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Quantitative-Morphologic Evaluation of Postnecrotic Cirrhosis*

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With 6 Figures in the Text

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"Postnecrotic necrosis" (KARSNER) has been an accepted term in the various classifications of liver cirrhosis (Fifth Pan-American Congress of Gastroenterology GALL; STEINER), but investigators differ widely in their definitions. Differences in the evaluation of their morphologic criteria have resulted in discrepancies in diagnosis, interpretation, and clinical-pathological correlation (BAGGENSTOSS and STAUFFER; DASILVA et al.; MCDONALD and MALLORY; RATNOFF and PATEK), as well as a widely varied reported incidence of postnecrotic cirrhosis (Table 1). Thus a comparison of the incidence of this form of cirrhosis as reported by pathologic institutes in different geographic areas is difficult, frequently impossible. The frequent overlapping of the morphologic features of portal cirrhosis and postnecrotic cirrhosis, a matter of subjective interpretation, has led to use of the terms "mixed" and "intermediate" types of cirrhosis [BAGGENSTOSS and STAUFFER; GALL; POPPER et al. (2); THALER]. For clarification of this problem, the cardinal features of cirrhosis, when possible, should be analyzed by quantitative methods.

Table 1. *Incidence of postnecrotic cirrhosis (morphologic observations)*

%	
2.11	ADELHEIM, Riga — Quoted after FIESSINGER, 1931
1.00	ASCHOFF, Freiburg — Quoted after FIESSINGER, 1931
2.50	MARESCH, Vienna — Quoted after FIESSINGER, 1931
5.60	ROESSLE, Berlin — Quoted after FIESSINGER, 1931
5.67	HENSCHEN and BRUCE, Stockholm, 1931
8.40	MALLORY, Boston, 1932
10.00	KARSNER, Cleveland, 1943
5.63	PATEK, New York, 1948
26.40	KNUECHEL, Karlsruhe, 1953
18.70	LUNZENAUER, Berlin, 1955
9.24	MCDONALD, Boston, 1956
50.52	MONTENEGRO, Sao Paulo, 1957
18.60	KETTLER, Berlin, 1958
58.40	BOERNER, Bonn, 1960
8.10	GALL, Cincinatti, 1960
55.66	POPPER, New York—Chicago, 1960
55.26	RUBIN, New York—Chicago, 1961

Listed according to year of publication.

The present study was undertaken to quantitate the following morphologic features which appeared important for the characterization of postnecrotic cirrhosis: (1) the size of the regenerative nodules; (2) the ratio of multilobular to pseudolobular nodules, and (3) the number of areas of primary collapse in multiple liver sections.

Material and Methods

From the autopsy material of Cook County Hospital, 300 cases of liver cirrhosis were examined between 1956 and 1960; 219 cases fulfilled the required criterion of advanced cirrhosis in that there was a complete nodular transformation of the hepatic parenchyma. In most cases, preserved organs or large slabs of liver tissue were available; in 71 cases wet

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tissue from stock bottles had to be used. From this material the following determinations were made: 1) Average nodular size and range of nodular size were measured in 145 cases with five to eight histologic sections, and in 64 cases with fewer than five sections but always more than one section. 2) Percentage of multilobular and pseudolobular nodules was figured in 146 cases with five or more sections, and in 73 cases with two to four sections. 3) Number of areas of collapse with three or more portal tracts enclosed in mesenchymal tissue was counted. The results from 1, 2, and 3 were compared with sex and age of the patients and weight of the cirrhotic livers.

Numbers and Sites of Sections

Usually, the cirrhotic process does not affect the liver uniformly. Therefore, the number of sections and the sites from which they were taken had to be considered. Tissue sections were obtained from seven standardized sites of the liver (size of the sections, 2×3 cm). The sites of the liver to which variations in the cirrhotic pattern had been ascribed were included: vicinity to capsule, inferior or superior surface, left and right lobe, caudate or quadrate lobe. Standardized sites were selected accordingly: (1) midportion of the liver, including the capsule of the superior surface; (2) midportion of the liver, distant from the capsule; (3) midportion of liver, including the capsule of the inferior surface; (4) left lobe with edge; (5) right lobe with edge; (6) caudate lobe; (7) quadrate lobe. An additional large section (3×4 cm) included the capsule of the superior surface of the liver and extended deeply into the subjacent parenchyma.

The sections were stained with hematoxylin-eosin; Mallory's aniline blue-orange "G" as a connective tissue stain for evaluation of the nodular pattern and visualization of the areas of early collapse; Van Gieson's elastica (Hardt's modification) for demonstration of older areas of collapse and remaining vascular landmarks. Silver impregnation for reticulin (Gomori) was done in selected cases.

Measurement of Nodules

All distinct nodules were measured by two methods: (A) projection of the histologic sections (Mallory's aniline blue stain) and determination of the largest diameter of the individual nodules on the projection screen ($24\times$ magnification)[1]; (B) measurement of the largest diameter of cirrhotic nodules under the low power microscope ($10\times$ magnification) with a ruler graded to 0.25 mm.

In the first five cases, the following determinations were done: (A) measurement of every nodule on the microscopic section by the projection method. (B) measurement of ten adjacent nodules by the microscopic method. Two of the five cases represented the opposite extremes (i.e. small nodular and coarse nodular cirrhosis), the others, cirrhosis with apparent medium-sized nodules. To simplify the procedure, in the subsequent 50 cases only 10 adjacent nodules were measured, wherein the smallest and the largest nodules of

[1] *Essential considerations for quantitative evaluation of morphologic features in tissue sections are:*

a) The thickness of the section must be adapted to the size of the object to be measured. The acceptable limitation of the error in evaluation is up to 10%, provided the largest dimension of the structures measures 5 microns or above; and the thickness of the sections used is 5 microns or more. A certain magnification is also necessary, and under the conditions mentioned, $10\times$ will suffice. Even the visual acuity of the observer (age) must be considered in the evaluation of measurements (Haug).

b) From the point of view of comparison, uniformity of the concentration of fixative as well as duration of the fixation is required. Shrinkage of the volume of the liver is reported to be up to 52% in the formalin fixed, paraffin embedded tissue. Moreover, shrinkage affects the various tissue components of the organ differently. These factors have to be considered to obtain the approximate actual size of the structures measured (Wuestenfeld). Uniformity of preparation was carefully maintained in all cases studied. The above factors, therefore, would have only negligible effect on relative measurements regardless of their effect on absolute values.

each section were included. The range of nodular size was determined by measuring the differences between the largest and the smallest cirrhotic nodule in each section. Recorded were: the largest diameter of the individual nodules, the average value for each section, for each case (multiple sections), and for the entire material. The range of nodular size was also registered for each slide, for each case, and for the total number of cases.

Differential count of multilobular versus pseudolobular nodules for determination of their ratio. In every section, five 10× areas (four corners and one center area of the section) were examined. All nodules which enclosed portal areas or definite central veins or both were designated as multilobular nodules. When doubt existed as to the presence of central veins, the nodule was not counted as multilobular. Four possible sources of error had to be considered: (1) missing portal areas in two dimensional evaluation of a nodule; (2) misinterpretation of tongue-like projections without demonstrable connection with multilobular nodules, as portal tracts; (3) mistaking venous transformation of sinusoids for central veins, and (4) misinterpreting connective tissue strands encased in nodular parenchyma as portal tracts. These errors, which occur as a result of the two dimensional evaluation (HAMMER) of cirrhotic nodules, are compensated for by the great number of nodules examined in the individual sections and by using multiple sections. In the differentiation between multilobular and pseudolobular nodules, the main emphasis was placed on finding portal tracts enclosed in the nodular parenchyma.

