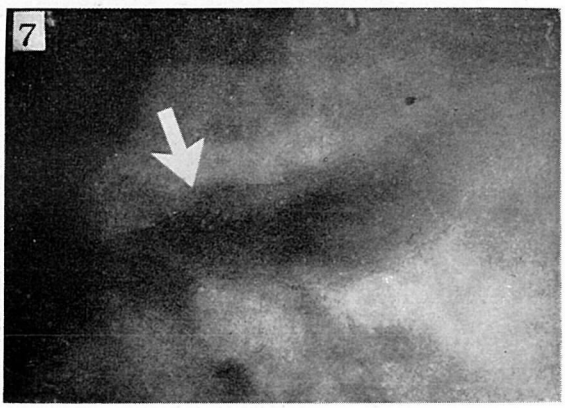
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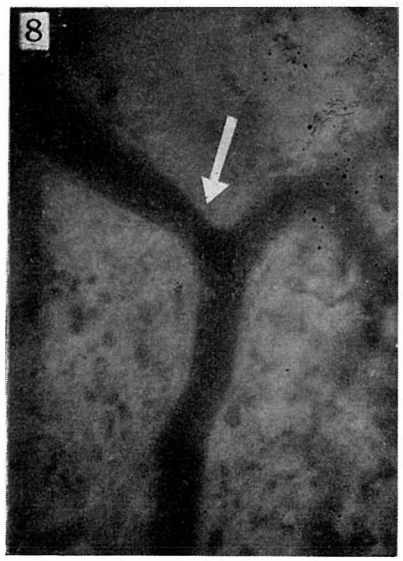
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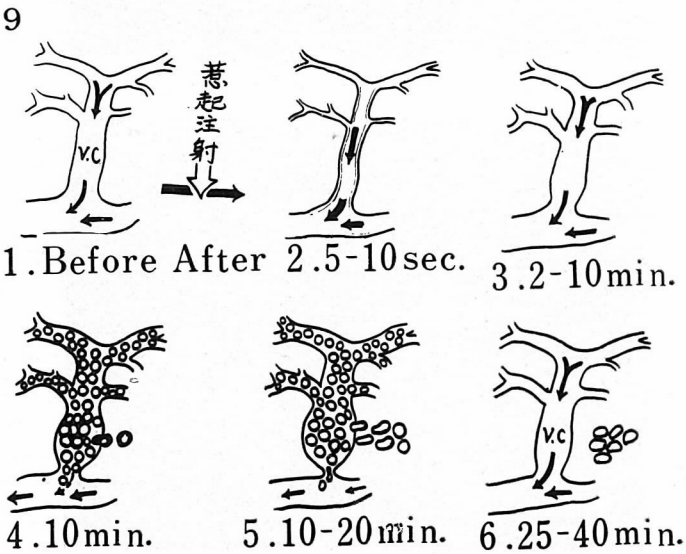
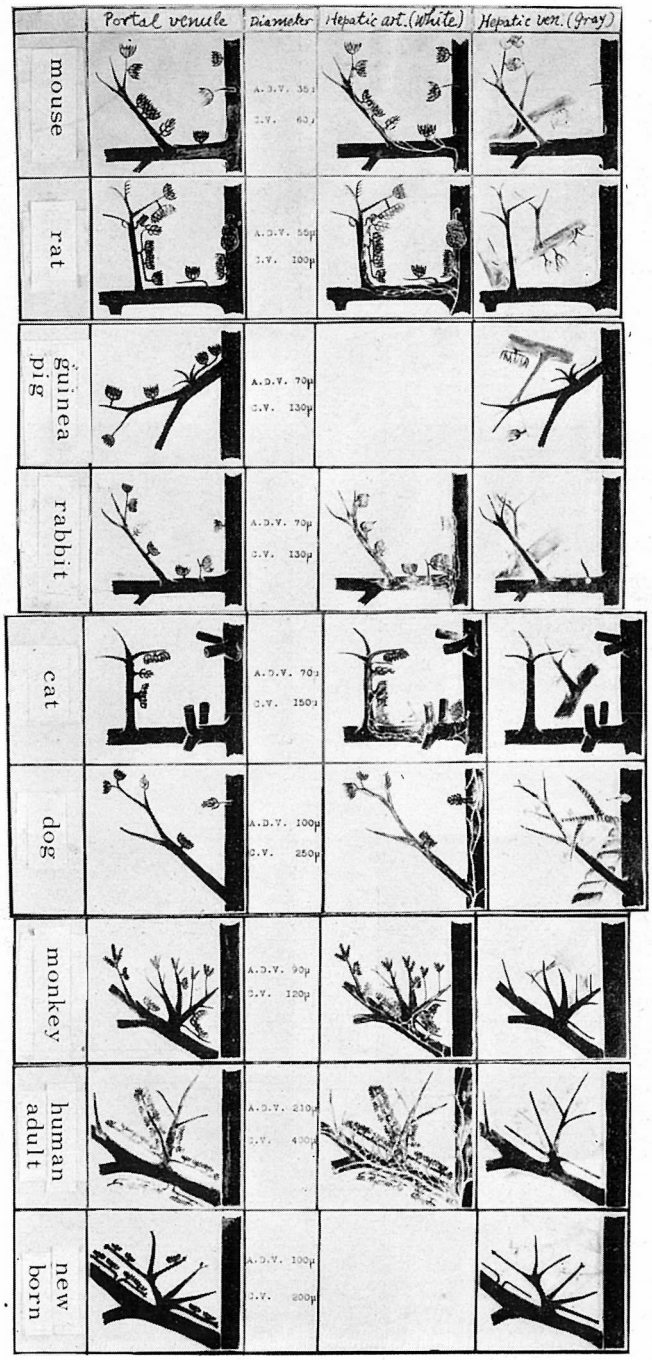
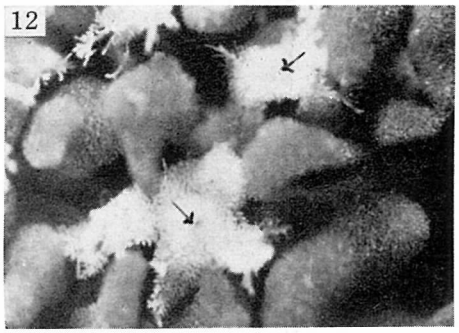

