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# Staging of Chronic Nonsuppurative Destructive Cholangitis (Syndrome of Primary Biliary Cirrhosis)

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**Summary.** Staging of liver biopsy specimens from patients with chronic nonsuppurative destructive cholangitis (CNDC or syndrome of primary biliary cirrhosis) has become an important part of clinical studies that are currently done in many centers. Therefore, staging methods should be based on uniform criteria that are applicable to all specimens and are easily reproducible. Most pathologists staging CNDC use the system proposed by Scheuer and modified slightly by Popper and Schaffner; and generally these methods serve well. But the features relied upon as characteristic of the earlier phases of CNDC (namely, inflammatory destruction of intrahepatic bile ducts and proliferation of ductules) are not always present in biopsy specimens from early cases, and occasionally they coexist with more advanced lesions, such as bridging necrosis.

We suggest a new staging system, based on our experience with 219 individual biopsy specimens from 101 patients with well established CNDC. Our proposed criteria are: stage I – portal hepatitis; stage II – periportal hepatitis; stage III – septal fibrosis or bridging necrosis, or both; and stage IV – cirrhosis. In most instances, we found these features easy to recognize, and one or another of them was always present. Intra-observer and interobserver variations were small. Experience with the proposed staging system indicates that stages III and IV are encountered 3 or 4 times as commonly as stages I and II. Incidence of inflammatory bile duct destruction seemed to vary little from stages I to II. Cholestasis and positive copper stains were most common in stages III and IV.

**Key words:** Histology – Liver Biopsy – Primary biliary cirrhosis – Staging.

**Zusammenfassung.** Die histologischen Stadien der chronisch-destruierenden, nichteitrigen Cholangitis (CNDC oder Syndrom der primären biliären Zirrhose) müssen genau bestimmt werden, um (1) den Krankheitsablauf zu verfol-

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gen und damit – in weiten Grenzen – die Lebenserwartung einzelner Patienten zu bestimmen, und (2) um den Erfolg von Behandlungsversuchen an Patientengruppen zu bewerten. Die histologischen Stadien der CNDC werden meist nach der Methode von Scheuer oder, in leichter Abwandlung, nach der von Popper und Schaffner bestimmt. Diese Methoden funktionieren ausgezeichnet, wenn die für die Frühstadien namengebenden Veränderungen (entzündliche Gallengangszerstörung und Proliferation der Gallenkanälchen) im Präparat sichtbar sind. Leider ist das in manchen Fällen nicht so, oder die histologischen Veränderungen, die die Frühstadien kennzeichnen sollen, kommen gemeinsam mit den Merkmalen späterer Stadien vor.

Auf Grund unserer Erfahrungen mit 219 Leberbiopsiepräparaten von 101 Patienten mit nachgewiesener CNDC möchten wir eine neue Stadieneinteilung vorschlagen. Die Einteilungskriterien sind: Stadium I – portale Hepatitis; Stadium II – periportale Hepatitis; Stadium III – septale Fibrose oder Brückennekrose, oder beides; und Stadium IV – Zirrhose. Die namengebenden histologischen Veränderungen waren leicht zu erkennen und in jedem Präparat vorhanden. Die Einteilungsergebnisse waren gut reproduzierbar, sowohl vom gleichen Untersucher als auch von 2 verschiedenen Untersuchern. Die Stadien III und IV fanden sich in unserem Material drei- bis viermal häufiger als die Stadien I und II. Entzündliche Gallengangszerstörung fand sich in den Stadien I und II mit etwa gleicher Häufigkeit. Färbbares Gallen- und Kupferpigment war am häufigsten in den Stadien III und IV.

*C*hronic *n*onsuppurative *d*estructive *c*holangitis (CNDC) is a chronic, progressive liver disease manifested by a disturbance in bile secretion and by segmental inflammatory destruction of intrahepatic bile ducts. This process results in increasing loss of these bile ducts, associated with periportal hepatitis and eventually cirrhosis. The term "primary biliary cirrhosis" is a synonym of CNDC although it is undescriptive of any but the last stage of the disease. Chronic active hepatitis shares many morphologic features with CNDC but is an unrelated disease in most or all instances. Fully developed granulomatous bile duct destruction occurs very rarely in liver diseases other than CNDC.

