Grading and Staging the Histopathological Lesions of Chronic Hepatitis: The Knodell Histology Activity Index and Beyond

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In the last half of the 20th century, use of the liver biopsy has grown to serve multiple purposes: (1) confirmation of clinical diagnosis, (2) assessment of severity of necroinflammation and fibrosis, (3) evaluation of possible concomitant disease processes, and (4) assessment of therapeutic intervention. The current practice for reporting histopathological evaluation of chronic hepatitis involves separate statements for the cause of disease, if known, for severity of necroinflammatory lesions, and for the extent of parenchymal fibrosis. The Knodell histology activity index (HAI), published in HEPATOLOGY in 1981,[1] was the first system of its type and is widely regarded as the benchmark for objective, semiquantitative, reproducible description of the various morphological lesions of chronic hepatitis. The report has been cited more than 940 times since its publication. Other proposals for semiquantitative evaluation have followed.[2-8] Among these was the consensus report of Desmet et al.,[2] which appeared in 1994 in HEPATOLOGY and has been cited more than 440 times. It not only described a modified grading and staging system but also significantly updated the classification of chronic hepatitis to include etiology.

HISTORICAL PERSPECTIVES: THE TERMINOLOGY OF CHRONIC HEPATITIS

The work of the two decades preceding the Knodell HAI provided the foundation for our current understanding of the histopathology of chronic hepatitis. Early descriptions and classifications focused on differentiating acute and chronic hepatitis and on lesions that predicted disease progression. Although all workers acknowledged the difficulty of predicting the evolution of either acute or chronic hepatitis based on liver biopsy, the histological features considered worrisome for progression included piecemeal necrosis,[9] plasma cell infiltrates, lymphoid aggregates, periportal septum formation,[10,11] bridging necrosis (primarily central-central),[12] and hepatitic bile duct lesions.[13] The first histological classification, which was published by an international group in 1968,[10] codified the terminology, *chronic persistent* and *chronic aggressive* hepatitis. Both conditions involved portal inflammation but were distinguished by the severity of piecemeal necrosis, inflammation, and structural remodeling of the liver. Inflammatory activity was graded as moderate or severe, but exact criteria were not given. The classification system also incorporated the concept that chronic persistent hepatitis had a generally good prognosis whereas chronic aggressive hepatitis could evolve to cirrhosis.[10] In addition, the authors noted that the terms "persistent" and "aggressive" encompassed several etiologies and were not to be considered distinct diagnostic entities.

In 1971, Popper and Schaffner affirmed the value of liver biopsy for diagnosis and prognosis and recommended use of "topographic" descriptors for hepatitis, that is, *chronic lobular*, *chronic portal*, or *chronic periportal hepatitis*.[14] The last of these, synonymous with chronic aggressive hepatitis, was believed to progress, whereas chronic portal hepatitis, synonymous with chronic persistent hepatitis, was considered a nonprogressive process. The investigators astutely commented that long-term studies of patients with the latter type of hepatitis were not available. *Chronic lobular hepatitis* was a term for histological findings similar to those of acute hepatitis, but with a clinical duration of more than 3 months. It was thought to be nonprogressive except when seen in combination with chronic periportal hepatitis.

Two other reports in the 1970s were influential in the morphological characterization and evolution of acute and chronic viral hepatitides, one published by an international group of hepatopathologists,[11] the other by Ishak.[15] Although these studies emphasized histological findings in viral hepatitis, they included discussion of other forms of chronic hepatitis and their known clinical correlations. Ishak[15] discussed the unique and newly recognized findings in chronic hepatitis B, including ground-glass cells, liver cell dysplasia, and hepatocellular carcinoma. His perceptive observations of chronic persistent hepatitis in biopsy specimens from intravenous drug abusers included foreign material in portal macrophages, portal inflammation with lymphoid aggregates or follicles, and eosinophils. Many of these findings are now familiar in association with chronic hepatitis C infection.[16,17]

THE KNODELL HISTOLOGY ACTIVITY INDEX

With their 1981 publication, Knodell et al.[1] introduced semiquantitative and reproducible histological scoring of liver biopsies. Lesions were assigned weighted numeric values, which resulted in a score, the HAI (Table 1). The purpose was 2-fold: first, to provide a systematic methodology and terminology to replace or supplement the traditional qualitative one, and second, to develop a means of evaluating serial biopsies in asymptomatic patients for tracking disease progression or the response to therapeutic intervention. The study consisted of 14 liver biopsy samples from 5 patients (1

Abbreviation: HAI, histology activity index.