9
V.C
惹起注射
1. Before After 2. 5-10 sec.
3. 2-10 min.
4. 10 min.
5. 10-20 min.
V.C
6. 25-40 min.

10 Distribution of the hepatic vascular tree (with resin cast)



A. D. V. axial distributing vein (H. Popper) C. V. conducting vein


11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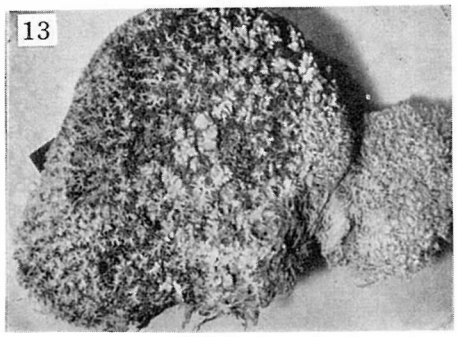
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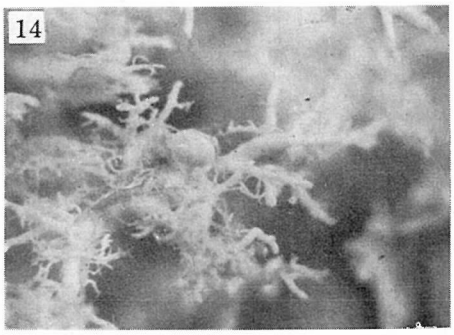
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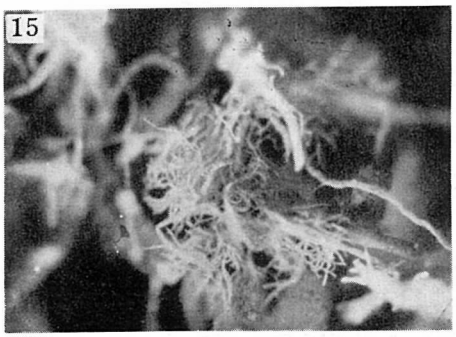
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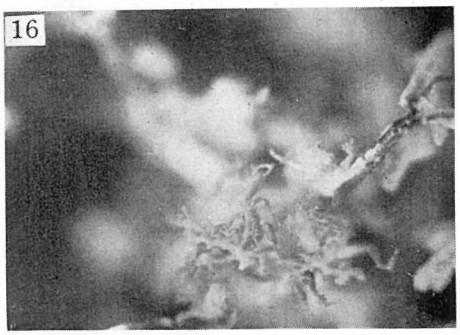
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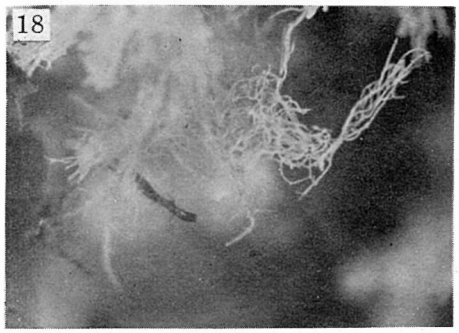
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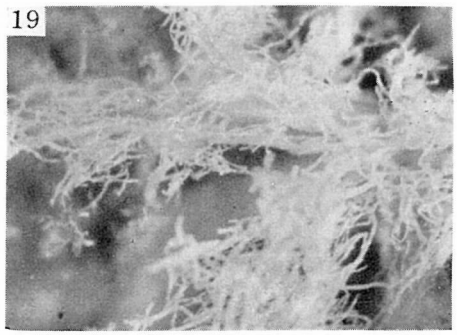
