NODULAR REGENERATIVE HYPERPLASIA OF THE LIVER*

PAUL E. STEINER, M.D.
From the Institute for Cancer Research and Department of Pathology, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

The purpose of this communication is to emphasize that hepatocytic hyperplasia or regeneration may take place in the absence of fibrous tissue proliferation, that it may be nodular, and that the resulting lesion, here called nodular regenerative hyperplasia, may simulate cirrhosis without, however, meeting the precise criteria and definition of cirrhosis. This condition is not cirrhosis, does not necessarily lead to cirrhosis, has a different significance from that lesion, and ought not be confused with it if statistics are to be meaningful.

For distinction and discussion in this paper, cirrhosis may be defined as a pathologic process in the liver, characterized by nodular hyperplasia or regeneration plus a fibrous tissue increase in the form of scars, bands, membranes or septums, both components together resulting in distortion of the normal lobular architecture. The normal lobular pattern is altered by the combined effects of the two abnormal processes, and both components are essential by definition. This is in agreement with opinions voiced at the Havana[1] and Kampala[2] conferences.

Nodular regenerative hyperplasia, as here described, fails to meet that definition of cirrhosis because it lacks the fibrous bands, scars or septums. On the other hand, the fibrous tissue may be increased in a liver without appreciable parenchymal hyperplasia, and this condition, designated hepatofibrosis, also is not cirrhosis. That is not to deny that these two conditions, nodular regeneration and hepatofibrosis, are important.

The essential features of nodular regenerative hyperplasia are illustrated in a series of cases by Figures 1 to 12. The nodular appearance of such livers is shown by Figures 1 to 7. Higher magnifications of some nodules in Figures 3 to 7 show that this nodularity is due to liver cell proliferation, and this fact is verified also by the higher power views in Figures 8 and 9. The absence of new fibrous tissue and of fibrous scars or septums is shown in Figures 1 to 7 and 10 to 12; only pseudo-septums are present. They are false in the sense that they are composed of structures other than connective tissue.

Stains for connective tissue and for reticulum were made in some of these cases. New collagen was not formed about the nodules. The

* Aided by a research grant from the National Cancer Institute (C-3251).
Received for publication, February 7, 1959.

reticulum fibers around the nodules showed dislocation and a relative increase because of atrophy of the parenchyma and compression. With experience and thin well-stained sections, the condition can be recognized and distinguished from cirrhosis without stains for fibrils.

Regions in which atrophy of liver cells (Figs. 10 to 12) or necrosis of liver cells (Fig. 12) had occurred may display some degree of condensation of the pre-existing stromal elements without this fibrillar substance becoming compact or fused. When such regions are linear, they may falsely simulate the septums or bands of cirrhosis. Such suggestions of cirrhosis are also caused or enhanced by the compressive effects of the expanding regenerated nodules of liver cells distorting or displacing normal anatomic structures such as portal tracts or central veins (Fig. 11). The resulting alterations appear nodular, and may be mistaken for cirrhosis unless a more precise analysis is made.

In nodular regenerative hyperplasia the nodules are small, usually less than an anatomic lobule in size, and one or more to the lobule. Rarely are they larger than a liver lobule. Grossly, a slight degree of irregularity of the lobular architecture is usually visible, as well as an accentuation of the lobules. The condition is present throughout the liver, which is smaller on the average than normal. The appearance is suggested by the original diagnoses which were mild cirrhosis or chronic passive congestion.

The nodules are recognized as being composed of new liver cells by their abnormal relation to the portal tracts and the veins (Figs. 4 to 11), irregularity of the liver cords, enlargement of the liver cells, great frequency of binucleate cells, occasional presence of mitotic figures, and by the evidences at the margins of the compressive effects of expanding nodules (Figs. 1 to 7 and 10 to 12).

The only serious confusion in differential diagnosis is with the appearance in a section marginal to a portal area in a liver which has also a severe grade of passive congestion. There is no problem in differential diagnosis when the plane of the section strikes the portal tract because the typical lesion of central passive congestion is then easily recognized.