Counting areas of primary collapse. Evidence of areas of primary collapse was evaluated according to the accepted criteria (STEINER, BAGGENSTOSS), i.e. presence of three or more distinct portal tracts enclosed in collapsed collagenized or non-collagenized reticulum framework. Independent of the evaluation of these data, areas of collapse with less than three enclosed portal areas were studied. The latter data will be analyzed to attempt a revision of the accepted criteria of collapse areas. These data will be reported elsewhere.

Statistical evaluation. If one accepts the two separate types of cirrhosis, portal and postnecrotic, as having distinct morphologic features, one would expect a bimodal distribution curve of the incidence of features that distinguish the two types of cirrhosis: (1) nodular size and range of nodular size; (2) percentage of multilobular and pseudolobular nodules; (3) areas of collapse. The two modes of this curve would represent portal and postnecrotic cirrhosis respectively.

The technique employed in this study is a quantitation of the three factors mentioned. The purpose of this study is to test the assumption of the presence of bimodality of the distribution curve of these parameters, thus providing justification for the strict separation of these two types of cirrhosis. On the other hand, assuming that there is no basic morphologic difference between these two types of cirrhosis, one would expect that the distribution of each of the factors studied would result in a unimodal curve. With regard to these three parameters the assumption was made that their distribution would not significantly differ from a Gaussian curve. Predictions were made of the number of cases falling within the various segments of the normal distribution curve. These segments were: (1) the mean plus or minus one standard deviation; (2) all values larger than the mean plus one standard deviation; (3) all values less than the mean minus one standard deviation. The predicted values of these segments based on a normal distribution are approximately: (1) 67%, (2) 16%, (3) 16%. The distribution of the observed frequencies was then compared with the predictions.

Analysis of variance was employed to determine if the nodular size was influenced significantly by the site chosen for study. Analysis of the areas of collapse was by means of prediction based on the binomial distribution.

Results

In 35 sections (5 cases), the average nodular size and range of nodular size were determined by two methods: counting all nodules and counting 10 adjacent nodules. The difference between these methods is highly significant. However, the values by the "10 count" method are closely correlated with those by the "all count" method (for average nodular size, $r = 0.68$, $p < 0.001$) i.e. the values obtained by the "10 count" method constantly found to be higher than those of the "all count" method. Since we were interested in the relative distribution

of nodular size rather than the absolute size of nodules, the "10 count" method, because of its obvious simplicity, was adopted. The results obtained by using this method in 50 cases are illustrated in Table 2. Two-thirds of the cases were within one standard deviation of the mean. The remaining third was almost equally distributed, falling into the low and high extreme ranges. Thus, the extreme cases described in the literature as two different entities, fine nodular (synonymous with portal, septal, nutritional etc.) cirrhosis and coarse nodular (synonymous with post-necrotic, post-collapse) cirrhosis, proved to be of the number of one would expect in a homogeneous population of normal distribution.

Table 2. *Average nodular size by "10 counts" in 50 cases*
Grand mean (M) 1.4 4mm; standard deviation (s) 0.579 mm.

	Groups		
	A ($<m-s$)	B ($m \pm s$)	C ($>m+s$)
Expected number of cases .	8	34	8
Observed number of cases	7	35	8

Table 3. *Range of nodular size by "10 counts" in 50 cases*
Grand mean 2.8 mm; standard deviation 1.5 mm.

	Groups		
	A	B	C
Expected number of cases	8	34	8
Observed number of cases	6	39	5

Table 4. *Comparison of classification by average nodular size and range of nodular size by "10 counts" in 50 cases*

	Groups		
	A	B	C
Distribution classified average nodular size	7	35	8
Distribution classified by range of nodular size	6	39	5

$r = 0.92$; $p < 0.0001$.

A similar curve of distribution was obtained by determination of the range of nodular size (Table 3). Classification by range and average nodular size is compared in Table 4. The average nodular size and range of nodular size showed such a close relationship ($r = 0.92$ $p < 0.00001$) that for further study the range alone was employed. In 159 additional cases only the largest and smallest nodules were measured to determine the range of the nodular size. Although the observed values are skewed to the right, which undoubtedly is the result of always being able to pick out the largest nodules, there was no evidence of bimodality. These results are summarized in Table 5.

Table 5. *Range of nodular size in 209 cases*
Grand mean 2.748; standard deviation 2.047

	Groups		
	A	B	C
Expected number of cases	33	143	33
Observed number of cases	1	166	42

$\chi^2 = 35$; $p < 0.001$.

With regard to both, range and average nodular size, no significant difference could be demonstrated between the different sites of the liver (Table 6). There-

Table 6. *Analysis of variance to evaluate the difference between sites of the liver with regard to average nodular size and range*

Variance source	Average nodular size			Range of nodular size		
	DF	SS	MS	DF	SS	MS
Between sites	6	3.5904	0.5984	6	21.0541	3.5090
Between patients. . .	4	67.7762	16.9440	4	200.6126	50.1532
Residual	24	8.5372	0.3556	24	78.7487	3.2812
Error	35	15.3013	0.4372	35	130.0531	3.7158
Total	69	95.2051	18.3352	69	430.4685	60.6592
	$F<1.37$; $P>0.20$			$F<1.00$; $P>0.50$		

DF = Degrees of Freedom, SS = Sums of Squares, MS = Mean Square, F = FISHER's Variance Ratio, P = Probability of occurrence by chance alone.

fore, the stored large slabs of cirrhotic livers, in which standardization of the sites are impossible, could also be utilized for this study.

To simplify the requirements for characterization of the nodular size of the cirrhotic liver, the statistical reliability of the mean nodular size obtained by evaluation of three sections was tested. A comparison of the mean of three random sections with the results from 7 to 11 other sections in 10 cases showed no significant difference in mean nodular size and range of nodular size ($t<1$ $p<0.05$). Therefore the classification of cirrhotic livers by the three sections method would be comparable to that when 5 or more sections are used.

Significant differences were evident on comparison of the mean nodular size and range of nodular size as determined for one single large section, and the values obtained by measuring 10 nodules from five to seven standard size sections (average nodular size: $t=5.01$ $p<0.001$, range: $t=3.26$ $p<0.05$). Therefore, a single large section cannot replace multiple (at least three) routine sections.

According to either the mean nodular size or range of the nodular size, advanced cirrhosis could be divided into 3 groups: Group A, smaller than mean values minus one standard deviation, classified as "fine nodular cirrhosis"; Group B, "mean nodular cirrhosis", including the cases with mean values, plus-minus one standard deviation; Group C, cases of cirrhosis with higher than mean values, plus one standard deviation, "coarse nodular cirrhosis" (Fig. 1). There was no sharp demarcation between the groups, but rather a smooth transition, and a steep increase in the number of cases toward a grand mean. The borderlines were determined by statistical methods.

Table 7. *Percentage of pseudolobules*

Calculated as: $\frac{\text{Number of pseudolobules}}{\text{Total number of nodules}} \times 100$

Grand mean 72.82%; standard deviation 16.73%.