A precise histologic staging of chronic nonsuppurative destructive cholangitis (CNDC or syndrome of primary biliary cirrhosis) is crucial for (1) determining progression of the disease and thus, within broad limits, the life expectancy of individual patients, and (2) for monitoring response of groups of patients in treatment trials. At present, microscopic study of biopsy specimens is the only method to determine with reasonable certainty which phase of CNDC a patient is in and what effect treatment may have had in this regard.

Most pathologists staging CNDC use the system proposed by Scheuer (Scheuer, 1967, 1973) and modified slightly by Popper and Schaffner (Popper and Schaffner, 1970). The stages in that system are matched to four pathologic features: stage I – inflammatory destruction of interlobular bile ducts; stage II – proliferation of ductules; stage III – fibrosis; and stage IV – cirrhosis. In the majority of instances, these criteria describe the stages of the disease well. In an appreciable number of cases, however, we found staging most difficult – ei-

ther because morphologic features that should indicate a phase of the disease, such as ductular proliferation, were not present, or because features of more than one stage coexisted (for example, ductal inflammation with fibrosis).

Consequently, we wish to propose a new staging system for *well established* cases of CNDC. Its criteria are pathologic features that are easy to recognize, and one or another of these features is always present. We feel that the proposed staging criteria reflect accurately the progress of the disease. They were formulated on the basis of our experience in reviewing liver biopsy specimens from more than 150 patients with CNDC. To test the system, we have used the proposed criteria to stage liver biopsy specimens from 101 patients with well established CNDC who participated in our D-penicillamine control trial.

## Materials and Methods

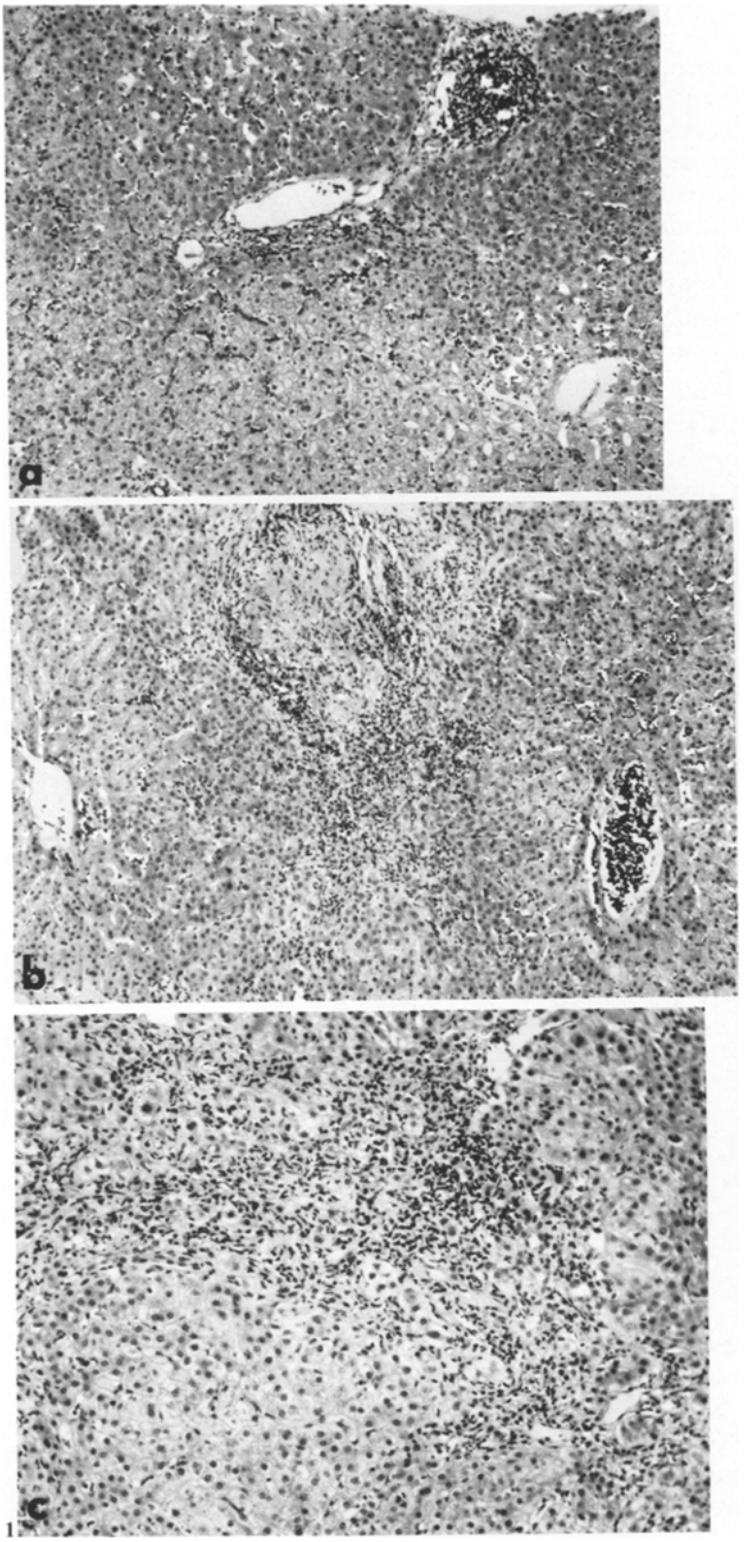
At the time of our study, 106 Mayo Clinic patients with precirrhotic or cirrhotic CNDC were taking part in a randomized double blind control trial (Dickson et al., 1977). In all instances, the diagnosis was considered well established because the patients had (1) histologic or chemical abnormalities, or both, of more than 3 months' duration, (2) levels of serum alkaline phosphatase that were more than 3 times normal, (3) mitochondrial antibody present in the serum, (4) normal extrahepatic bile ducts, as determined – if indicated – by intravenous cholangiography, endoscopic retrograde cholangiography, or operative cholangiography, and (5) pretreatment liver biopsy specimens that were diagnostic for or compatible with CNDC. (Most patients whose pretreatment liver biopsy specimens were classified as "compatible with CNDC" had diagnostic morphologic changes in one or more subsequent specimens that were obtained at yearly intervals as required in the D-penicillamine control trial.)