In regenerative nodular hyperplasia, band-like zones, mimicking the fibrous bands, septums, or membranes of cirrhosis, may be produced by the compressive effects of expanding nodules without any fibrous increase having occurred. In such regions atrophy or the actual loss of liver cells, whether by a process of atrophy or necrosis, permits the pre-existing fibrillar stroma to come closer together. Partial collapse leads to a relative increase of stroma in the area, but

the fibrils are not fused, and many remain separated by epithelial cells. Viewed uncritically, such a zone may suggest the fibrous band of true cirrhosis and lead to this diagnosis.

It is true that with the complete and final disappearance of parenchymal cells from such an area, the resulting collapse permits juxtaposition of the fibrillar framework and its eventual fusion to form a fibrous band or septum. By accretion and the formation of additional collagen, this band may grow, as it does in cirrhosis. Thus, cirrhosis may develop from nodular hyperplasia if the causative factors persist long enough. On the other hand, the condensed band-like area in nodular hyperplasia may re-expand by regeneration of its hepatocytes just as it does in the regeneration which often follows in the areas of collapse accompanying severe central passive congestion.

Nodular hyperplasia is not in itself a progressive lesion. Only if liver injury, which precedes it, is repeated and severe do the effects produce a fibrous increase and, thus, cirrhosis.

The cause of this lesion is liver damage; it represents a reparative, proliferative phase which is nodular. The livers were slightly below average weight, indicating loss of hepatic substance which had not yet been fully compensated by regeneration.

The injury which induces this nodular type of hyperplasia or regeneration is probably irregular in its distribution within the lobule. The stimulus to regeneration produced by the insufficient liver volume consequent to partial hepatectomy leads to uniformly enlarged anatomic lobules.

Nodular hyperplasia, of the type here described, is not rare. It has been possible without difficulty to accumulate about a dozen specimens in necropsy collections examined in Africa in 1957 and at the University of Chicago. Its frequency has not been systematically determined; it would vary with the frequency of the ailments which it accompanies. It has been found associated with a variety of major diseases, the commonest of which have been the passive congestion of severe heart failure and tuberculosis. In no instance was hepatic abnormality recognized clinically.

There is no reason, statistical or otherwise, to believe from the nature of the major disease with which nodular regenerative hyperplasia was associated that it was the early stage of the common forms of cirrhosis. At the same time it is probable that some of the cases, with repetition of the insults, might have developed the special pattern of central cardiac cirrhosis. From what is known of the etiology and pathogenesis of the two commonest varieties of cirrhosis, namely, postnecrotic and portal cirrhosis, nodular regenerative hyperplasia as here

described is not necessarily a way station in their development. It is, therefore, not called "early" cirrhosis.

By the use of criteria and standards which were less precise than those here defined and advocated, some of these cases had earlier been diagnosed as mild or "early" cirrhosis. To regard them as such is now believed to be undesirable, inasmuch as their significance is different and they would confuse the thinking on the pathogenesis of true cirrhosis. Probably only those cases occurring in cardiac decompensation would ever have progressed to cirrhosis, and that of the ambiguous central lobular type. Until the situation is clarified, it is probably best to retain nodular regenerative hyperplasia without fibrosis as a category separate from the cirrhosis and the hepatofibrosis groups. The statistics on cirrhosis would be more meaningful, precise, and comparable if the cases of nodular hyperplasia and hepatofibrosis were kept in separate categories.

Edmondson has emphasized the condition of "multiple nodular hyperplasia" as it is seen in cirrhotic livers.[8] The nodules are sometimes large. By definition, this condition may be accepted as, in greater or less degree, a regular part of the lesion of cirrhosis.

Summary

Nodular regenerative hyperplasia of the liver is characterized by innumerable small areas of focal regeneration more or less distinctively demarcated by adjacent compressive, atrophic, other degenerative, and circulatory effects. Lacking a true increase in fibrous tissue, the lesion does not conform to the definition of cirrhosis, which it may sometimes resemble. It represents a regenerative phase, after parenchymal damage of local character, within the lobules but generalized throughout the liver.

It was found fairly commonly in damaged livers associated with a wide variety of conditions, the commonest of which was passive hyperemia of cardiac decompensation. It is not in itself a progressive lesion, and is not "early" cirrhosis. If the causative factors for the hepatic damage persist, it is conceivable that cirrhosis of the central or cardiac type may develop, but the lesion is not an early stage of portal or postnecrotic cirrhosis. Statistics on cirrhosis would be more accurate, meaningful, and comparable if cases of nodular regenerative hyperplasia were classified separately.