	Groups		
	A	B	C
Expected number of cases	35	148	35
Observed number of cases	34	156	29

The percentage of pseudolobules (calculated by the number of pseudolobular nodules over the total number of nodules times 100) was normally distributed (Table 7). In rare instances 100% pseudolobularity was observed. A 100% multilobularity of the nodules was never approached. Cirrhosis with a predominance of multilobular nodules had at

least 15% pseudolobular nodules. The vague relationship of pseudolobularity or multilobularity of nodules to nodular size became evident in some of the fine nodular cirrhotic livers with predominance of multilobular nodules. There were no cases of cirrhosis with uniformly large multilobular nodules. In general the predominance of large nodules (Group C) coincided with a predominance of multilobular nodules. Distinct groups of uniformly small pseudolobular and uniformly coarse multilobular cirrhosis were not found. The mean proportion of

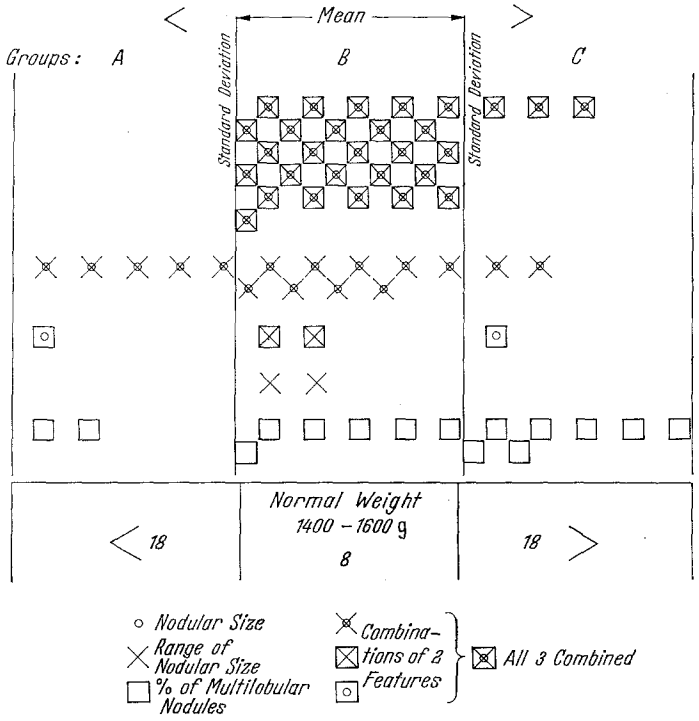

Fig. 1. Distribution of 50 cirrhotic livers, according to average nodular size, range of nodular size, and percentage of multilobular nodules

pseudolobular nodules in the entire material was 72% with a standard deviation of 17%.

Difficulties were not encountered in the identification of recent areas of collapse, which were distinct due to the well defined portal tracts. These were surrounded by the collapsed reticulum framework in which collagenization had not yet begun, or in which there was incomplete collagenization. The collagen fibers of the portal tracts stained deeper blue with Mallory's aniline-blue. The individual thick collagen fibers were arranged concentrically (Fig. 2). In more advanced collagenization of the areas of collapse, Van Gieson's elastica stain (Hardt's modification) proved advantageous. Plump elastic fibers within the portal areas showed a tendency to concentric alignment while only occasional short and thin elastic fibers were seen within the collagenized areas of collapse. In older areas of collapse, because of diffuse increase of elastic fibers, the portal tracts became more and more indistinct and finally indistinguishable from the adjacent areas of fibrous connective tissue bands and scars. In a still later stage

the elastic tissue may uniformly decrease in the collagenized collapse areas and in the portal tracts.

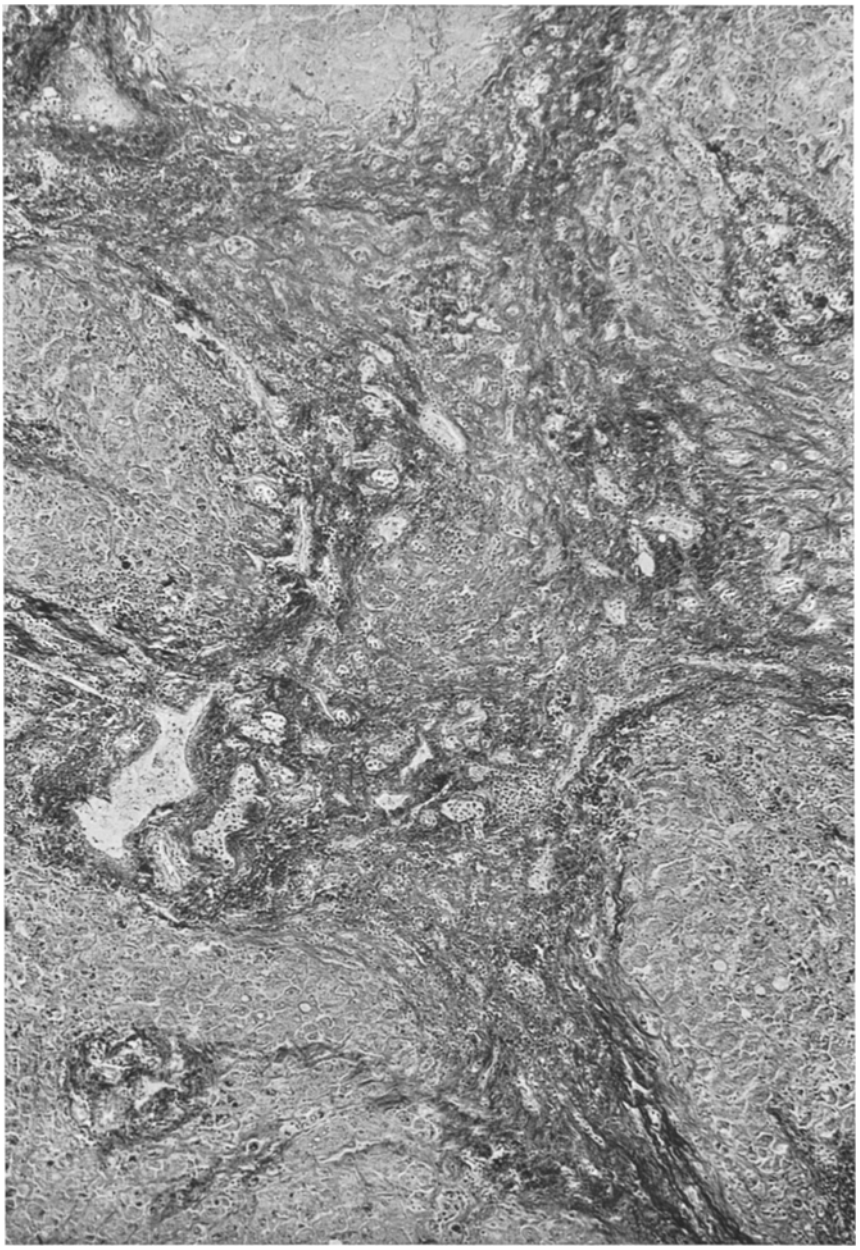

Fig. 2. Collagenization of collapsed reticulum framework. The borderline of enclosed portal tracts are somewhat indistinct, MALLORY's aniline blue-orange G, 45 ×

Areas of collapse may be absent in some sections and present in others. Differences could not be demonstrated among any of the seven standardized areas in regard to presence or absence of areas of collapse ($X^2 = 3.8$ $p > 0.05$). The number of areas of collapse in sections from sites 1, 2, and 3 averaged 30%

higher than the number of areas of collapse seen in sections sites 4 through 7. In other words, quantitative but not qualitative differences were evident by comparing the counts from multiple sections taken from standardized sites of the liver. Determination of the average number of areas of collapse in individual cases revealed that as the average number of areas of collapse increased, the number of sections failing to show any areas of collapse decreased. It is noteworthy that sections without any areas of collapse became exceptions, if the mean value of areas of collapse for five to seven sections was more than one (Table 8).