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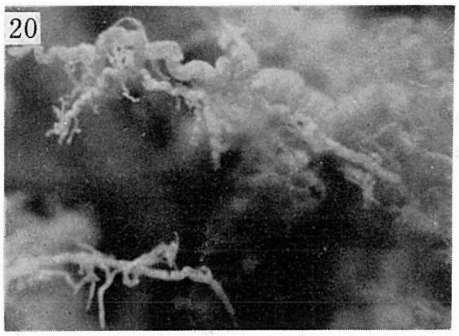
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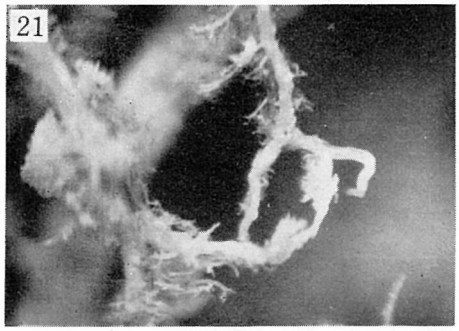
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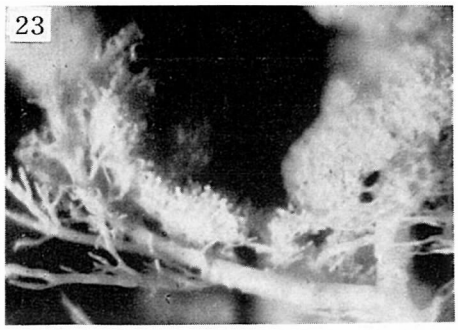
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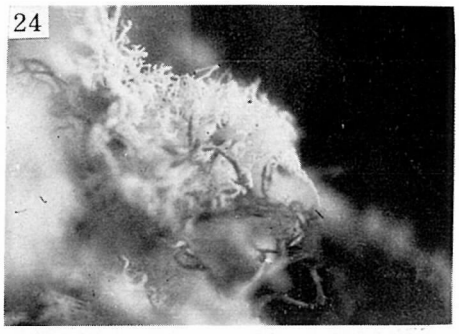
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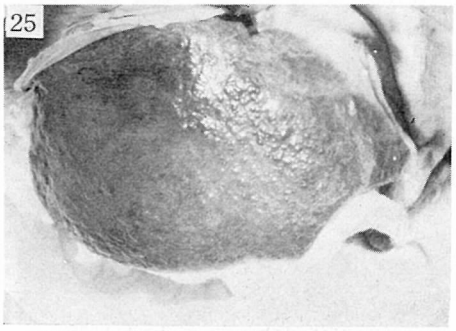
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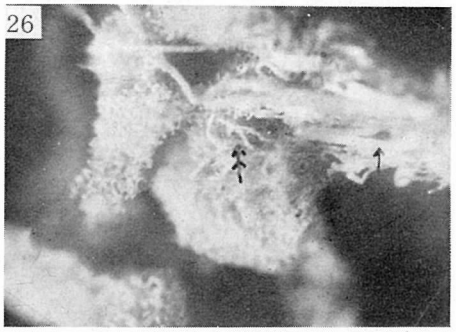
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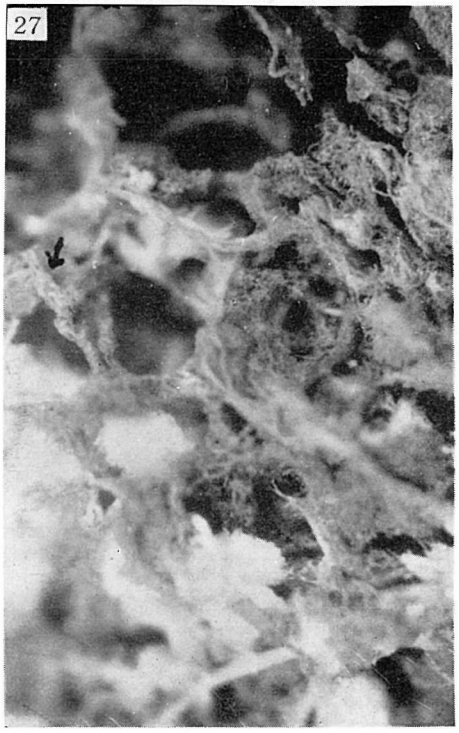
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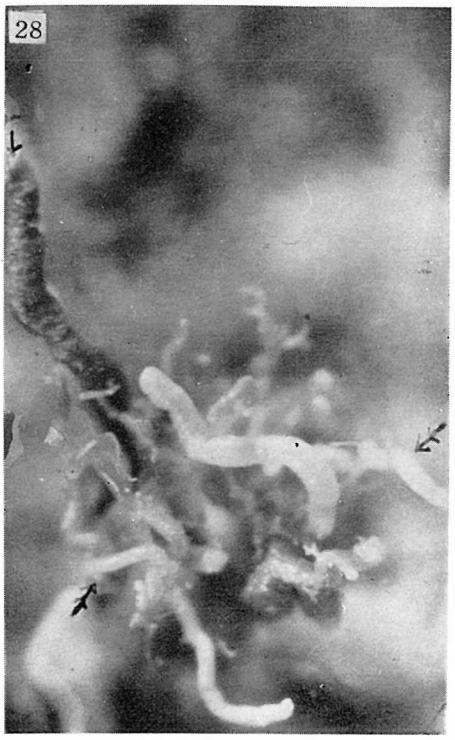
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Diagram 1.