REFERENCES

1. Fifth Pan-American Congress of Gastroenterology, La Habana, Cuba, January 20-27, 1956. Report of the Board for Classification and Nomenclature of Cirrhosis of the Liver. Sherlock, S. (chairman). *Gastroenterology*, 1956, 31, 213–216.

2. Symposium in Kampala, August 1956. Cancer of the Liver Among African Negroes. *Acta Unio internat. contra Cancrum,* 1957, 13, 519–522.
3. Edmondson, H. A. Tumor Lesions: Multiple Nodular Hyperplasia. In: Atlas of Tumor Pathology, Section VII, Fascicle 25, Tumors of the Liver and Intrahepatic Bile Ducts, pp. 191–192, Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Armed Forces Institute of Pathology, Washington, D.C., 1958.

[*Illustrations follow*]

LEGENDS FOR FIGURES

All sections were stained with hematoxylin and eosin.

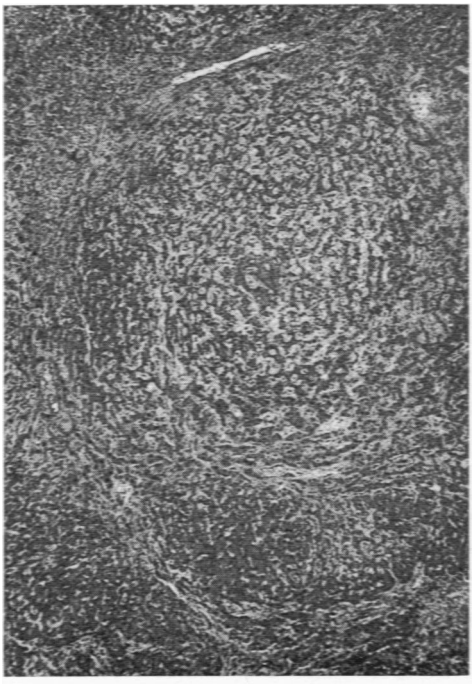
Figures 1 to 3 show the low power appearances of the liver in 3 cases.

FIG. 1. One distinct regenerative nodule and others that are less distinct, separated by pseudo-septums of several types. Case 1. Man, age 87. Liver weight, 1,300 gm.; finely granular. × 42.

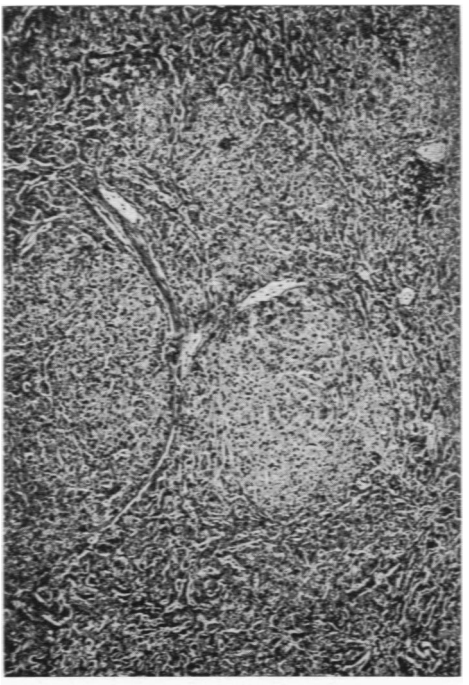
FIG. 2. The regenerative nodules are small but clearly seen because of their central large pale cells. The pseudo-septums are poorly developed. Case 3. Woman, age 71, died of complications after resection of a cecal tumor. Liver weight, 1,550 gm.; had irregular lobules. × 42.

FIG. 3. Portions of several nodules distinctly demarcated by atrophic and congested zones but without increase in fibrous tissue. Case 4. Woman, age 65, died after repeated episodes of cardiac decompensation with coronary occlusion. Liver weight, 1,630 gm.; lobules irregular in size. × 42.