Table 8. *Distribution of areas of collapse (AC)*

No. cases	No. sections	Mean no. of AC	No. sections without coll.	No. cases	No. sections	Mean no. of AC	No. sections without coll.
30	191	0	191 (100%)	10	46	3.1—4.0	2 (4.4%)
29	174	0.1—1.0	96 (55%)	4	20	4.1—5.0	0 (0%)
23	137	1.1—2.0	6 (4.4%)	4	22	5.1—6.0	0 (0%)
10	54	2.1—3.0	2 (3.7%)	4	22	6.1 and more	1 (4.6%)

In a single case one may see areas of collapse of various ages. Indeed, in a single section one may see different degrees of collagenization of the areas of collapse in the same microscopic area. Since with increasing age the portal tracts become indistinguishable from the surrounding areas of collapse, only recent or moderately advanced areas of collapse could be unequivocally identified. One may safely assume, therefore, that the actual number of areas of collapse had to be higher than could be determined by the methods employed.

Some large areas of collapse enclosed relatively few or no portal tracts. In other areas of collapse, which were compressed to small size by adjacent large regenerating nodules, numerous portal tracts could be identified. Areas of collapse, according to the accepted criteria (three or more enclosed portal tracts), were found in 77.6% of the entire material by surveying multiple sections. The incidence in Group A (fine nodular cirrhosis) was 42.85%, in Group B (mean nodular cirrhosis) 62.5%, and in Group C (coarse nodular cirrhosis) 100%. Although the incidence of areas of collapse in Group C was highest, the number of such areas in each case was unrelated to the average nodular size of the respective group. Thus, no direct relationship could be established between the number of areas of collapse and size of nodules or range of the nodular size.

No relationships could be demonstrated between any of the following parameters: weight of liver, age of patient, sex of patient, average range of nodular size, nodular size, percentage of multilobular or pseudolobular nodules, incidence of collapse. It was found that the majority of the cirrhotic livers weighed either more or less than the usually accepted range (1400—1600 gms). None of the three groups showed any particular tendency to the low or high values in liver weight (Fig. 1).

Discussion

The lack of uniformity in terminology, diagnostic criteria, and interpretations of postnecrotic cirrhosis is still the cause of disagreement [KARSNER; MALLORY (1, 2); KLEMPERER; MARCHAND; HIMSWORTH; SMETANA; BAGGENSTOSS and STAUFFER]. Is postnecrotic cirrhosis an etiologic term (posthepatitic or post-toxic

cirrhosis) or does it indicate a specific pathogenetic pathway (post-collapse cirrhosis), or should it be applied as a purely morphologic diagnostic term? The etiologic implication (posthepatitic or post-toxic) of postnecrotic cirrhosis is no longer acceptable, for areas of collapse are observed in experimental (HARTROFT) and human cirrhosis [POPPER et al. (2); RUBIN et al.] of nutritional etiology. Experimentally, coarse nodular cirrhosis has been produced by ethionine [POPPER et al. (1)]. Some investigators proposed use of the term postnecrotic cirrhosis in a pathogenetic sense, implying that postnecrotic cirrhosis is the result of a submassive or massive liver cell necrosis with subsequent collapse of the reticulum framework (post-collapse cirrhosis) (BAGGENSTOSS; POPPER and ELIAS; THALER). STEINER considered postnecrotic cirrhosis to be a purely morphologic entity characterized by the presence of areas with evidence of primary collapse, without any reference to a specific nodular pattern or nodular size. BAGGENSTOSS believed that one was forced to choose between the size of scars or the size of nodules as the pivotal diagnostic point in classifying hepatic cirrhosis. The Registry of Liver Pathology of the Armed Forces Institute of Pathology stated, "it is believed that postnecrotic cirrhosis should be employed as a morphologic diagnosis only, and should not be interpreted as implying a specific etiology".

Our evaluation of the criteria of postnecrotic cirrhosis is based on: (1) measurement of the nodules; (2) differential count of the multilobular versus pseudolobular nodules; (3) recording of the areas of primary collapse. An exact definition of the parenchymal nodules and of the areas of collapse is essential. Nodules are pathologic structures of the liver parenchyma, surrounded by wide or narrow connective tissue bands. One may differentiate between: (A) active or passive, and (B) pseudolobular and multilobular nodules.

A. Passive nodules are portions of liver parenchyma surrounded by connective tissue bands. The proliferating connective tissue forms active septums which dissect the liver parenchyma, resulting in formation of passive nodules (Fig. 3). Active nodules arise either from the rapid and disorderly regeneration of liver parenchyma surrounded by collapsed reticulum framework, or from passive nodules with active regeneration of hepatic cells. The collapsed reticulum framework may be compressed by active nodules and may become collagenized to form passive septums or bands [POPPER; POPPER et al. (2); RUBIN et al.].

B. Pseudolobular nodules consist of small or large segments of the lobules with absence of landmarks such as portal tracts and central veins. Passive pseudolobular nodules are derived from the active septal dissection of the liver lobules. Active pseudolobular nodules take their origin from small clumps of liver parenchyma entrapped in areas of collapse (Fig. 4), or strands of fibrous connective tissue. The term "monolobular nodules" was used in the literature for hexagonal lobular pattern[1] accentuated by perilobular fibrosis. This is seen in biliary fibrosis and in the so-called posthepatitic cirrhosis described by GALL. A similar pattern "physiologically" occurs in the liver of the pig (ELIAS). In our opinion, the term "monolobular nodule" is a misnomer, because such a lobule as a well delineated unit does not exist. The fibrotic process apparently sur-

[1] At present, we are still using the term lobules as hexagonal lobules; however, we are studying the possibility of the application of the acinar concept of RAPPAPORT (1, 2) for the pathogenesis and classification of hepatic cirrhosis.

rounding a lobule is, in fact, a replacement fibrosis, replacing degenerated and necrotic lobular parenchyma.