We studied 219 liver biopsy specimens from 101 patients (no biopsy specimen was available from 5 patients at this time). There were 15 men and 86 women. Their ages ranged from 29 to 79 years (the mean age was 50 years). The material consisted of pretreatment biopsy specimens that had been obtained – at yearly intervals – while the patients participated in the D-penicillamine therapeutic trial. The specimens, all obtained by routine needle techniques, were of adequate size. They were cut at 7 μm and stained with hematoxylin-eosin, van Gieson's stain, Gomori's stain for iron, and the rhodanine method for copper (Lindquist, 1969).

Each specimen was staged by two of us (JL and GM), independently of each other, by our preestablished morphologic criteria. In addition, the entry (pretreatment) biopsy specimens from 94 patients were staged twice, at an interval of 5 to 8 weeks, by one of us (JL). The staging was done under coded identification; and though the pathologists knew the diagnosis, they had no knowledge of the clinical and biochemical data. The results of copper stain and other relevant morphologic features were recorded with the stage assigned at each examination. Intermediate stages were recorded as I–II, II–III, and III–IV. This was done if features such as periportal inflammation, bridging necrosis, or nodular inflammation were mild, were recognized at one time but not at another, or were recognized by one observer but not by another.

### *Staging Criteria*

*I. Portal Stage.* Portal hepatitis (Ludwig, 1977), with little or no periportal inflammation or piecemeal necrosis (Fig. 1 a). The biopsy evidence at this stage may be indistinguishable from that of chronic persistent or various other types of hepatitis (Ludwig, 1977). Although granulomas and inflammatory destruction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c