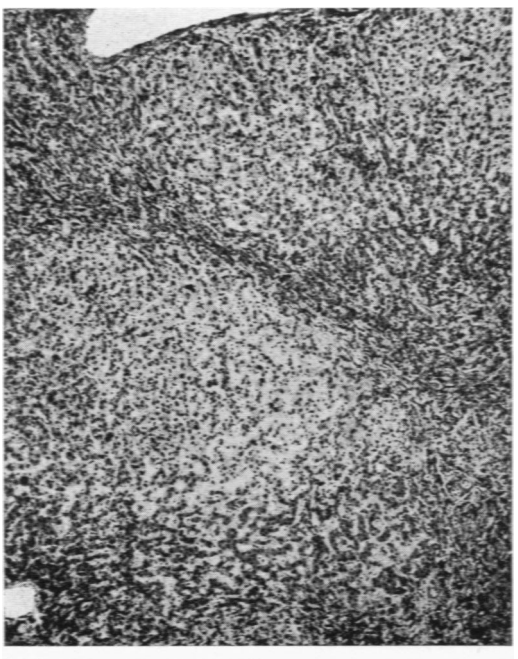
FIG. 4. Distinct regenerative nodule adjacent to a small portal tract, demarcated by a zone of atrophy and hyperemia. Case 1. × 85.



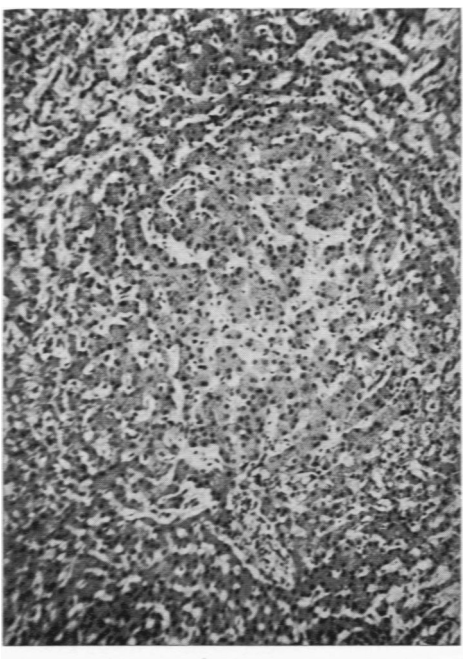
1



2



3



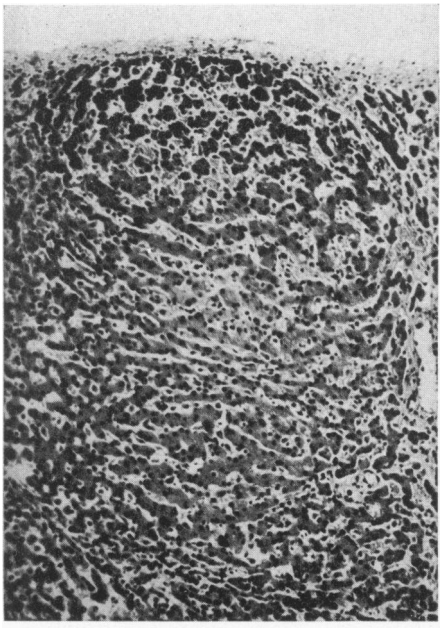
4

FIG. 5. Here the regenerative nodule is subcapsular, although others were present elsewhere. Adjacent compression effects and atrophy are distinct. Case 6. Man, age 56, died of Whipple's intestinal lipodystrophy. Liver weight, 1,720 gm.; anatomic lobules were not grossly visible. × 75.