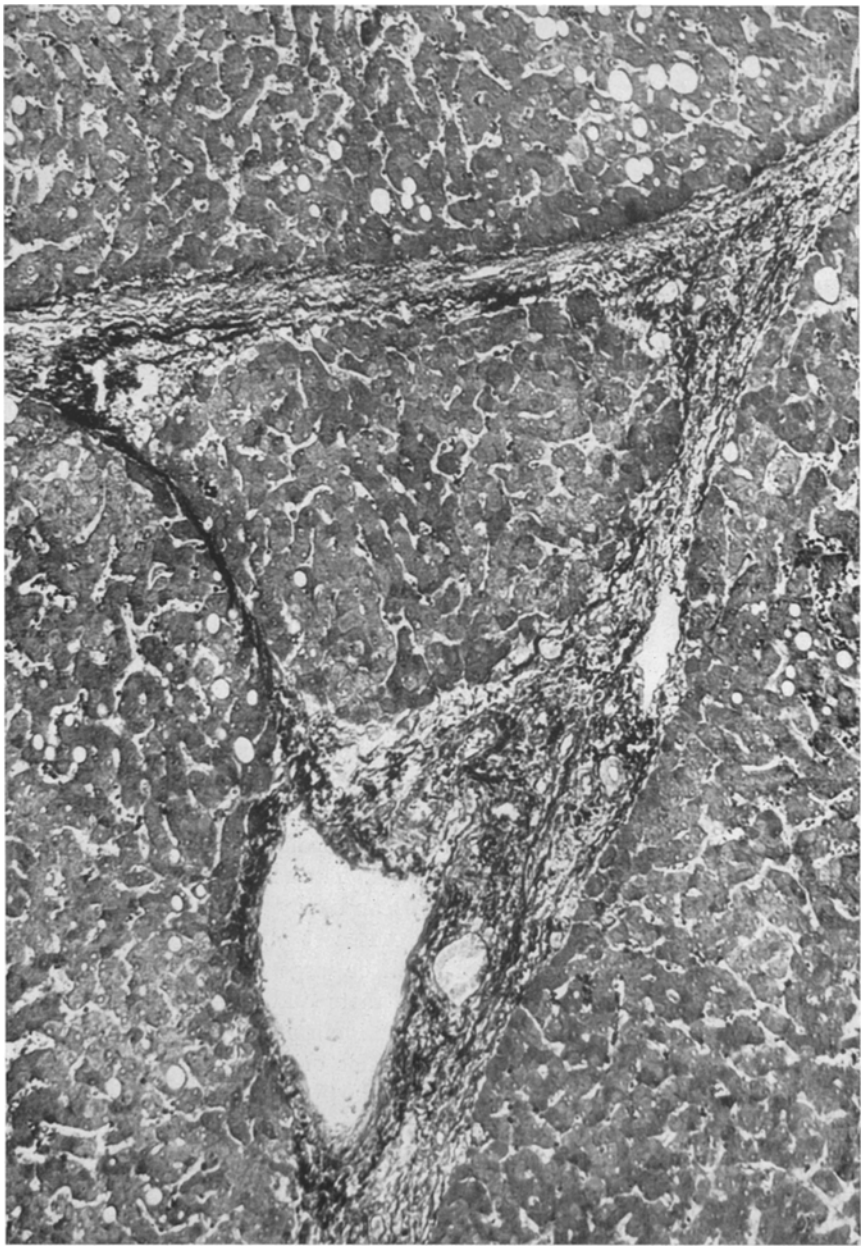

Fig. 3. "*Passive nodule*": Dissected portion of liver parenchyma, surrounded by fibrous connective tissue. Identical arrangement of liver cell plates within "passive nodule" and within "lobular" parenchyma. Mallory's aniline blue-orange G, 69 ×

Multilobular nodules are formed from small or large segments of two or more adjacent lobules bound together by connective tissue septa. In such instances, not only the landmarks, such as portal areas and central veins, but also the original arrangement of the liver cell plates still can be identified. Focal

hepatocellular regeneration resulting in "nodules within nodules" [POPPER et al. (2); RUBIN et al.] causes disarray and distortion of the liver cell plates (Fig. 5). If this regeneration is not only focal but diffuse and markedly active, it will result in a complete distortion of the hepatic parenchyma of the multi-

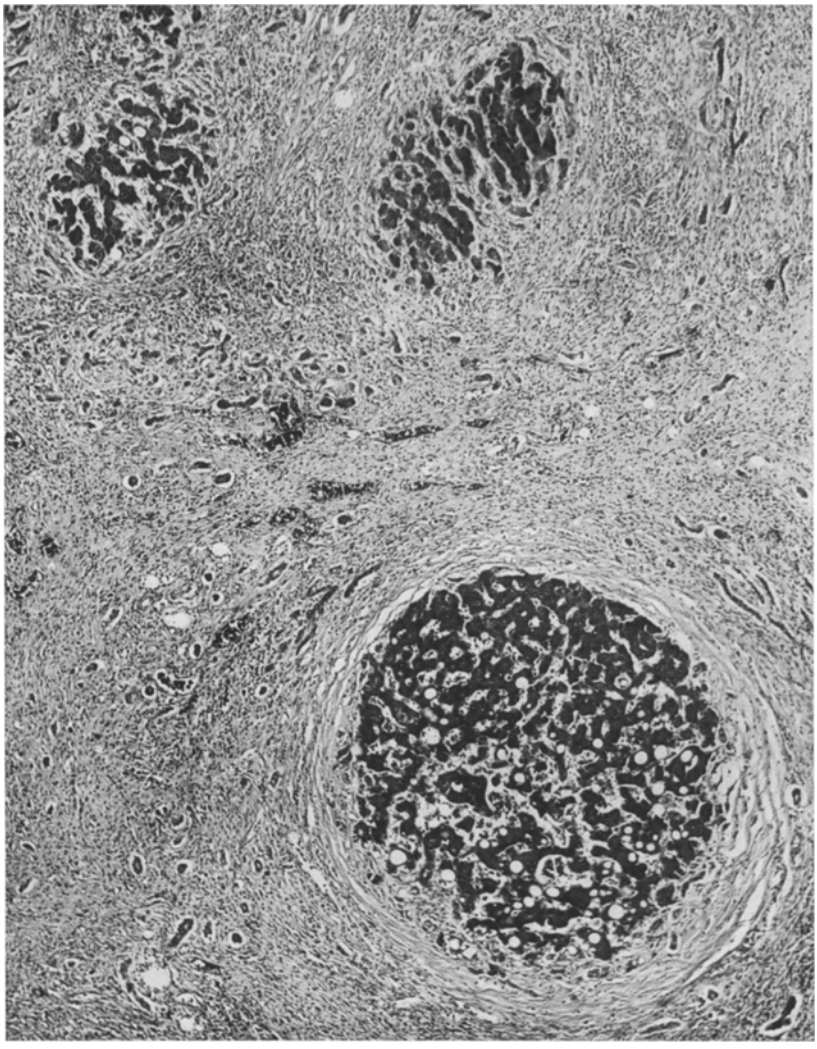

Fig. 4. Active pseudolobular nodule: collapse areas enclosing regenerative nodule, with disorderly arrangement of liver cell plates. Ill-defined clumps of liver cells forming starting points of nodular regenerates. GOMORI's trichrome, 50 ×

lobular nodules (Fig. 6). Marked regenerative activity usually results not only in disarray of the liver cell plates but also in predominance of two-or-more-cell-thick liver cell plates. These types of multilobular nodules should be called "active" in contrast to "passive" multilobular nodules that show preservation of the lobular pattern. Multilobular nodules are not always larger than pseudolobular nodules. The size of a nodule, pseudolobular or multilobular, depends on a dynamic process and may increase by active regeneration or decrease by necrosis and further septal dissection. Passive multilobular nodules may become

larger with transformation into active multilobular nodules. Similarly, pseudolobular nodules may also enlarge due to increased regenerative activity. The