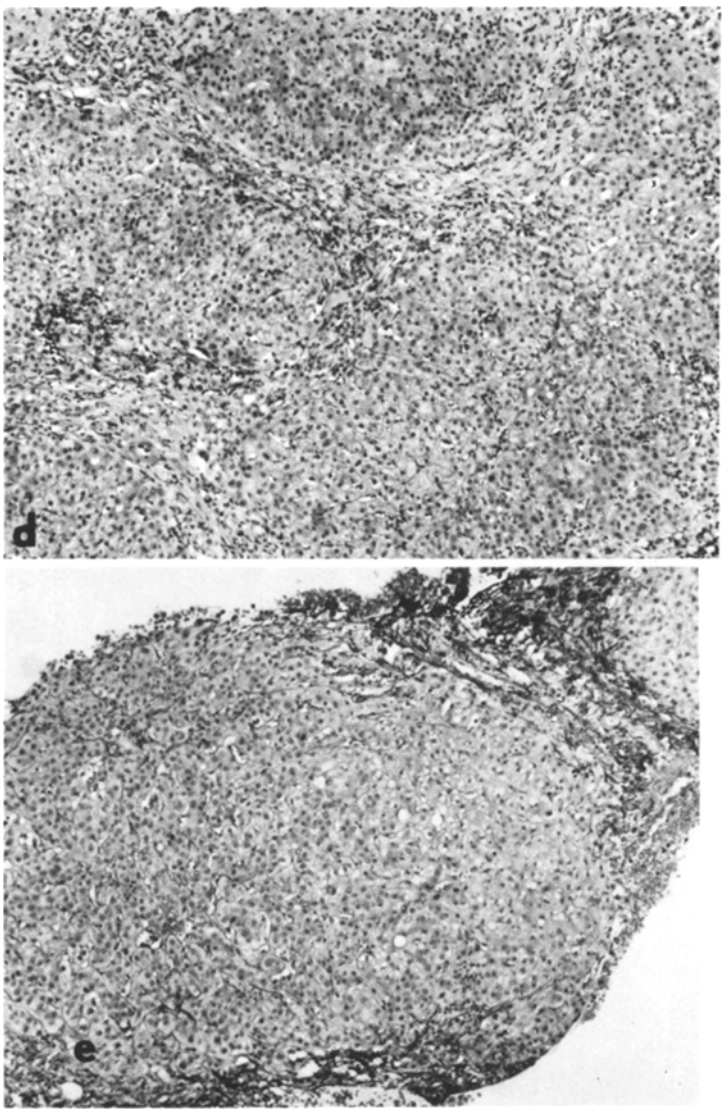



**Fig. 1 a–e.** The four stages of chronic nonsuppurative destructive cholangitis. **a** Stage I or portal stage: portal hepatitis, without periportal inflammation or piecemeal necrosis. In this specimen, no diagnostic duct lesions were present. HE. ×100. **b** Stage II or periportal stage: periportal hepatitis with peicemeal necrosis; absence of bridging necrosis and of septal fibrosis. The portal tract (top) contains a large granuloma, but no bile duct. HE. ×100. **c** and **d** Stage III or septal stage: bridging necrosis (**c**; HE. ×160) or fibrous septa, or both (**d**; HE. ×100) are present. **e** Stage IV or cirrhotic stage: fibrous septa and regenerative nodules are present. van Gieson ×100

of bile ducts may be identifiable, their presence or absence does not affect the staging.

*II. Periportal Stage.* Periportal hepatitis (Ludwig, 1977); absence of bridging necrosis and of septal fibrosis. Usually, piecemeal necrosis is present (Fig. 1 b).

The biopsy evidence at this stage may be indistinguishable from that of chronic active or various other types of hepatitis (Ludwig, 1977). Granulomas, inflammatory destruction of bile ducts, and ductular proliferation, in various combinations, are often identifiable; but presence or absence of these features does not affect the staging.

*III. Septal Stage.* Fibrous septa ("active septa") or bridging necrosis ("passive septa"), or both (Figs. 1c and d). The same comments apply that were made above for stage II.

*IV. Cirrhotic Stage* ("true" primary biliary cirrhosis): fibrous septa and nodular regeneration (Fig. 1e). In a few instances, the biopsy evidence at this stage may be difficult to distinguish from that of other types of cirrhosis.

### *Comparison of Staging Methods*

In Table 1 our four stages of CNDC are compared with those of Scheuer (Scheuer 1967, 1973) and of Popper and Schaffner (Popper and Schaffner, 1970). The staging concepts of these authors were based on previous work, primarily by Rubin, Schaffner, and Popper (Popper et al., 1962; Rubin et al., 1963; Rubin et al., 1965). Although the terminology differs somewhat, Popper and Schaffner would assign to most biopsy specimens the same stage as Scheuer does; but stage I is an exception. Popper and Schaffner restricted this stage to portal hepatitis ("the inflammatory exudate does not spill over into the parenchyma"), whereas Scheuer's (Scheuer, 1973) criteria for stage I allow for periportal hepatitis ("the limiting plates may or may not be intact"). An-