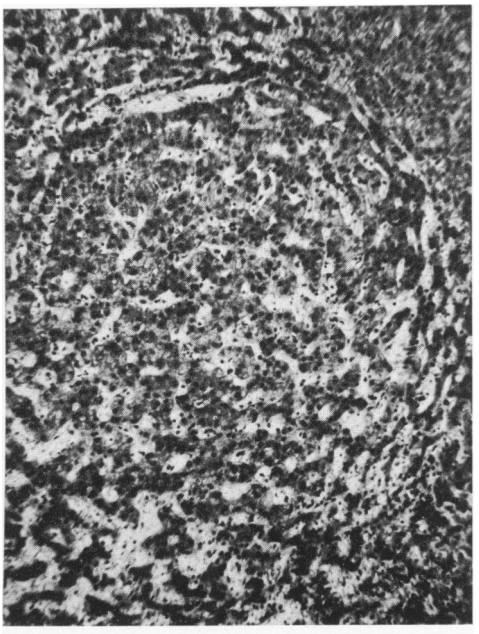
FIG. 6. The regenerative nodule is adjacent to a small central vein, seen above. Compression effects and atrophy of adjacent liver cords are evident. Case 5. Man, age 20, died after many bouts of decompensation; chronic rheumatic valvular disease. × 75.

FIG. 7. One distinct nodule and margins of others, set off by compressive and atrophic alterations. Woman, age 62. × 110.

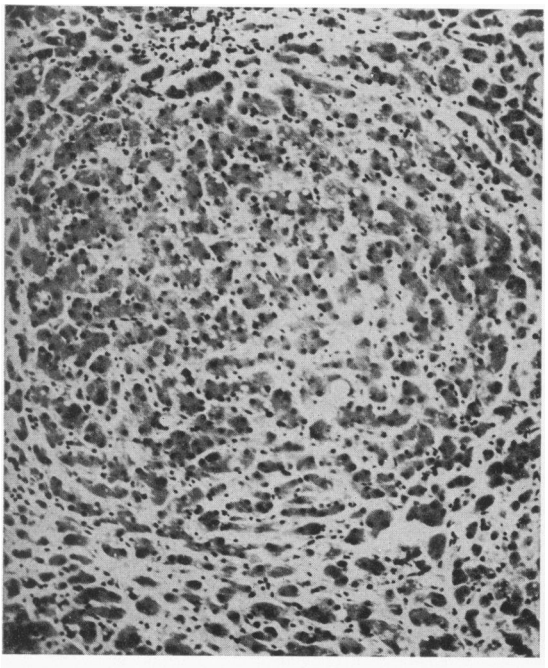
FIG. 8. A high power view within nodule to show atypical plump cords, enlarged liver cells, and frequent binucleate cells found in new hepatic tissue. Hyperchromatism and enlargement of many nuclei may be seen. Case 4. × 365.



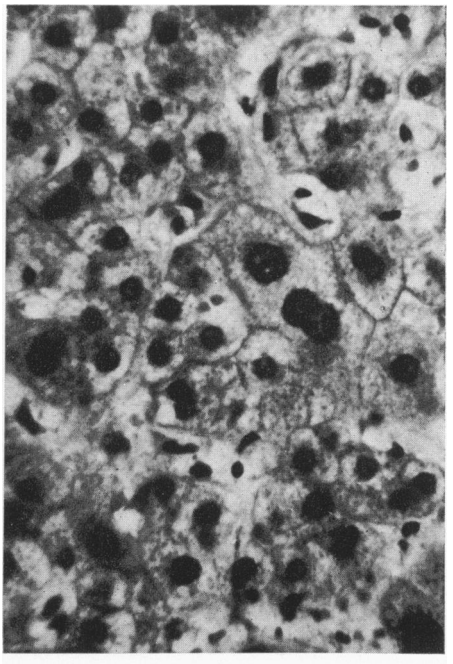
5



6



7



8

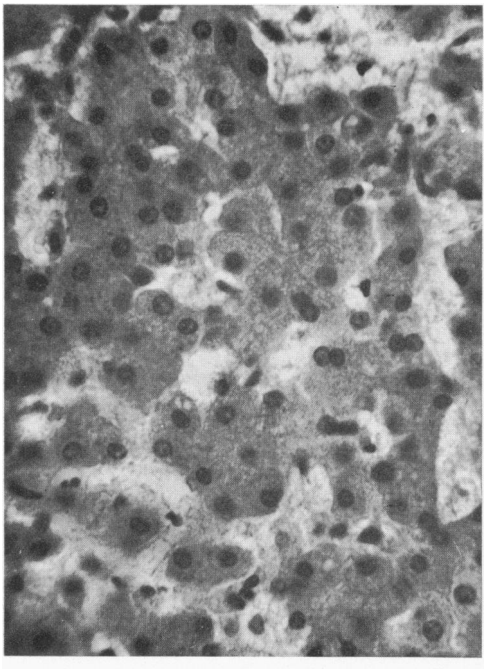
FIG. 9. Another high power view within nodule, showing atypical plump cords, enlarged liver cells, and frequent binucleate cells. Case 1. × 365.