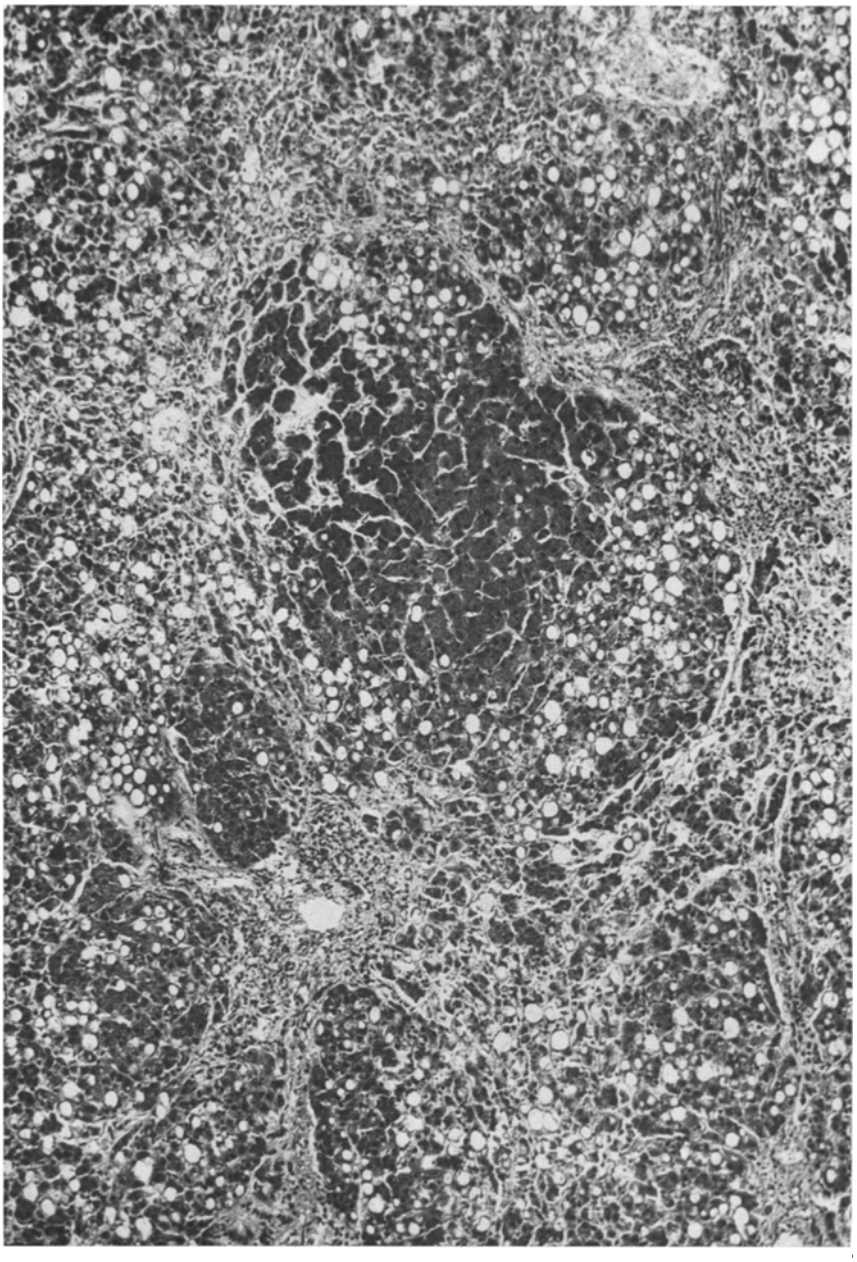

Fig. 5. Cirrhotic liver with fatty change, showing "nodule within nodule", with mosaic pattern of liver cell plates and absence of fatty changes in the regenerated liver cells. Gomori's trichrome, 61 ×

possibility of reconstruction of portal area-like structures transforming pseudolobular nodules into multilobular-like nodules also has to be considered. On the other hand, further dissection of large multilobular nodules by connective tissue septums may decrease their size or may even transform them into pseudolobular

nodules. As long as the cirrhotic process is active, the nodule remains poorly delineated and limiting plate is absent (EPPINGER; NUNES).

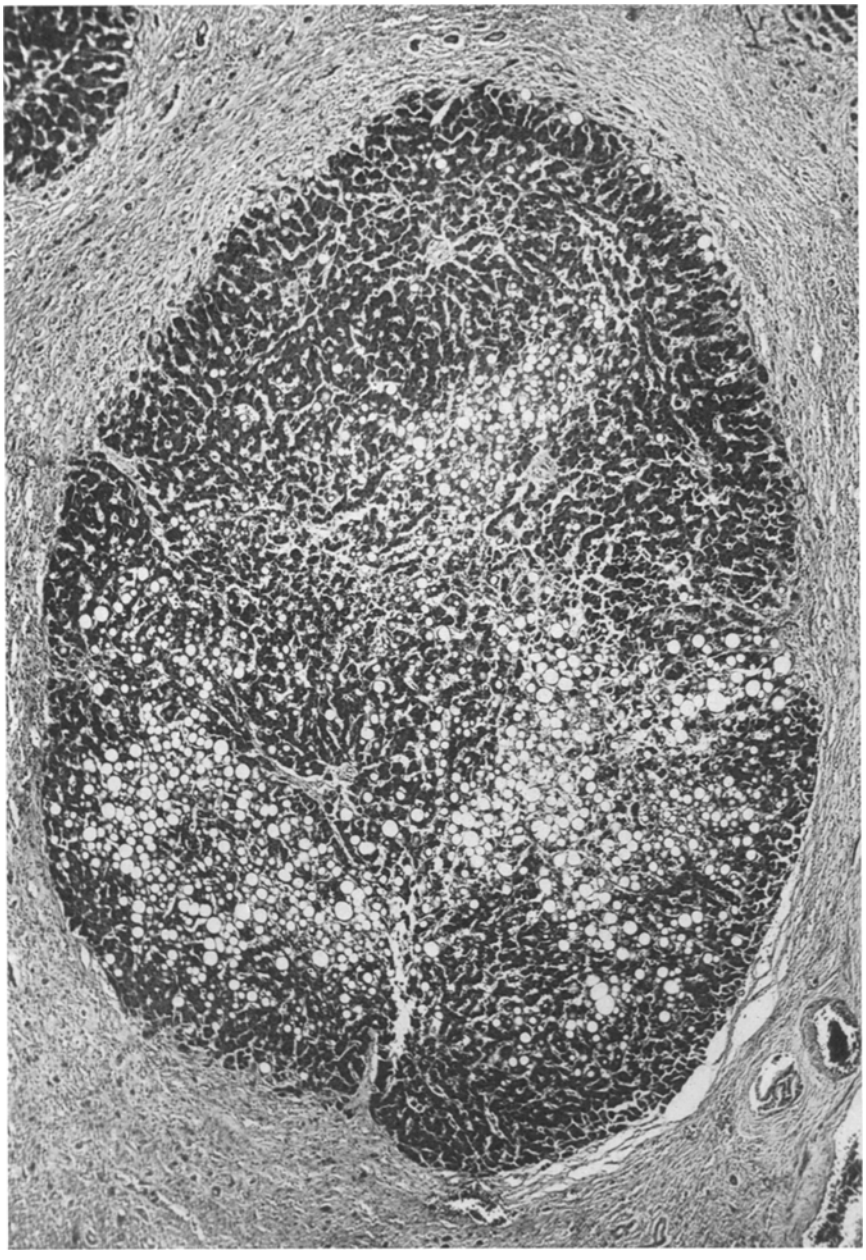

Fig. 6. Multilobular nodule with disarray of liver cell plates. Enclosed portal tracts show varying degree of fibrosis. GOMORI's trichrome, 42 ×

Evaluating the importance of so-called areas of primary collapse, two facts emerge:

(1) If one takes the primary areas of collapse as a significant diagnostic criterion, one has to accept as postnecrotic cirrhosis any cirrhotic liver showing

even one area of mesenchymal tissue with three or more enclosed portal tracts and without continuous liver parenchyma. Evaluation of multiple sections would significantly increase the chance of finding such areas of primary collapse. As was shown previously, in many instances only a few areas of collapse were observed in one or two of the five to seven sections examined. Therefore, the incidence of postnecrotic cirrhosis diagnosed on the basis of this criterion would greatly depend on how many sections were examined.

(2) As has been pointed out, areas of collapse enclosing one or two portal tracts can be larger than those with three or more portal tracts. The incidence of primary collapse would increase significantly, considering areas with less than three portal areas as evidence of collapse.