**Table 1.** Comparison of staging systems for CNDC

| Classification | Morphologic findings on biopsy | | | |
|---|---|---|---|---|
| | Stage I | Stage II | Stage III | Stage IV |
| Ludwig, Dickson, and McDonald | *Portal*<br>Portal hepatitis | *Periportal*<br>Periportal hepatitis | *Septal*<br>Bridging necrosis (passive septa) or septal fibrosis (active septa), or both | *Cirrhosis* |
| Popper and Schaffner | *Cholangitis*<br>Portal hepatitis with duct lesions | *Ductular proliferation*<br>Same as stage II of Scheuer | *Precirrhosis*<br>Same as stage III of Scheuer | *Cirrhosis* |
| Scheuer | *Florid duct lesion*<br>Portal hepatitis with duct lesions, or periportal hepatitis with duct lesions but without ductular proliferation | *Ductular proliferation*<br>Periportal hepatitis (and bridging necrosis?), with ductular proliferation but without fibrosis | *Scarring*<br>Septal fibrosis but absence of true regenerative nodules | *Cirrhosis* |

other difficulty must be overcome. As Scheuer concedes, the most important staging criterion, the inflammatory duct lesion, may not be present in a single biopsy specimen. On the other hand, this lesion is not uncommon in specimens that show bridging necrosis or fibrosis, or both. Obviously, in such instances, there will be semantic problems.

In stage II, ductular proliferation is a frequent finding; yet in some specimens it remains inconspicuous. We assume that other authors would assign specimens with bridging necrosis to stage II, provided ductular proliferation also is present. We are not certain how biopsy specimens would be staged that show bridging necrosis but no ductular proliferation. In the past, some biopsies were assigned to stage I, but cirrhosis followed. In the proposed system we assign specimens with bridging necrosis to stage III, regardless of whether ductular proliferation can be identified. Otherwise, there is no disagreement about stages III and IV.

### *Experience with Proposed System in 219 Instances*

*Reproducibility of Staging Results.* Intra-observer variations.—One of us (JL) staged twice the entry (pretreatment) biopsies from 94 patients as described under "Materials and Methods." In this series, the results of the two staging procedures were in complete agreement in 77% of the 94 instances. In 13 instances (14%) there was a difference of half a stage between the first and second evaluation; and in 9 (10%) there was a full-stage difference between the two evaluations.

Interobserver variations.—As mentioned, each of the 219 biopsy specimens was staged by two observers independently, with knowledge of the diagnosis but without knowledge of clinical data. Stages I, I–II, II, II–III, III, III–IV, and IV were recorded. The results of the two staging procedures were in complete agreement in 59% of the 219 instances and differed by only half a stage in 30%. In 10% there was a full-stage difference between the two evaluations, and in only 1% was there a two-stage difference.

*Incidence of Stages (Table 2).* In the pretreatment group of cases, 3.5 times as many specimens were assigned to stages III and IV (78%) as to stages I and II (22%). Some of the patients whose specimens were assigned to stages III and IV were asymptomatic or had developed symptoms only a short time before they entered the study. Of the entire group of 219 specimens, more than four times as many were assigned to stages III and IV (81%) as to stages I and II (19%). The data in Table 2 seem to indicate that the incidence of the four histologic stages of CNDC is approximately the same, whether patients have been treated or not. Our treatment trial, however, is still under way, and we have not yet identified the patients who received placebos. Table 2 shows, therefore, the expected incidence of histologic stages in study groups of this type but does not allow exclusion of the possibility of beneficial effects of D-penicillamine treatment.

**Table 2.** Incidence of stages in 219 liver biopsy specimens from 101 patients with CNDC

| Stage | Morphologic criteria | Patients[a] | | | | | |
|---|---|---|---|---|---|---|---|
| | | Pretreatment | | During treatment | | Total | |
| | | No. | (%) | No. | (%) | No. | (%) |
| I | Portal hepatitis | 5 | (5) | 8 | (7) | 13 | (6) |
| II | Periportal hepatitis | 17 | (17) | 12 | (10) | 29 | (13) |
| III | Bridging necrosis or septal fibrosis, or both | 42 | (41) | 46 | (39) | 88 | (40) |
| IV | Cirrhosis | 37 | (37) | 52 | (44) | 89 | (41) |

[a] From cases with intermediate classifications, this table shows the stage most fully validated – usually the higher stage

**Table 3.** Incidence of morphologic findings in various stages of CNDC (219 biopsy specimens from 101 patients)

| Stage | Morphologic criteria | No. cases | Number of specimens[a] | | | | |
|---|---|---|---|---|---|---|---|
| | | | Inflammatory duct destruction (florid duct lesion) | Ductular proliferation | Cholestasis | Positive for copper (rhodanine stain) | |
| | | | | | | All cases | With cholestasis |
| I | Portal hepatitis | 13 | 5 (38%) | 0 | 0 | 2 (15%) | 0 |
| II | Periportal hepatitis | 29 | 13 (45%) | 16 (55%) | 3 (10%) | 21 (72%) | 2 (7%) |
| III | Bridging necrosis or septal fibrosis, or both | 88 | 17 (19%) | 74 (84%) | 18 (20%) | 72 (82%) | 17 (19%) |
| IV | Cirrhosis | 89 | 13 (15%) | 83 (93%) | 32 (36%) | 80 (90%) | 29 (33%) |