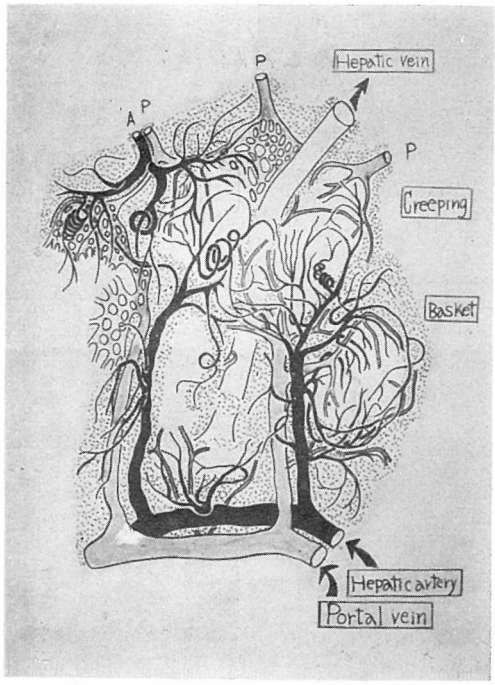

Table 1.

Difference of Vascular Morphology in Various Liver Cirrhosis

Classification by Prof. NAGAYO	Basket type. P + A	Creeping type. P + A	Periductal Plexus A	Anastomosis P-A	P-P	P-V	A-V
Liver: Normal	—	—	+	+	—	—	—
LAENNEC's Cirrhosis	++ ++ Uniform. Regular. Bundle-like.	++ ++ Parasol-like.	++	++	+	++	+
Secondary Cirrhosis	++ ++ Irregular. Bundle-like. Dense.	++ ++ Parasol-like. Plexus-like. Irregular.	++	++	+	++	+
Biliary Cirrhosis	± ± Coarse.	± ++ Coarse. Diffuse.	++ Bile duct; gross.	++	±	no Exam.	no Exam.
Congestive Cirrhosis	— —	— —	++	+	±	+	++

※ A: Hepatic artery. P: Portal vein. V: Hepatic vein.

Diagram 2.

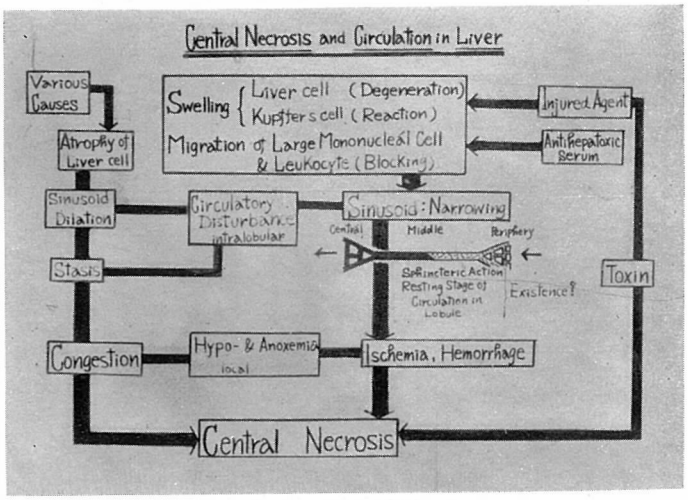

Diagram 3.

Relation between injury of the liver cell and intrasinusoidal circulation