Another shortcoming of usage of the areas of collapse as an exclusive diagnostic criterion of postnecrotic cirrhosis is, that by progressive collagenization of the areas of collapse the enclosed portal tracts become more and more indistinct and finally unrecognizable, merging into broad scars. Collapse cannot be used interchangeably with broad scars, if one adheres to the criterion of three enclosed portal tracts as the only criterion of collapse and the portal tracts can no longer be identified. Baggenstoss pointed out that the extent of nodular regeneration is an important factor for the final size of the adjacent areas of collapse and the resulting scars. The size of the nodules is an expression of the degree of regenerative activity of the cirrhotic liver and it influences the pattern of the adjacent areas of collapse and the shape of the adjacent fibrous bands. Large nodules can compress areas of collapse to relatively narrow bands with parallel arrangement of the collagen fibers, whereas small nodules permit the transformation of the adjacent areas of collapse to broad scars.

It is important to distinguish between primary and secondary collapse. Secondary collapse occurs only in cirrhotic livers. No landmarks, such as portal tracts, can be expected in the areas of collapse if pseudolobular nodules are involved. However, in areas with predominantly multilobular nodules, the differentiation between primary and secondary areas of collapse becomes virtually impossible because of the presence of portal tracts in multilobular nodules.

The exact number of central veins in areas of collapse could have been used as a measurement of the extent of collapse, expressing the number of lobules involved. However, this was almost impossible because numerous sinusoids in the areas of collapse assume a "central vein-like" appearance.

Having quantitated the incidence of the apparently crucial morphologic features of advanced cirrhosis, we compared our results with the results of other investigators based on qualitative evaluations of these features. Group C in our material presented the highest incidence of those morphologic features, which supposedly are characteristic of postnecrotic cirrhosis. Therefore, it is of interest to compare Group C with the postnecrotic cirrhosis of other investigators. The accompanying Table (9) summarizes the opinions of the various workers.

Karsner's definition of postnecrotic cirrhosis included coarse and unequal sized nodules and broad scars as found in Group C. Smetana emphasized the uniformity of the size of the nodules, in contrast to Karsner's postnecrotic cirrhosis and to Group C. A predominance of the multilobular nodules as

described by SMETANA, however, was observed in most cases of Group C.

BAGGENSTOSS and STAUFFER emphasized that evidence of collapse was found not only in coarse nodular but also in fine nodular cirrhosis. However, according to them, it was more frequently seen in the former. This is in complete agreement with our observations, inasmuch as areas of collapse were seen not only in Group C (coarse nodular cirrhosis), but also in Group B (mean nodular cirrhosis), and Group A (fine nodular cirrhosis). Whereas they were always present in Group C, the incidence of areas of collapse decreased from Group C to Group B to Group A. STEINER used the presence of areas of collapse as the sole criterion for postnecrotic cirrhosis, disregarding the other morphologic criteria, such as multilobularity of nodules, large or unequal size of nodules, and broad bands. Adhering to STEINER'S definition of postnecrotic cirrhosis, 77.6% of our cases of cirrhosis would belong to this group.

If one accepts that there are two distinct groups of cirrhosis with specific morphologic fea-

Table 9

Histologic features of postnecrotic cirrhosis	Edmondson and Anderson	Steiner	Gall	Boerner	Thaler	Montenegro	Havana Classification 1956	Ratnoff and Patek	Popper	Knuechel	Smetana	Baggenstoss and Stauffer	Himsworth	Karsner	Roessle	Mallory	Marchand
Irregular distribution of connective tissue	+	+	+	+	+	+	+	+	+	+		+		+			
Areas of collapse (grossly)-scars	+		(+)				+	+	+	+	+	+	+	+		(+)	+
Collapse, with approximation of portal tracs	(+)	(+)		+	+				+	++		++			(+)		
Variation in size of regenerative nodules	++	++	++	+	++	++		+	++	++	+	++		++		++	
Large nodules		++	+		++				(+)		+	++	+			++	+
Multilobular nodules		++	+	+	++				++			++					
Pseudolobular nodules		++	+			+			++				+				
Areas with normal architecture	++		++	+			+	·+				+	+	+		+	

+ Described, (+) emphasized, ++ occasionally or optionally present.

tures, one may expect a bimodal distribution curve of all the quantitated morphologic features with two independent modes. Assuming that overlapping in the incidence of some of these features may occur, a crossover between the two modes could be expected. However, in the material studied the quantitative evaluation of the average nodular size, the variation of nodular size, and the percentage of multilobular and pseudolobular nodules gave no justification for rejecting a unimodal distribution of the quantitated parameters. It appears that from the morphologic point of view the so-called postnecrotic cirrhosis represents only one extreme of cirrhosis in general.

The presence of collapse areas is by definition an all or none phenomenon. If one assumes equal chance for the presence or absence of collapse areas, then in the 219 cases studied, 50% or 110 cases should show collapse. The 95% confidence limits of the mean would be $110 \pm 12 = 158$ and 182, or from 72.1% to 83.1%. Therefore, if this is a representative sample, in 95 out 100 studies of 219 cases, 72% to 83% of the cases would be classified as postnecrotic cirrhosis assuming presence of collapse to be the sole criterion.

The recognition that "postnecrotic cirrhosis" represents one extreme of the normal distribution curve of all cirrhosis provides a more rational basis for the morphologic evaluation of cirrhotic livers than any single criterion, such as presence of collapse. It is possible that postnecrotic cirrhosis is a separate entity, but it could not be identified as such by the quantitative analysis of the morphologic criteria applied in this study.

Summary

This quantitative study has been undertaken for the exact evaluation of the morphologic criteria of "postnecrotic cirrhosis". Determination of the average nodular size, the range of nodular size, and the ratio of multilobular to pseudolobular nodules in 219 cirrhotic livers resulted in curves of normal distribution, with 66% of all cases concentrated around the mean value. There was an approximately equal distribution of the remaining 34% toward both extremes of the curves. According to average nodular size or range of nodular size, three groups of cirrhosis could be distinguished:

Group A: fine nodular cirrhosis (values smaller than the mean minus one standard deviation);

Group B: mean nodular corrhisis (values within the range of the mean plus or minus one standard deviation);

Group C: coarse nodular cirrhosis (values larger than the mean plus one standard deviation).

The incidence of areas of collapse in all cirrhotic liver examined by multiple sections was 77.6%. Group A showed areas of collapse in 44.85%, Group B in 66.15%, and Group C in 100%. Group C of our material was characterized not only by the large average size of the nodules, but also by the great variation of nodular size, and by the highest incidence of multilobular nodules and areas of collapse. Group A showed uniformity in the size of the nodules and the lowest incidence of areas of primary collapse.

This quantitative analysis of the basic morphologic criteria of hepatic cirrhosis failed to reveal a sharp or natural borderline between "postnecrotic cirrhosis" and "portal (LAENNEC's) cirrhosis".

Quantitative morphologische Bestimmungen bei postnekrotischer Lebercirrhose

Zusammenfassung

Zweck dieser quantitativen Untersuchung war die exakte Auswertung der morphologischen Kriteria der „postnekrotischen Cirrhose". Bestimmung der mittleren Knötchengröße, des Variationsbereiches der Knötchengröße und das Häufigkeitsverhältnis zwischen multilobulären und pseudolobulären Knötchen in 219 Lebercirrhosen ergaben Gaußsche Verteilungskurven. 66% aller Fälle lagen nahe dem Mittelwert. Die übrigen 34% der Fälle waren annähernd gleichmäßig zu beiden Seiten des Mittelwertes verteilt. Nach der mittleren Knötchengröße und dem Variationsbereich der Knötchengröße konnten drei Cirrhosegruppen unterschieden werden: Gruppe A: feinknotige Cirrhose (Werte kleiner als der Mittelwert minus einer Standardabweichung); Gruppe B: mittelknotige Cirrhose (Werte im Bereich des Mittelwertes, plus oder minus einer Standardabweichung); Gruppe C: grobknotige Cirrhose (Werte größer als der Mittelwert, plus einer Standardabweichung).