[a] Percentages are given for total number of biopsies in same stage

### *Morphologic Features Associated with Stages (Table 3)*

*Inflammatory Destruction of Intrahepatic Bile Ducts and Ductular Proliferation.* Inflammatory duct lesions occurred in all stages, and their incidence seemed to vary little from stages I to II. Ductular proliferation was found in stages II to IV, and seemed to be most frequent in stages III and IV.

*Bridging Necrosis.* Of the 88 biopsy specimens assigned to stage III, approximately half showed either bridging necrosis or fibrous septa, and half exhibited both lesions together. Most cases with bridging necrosis and without fibrosis had been classified previously by the Scheuer or Popper-Schaffner method as

stage I or II, particularly when they were associated with florid duct lesions or ductular proliferation.

*Cholestasis and Mallory's Hyalin.* If bile was present, it was usually found in periportal hepatocytes or in the periphery of regenerative nodules. Cholestasis was not frequent, except in the precirrhotic and cirrhotic stages of the disease. The low incidence of cholestasis should be emphasized. Morphologically, CNDC is not a cholestatic disease, and the diagnosis should not be based on the diagnosis of stainable bile. Approximately one-third (N=18) of the specimens with cholestasis also contained Mallory's hyalin. In six other specimens, there was hyalin but no stainable bile. For the association with copper, see below.

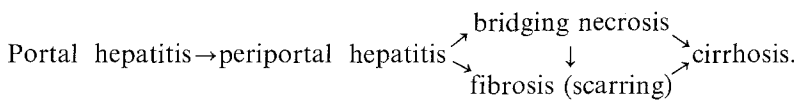
*Copper.* The rhodanine method for copper was positive in almost 80% of all specimens. The majority of those that stained positive had been assigned to stages III or IV. However, even in stages I and II, histologic evidence of copper was seen in substantial percentages of the specimens.

Positive copper stains were also graded subjectively on a scale from 1 to 3. Nineteen of the 23 positive specimens in stage I or II were graded 1, three were graded 2, and one was graded 3. Some of the specimens with grade 1 copper had the characteristic red granules in only a few periportal hepatocytes. In stage III specimens, 43 of 72 were graded 1, 13 were graded 2, and 16 were graded 3. In stage IV, 36 of 80 biopsy specimens were of grade 1, 17 of grade 2, and 27 of grade 3.

Among the 177 biopsy specimens in stages III and IV, staining for copper gave positive results in 152, of which 46 had cholestasis also. The copper stains in this subgroup varied from grade 1 to grade 3.

## Discussion

As in staging lymphomas, we found that the morphologic features of CNDC that are useful for the diagnosis (see Table 3) are not equally useful for staging. Ductal inflammation is an example of this difficulty. Biopsy specimens with florid duct lesions and bridging necrosis had been classified, by experienced observers who used Scheuer's or Popper and Schaffner's system, as stage I, II, or III, partly because bridging necrosis had not been dealt with in studies of CNDC. We feel that bridging necrosis belongs in stage III of this disease which progresses




The identification of portal, periportal, septal (active or passive septa, or both), and cirrhotic stages is usually straightforward. Intermediate stages probably should be reported as such, or the next higher stage should be assigned.

Observer variations must be accepted with any staging or grading system. If one allows for half-stage differences, interobserver agreement with our staging method was 89%, which seems quite acceptable. The smaller a specimen is, the more likely is an error in staging. It seems therefore advisable not to stage specimens that show less than 4 portal tracts. An exemption may be small specimens with advanced lesions – for instance, a specimen that show one bridging necrosis or one regenerative nodule. Specimens of this kind probably can be staged with some confidence. If the specimen is of adequate size, observer variation can be further reduced by applying additional rules. For instance, criteria can be formulated that allow an observer to distinguish early periportal hepatitis from portal hepatitis. Rules of this kind, however, complicate a staging system unnecessarily and tend to discourage pathologists who might otherwise use it.

A histologic staging system should (1) reflect the morphologic progression of the disease or condition, (2) be applicable to most routinely obtained specimens, and (3) be reproducible by many observers. We feel that the staging system proposed here fulfills these requirements.

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