Figures 10 to 12 illustrate in greater detail the zones between the nodules which falsely produce the appearance of septums or bands.

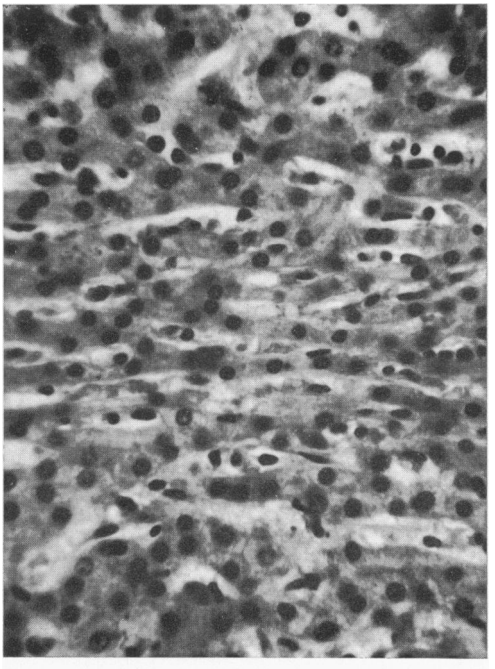
FIG. 10. A distinct band-like zone consists chiefly of greatly compressed liver cords with atrophic cells. Case 2. × 322.

FIG. 11. A branching structure, which separates regenerative nodules, consists of displaced and compressed portal and central structures and their surrounding supporting tissues. There is here no new formation of fibrous tissue. Case 3. × 85.

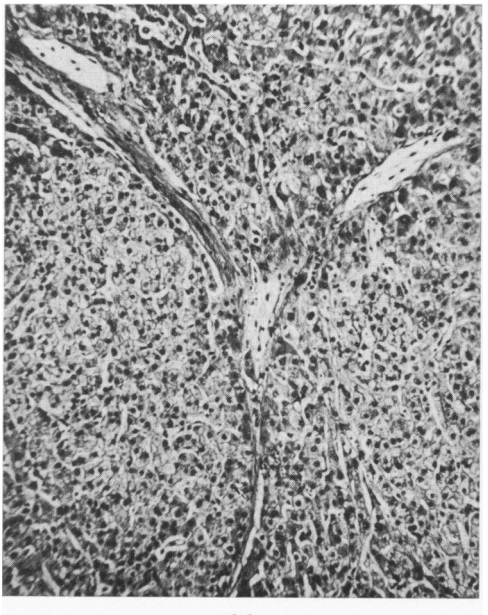
FIG. 12. The band-like zone at the margins of a distinct nodule is composed of collapsed hepatic stroma and leukocytes; hepatocytes have disappeared. Special stains showed condensation of pre-existing fibrillar structures in such areas, with a relative increase but no recognizable new formation. Case 8. × 322.



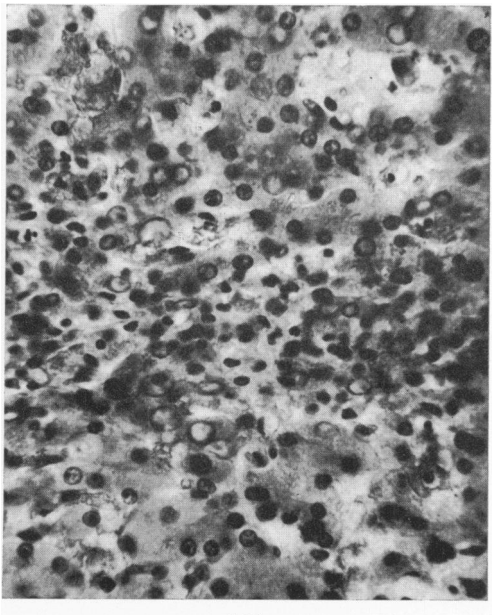
9



10



11



12