Kollapsfelder (nach den histologischen Kriteria von P. STEINER) lagen in 77,6% aller durch mehrere Schnitte untersuchten Lebercirrhosen vor. Gruppe A zeigte Kollapsfelder in 44,85%, Gruppe B in 66,5% und Gruppe C in 100%. Charakteristisch für die Gruppe C unseres Materials waren neben der groben Knötchengröße, die größte Variationsbreite der Knötchengröße und der größte Prozentsatz von multilobulären Knötchen und von Kollapsfeldern. Gruppe A dagegen zeigte gleichmäßige Knötchengröße und den kleinsten Prozentsatz von Kollapsfeldern.

Diese quantitative Analyse von Grundkriteria der Lebercirrhose ließ keine scharfe oder natürliche Trennungslinie zwischen „postnekrotischer Cirrhose" und „portaler (Laennecscher) Cirrhose" erkennen.

Bibliography

BAGGENSTOSS, A.: Postnecrotic cirrhosis. In: H. POPPER and F. SCHAFFNER, Progress in liver diseases, vol. 1. New York and London: Grune & Stratton 1961.

—, and M. STAUFFER: Posthepatitic and alcoholic cirrhosis. Gastroenterology **22**, 157 (1952).

BOERNER, P.: Die Einteilung und Benennung der Lebercirrhose. Virchows Arch. path. Anat. **333**, 269 (1960).

DA SILVA, L. C., M. R. MONTENEGRO, A. DE GODOY and J. F. PONTES: An evaluation of the problem of hepatic cirrhosis as seen in Sao Paulo, Brazil. III. Postnecrotic cirrhosis: Clinical aspects. Gastroenterology **34**, 1121 (1958).

ELIAS, H.: Liver morphology. Biol. Rev. **30**, 263 (1953).

EPPINGER, H.: Die Leberkrankheiten. Berlin: Springer 1937.

FIESSINGER, N.: La clinique des cirrhoses hepatiques. In: Conf. internat. de pathologie geographique, 1st Geneva 1931, p. 155. Geneva: Libraire Kundig 1931.

Fifth Pan-American Congress of Gastroenterology, La Habana, Cuba. Report of the board of classification and nomenclature of cirrhosis of the liver. Gastroenterology **31**, 213 (1956).

GALL, E.: Hepatic cirrhosis. Amer. J. Path. **36**, 241 (1960).

HAMMER, J.: Ein Fall von Thyreoaplasia. Z. angew. Anat. **5**, 218 (1920).

HARTROFT, W., and J. GRISHAM: Cirrhosis of postnecrotic type in choline deficient rats. Fed. Proc. **19**, 186 (1960).

Haug, H.: Bedeutung und Grenzen der quantitativen Meßmethoden in der Histologie. Med. Grundl.-Forsch. **5**, 299 (1962).
Henschen, F., and T. Bruch: Über die Häufigkeit und Formen der Lebercirrhose in Stockholm. In: Conf. internat. de pathologie geographique, 1st Geneva 1931, p. 237.
Himsworth, H.: Lectures on the liver and its diseases. Cambridge (Mass.): Harvard University Press 1947.
Karsner, H.: Morphology and pathogenesis of hepatic cirrhosis. Amer. J. clin. clin. Path. **13**, 596 (1943).
Kettler, L.: Die Leber. In Ed. Kaufmann, Lehrbuch der speziellen Pathologie, 11 and 12 ed., vol. II, part 2. Berlin: W. de Gruyter & Co. 1958.
Klemperer, P.: Pathology of icterus. N.Y. St. J. Med. **33**, 1309 (1933).
Knuechel, H.: Untersuchungen zur morphologischen Differentialdiagnose der Lebercirrhosen. Frankfurt. Z. Path. **64**, 9 (1953).
Lunzenauer, K.: Über die hämatogenen Leberzirrhosen. Frankfurt. Z. Path. **67**, 337 (1955).
Mallory, F. B.: (1) Cirrhosis of the liver. Bull. Johns Hopk. Hosp. **22**, 69 (1911).
— (2) Cirrhosis of the liver. N. Engl. J. Med. **206**, 1231 (1931).
Marchand, F.: Über Ausgang der akuten Leberatrophie in multiple knotige Hyperplasie. Beitr. path. Anat. **17**, 206 (1895).
McDonald, R., and C. K. Mallory: The natural history of postnecrotic cirrhosis. Amer. J. Med. **24**, 334 (1958).
Montenegro, M. R., L. C. Da Silva and J. F. Pontes: An evaluation of the problem of hepatic cirrhosis as seen in Sao Paulo, Brazil. II. Postnecrotic cirrhosis: Morphologic aspects. Gastroenterology **34**, 1108 (1958).
Nunes, M.: Über die Histopathogenese der posthepatitischen Leberzirrhose. Beitr. path. Anat. **112**, 271 (1953).
Patek, A. J.: Postnecrotic cirrhosis. In: L. Schiff, Diseases of the liver, p. 459. Philadelphia and Montreal: J. B. Lippincott & Co. 1956.
Patek jr., A. J., J. Post, O. D. Ratnoff, H. Mankin and R. W. Hillman: The dietary treatment of cirrhosis of the liver. J. Amer. med. Ass. **13**, 543 (1948).
Popper, H.: Transition of hepatitis to cirrhosis. Amer. J. dig. Dis. **2**, 397 (1957).
— G. Clearkin, G. Kent, M. Parthasarathy and C. Bruce: (1) Coarse nodular cirrhosis produced by ethionine. Amer. J. Path. **31**, 594 (1955).
—, and H. Elias: Histogenesis of hepatic cirrhosis. Amer. J. Path. **31**, 405 (1955).
— E. Rubin, S. Krus and F. Schaffner: (2) Postnecrotic cirrhosis in alcoholics. Gastroenterology **39**, 669 (1961).
Rappaport, A.: Structural and functional unit of the liver. Anat. Rec. **11**, 19 (1954).
— Übersichten und Betrachtungen zur Pathophysiologie der Leberstruktur. Klin. Wschr. **38**, 561 (1960).
Ratnoff, O. D., and A. J. Patek: Postnecrotic cirrhosis of the liver. J. chron. Dis. **1**, 266 (1955).
Registry of liver pathology. Gastroenterology **20**, 178 (1952).
Roessle, R.: Entzündungen der Leber. In: F. Henke u. O. Lubarsch, Handbuch der pathologischen Anatomie und Histologie, Bd. V, Teil 1, S. 338. Berlin: Springer 1930.
Rubin, E., S. Krus and H. Popper: Pathogenesis of postnecrotic cirrhosis in alcoholics. Arch. Path. **73**, 288 (1962).
Smetana, H.: Histogenesis of coarse nodular cirrhosis. Lab. Invest. **5**, 175 (1956).
Steiner, P.: Precision in classification of liver cirrhosis. Amer. J. Path. **37**, 21 (1960).
Thaler, H.: Über die formale Genese der posthepatitischen Leberzirrhose. Beitr. path. Anat. **112**, 173 (1957).
Wuestenfeld, E.: Experimentelle Beiträge zur Frage der Volumenveränderung und Eindringungsdauer in der histologischen Technik. Z. wiss. Mikr. **62**, 241 (1955); **63**, 86, 193 (1957).

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