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TABLE 1. HAI for Numerical Scoring of Liver Biopsy Specimens

I. Periportal +/− Bridging Necrosis	Score	II. Intralobular Degeneration* and Focal Necrosis	Score	III. Portal Inflammation	Score	IV. Fibrosis	Score
A. None	0	A. None	0	A. No portal inflammation	0	A. No fibrosis	0
B. Mild piecemeal necrosis	1	B. Mild (acidophilic bodies, ballooning degeneration and/or scattered foci of hepatocellular necrosis in <1/3 of lobules or nodulles)	1	B. Mild (sprinkling of inflammatory cells in <1/3 of portal tracts)	1	B. Fibrous portal expansion	1
C. Moderate piecemeal necrosis (involves *less* than 50% of the circumference of most portal tracts)	3	C. Moderate (involvement of 1/3-2/3 of lobules or nodules)	3	C. Moderate (increased inflammatory cells in 1/3-2/3 of portal tracts)	3	C. Bridging fibrosis (portal-portal or portal-central linkage)	3
D. Marked piecemeal necrosis (involves *more* than 50% of the circumference of most portal tracts)	4	D. Marked (involvement of >2/3 of lobules or nodules)	4	D. Marked (dense packing of inflammatory cells in >2/3 of portal tracts)	4	D. Cirrhosis†	4
E. Moderate piecemeal necrosis *plus* bridging necrosis‡	5						
F. Marked piecemeal necrosis *plus* bridging necrosis‡	6						
G. Multilobular necrosis§	10						

NOTE. HAI score is the combined scores for necrosis, inflammation, and fibrosis.
*Degeneration—acidophil bodies, ballooning; focal necrosis-scattered foci of hepatocellular necrosis.
†Loss of normal hepatic lobular architecture with fibrous septae separating and surrounding nodules.
‡Bridging is defined as ≥2 bridges in the liver biopsy specimen; no distinction is made between portal-portal and portal-central linkage.
§Two or more contiguous lobules with panlobular necrosis.
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with chronic hepatitis B and 4 with non-A, non-B hepatitis) over a 1- to 3-year span. The HAI comprised 3 categories for necroinflammation and 1 for fibrosis, with points for the severity of the lesion in each category. The sum total of points constituted the final score, or HAI. A change greater than ±4 between serial biopsy specimens was considered significant.

The first category, periportal and bridging necrosis, included 7 levels of increasing severity, whereas the other 3 categories had just 4 levels. In effect, this gave greater weight to the first category on the rationale that periportal (piecemeal) and bridging necrosis are indicative of progression to cirrhosis. An interesting point in the organization of the HAI was the use of a discontinuous value scale in all 4 categories. Thus, the 7 levels in the first category ranged from 0 to 10 but omitted "2" and "7-9." Similarly the levels in the other categories ranged from 0 to 4 but without "2." This, in effect, forced a rating of either "low" (0-1) or "high" (3-4) in the latter categories. Some investigators have argued that this increases the accuracy of the HAI.[18] Agreement between the HAI and the conventional qualitative terminology (chronic persistent or chronic active hepatitis) was shown in the original study.[1] Interobserver and intraobserver differences were examined and found to be small for the HAI, whereas interobserver variation was significant when the conventional terminology was applied to the same biopsy samples.

The most frequently cited criticism of the Knodell HAI is that it is the sum of necroinflammatory and fibrosis scores and, therefore, does not distinguish ongoing hepatitis from parenchymal remodeling with fibrosis. It should be noted, however, that the authors specifically addressed this issue: "Overall HAI scores can also be broken into individual components of necrosis, inflammation and fibrosis to yield additional information not provided by conventional composite scales for grading necroinflammatory liver disease."[1] The general practice, nonetheless, is to report the HAI as a single summary score.

AND BEYOND . . . THE NOMENCLATURE OF CHRONIC HEPATITIS

The explosion of scientific information on viral and nonviral hepatitides in the last decades of the 20th century led pathologists to question the conventional nomenclature of chronic persistent and chronic active (aggressive) hepatitis[5-7,19] because of a growing understanding that etiology may be more significant than morphological classification in predicting the natural history of liver disease. This shift in thinking was driven largely by the apparent dissociation between the mild histology of nonA-nonB hepatitis (hepatitis C) and its progressive clinical course. It was found that, in many cases, the lesions of this form of viral hepatitis fell between those described as chronic persistent and chronic active hepatitis and could not be clearly categorized.[5,9,20] Most often, the lack of severe piecemeal necrosis and confluent lobular necrosis resulted in the diagnosis of chronic persistent hepatitis, implying a benign course. At the same time, the lobular component was being recognized as more significant than portal lesions with respect to disease progression.[20,21] Also, confluent necrosis, which when present in severe autoimmune hepatitis and hepatitis B confers an ominous prognosis, is uncommon in hepatitis C, and yet progression to fibrosis or cirrhosis occurs in all 3 diseases. Scheuer stressed the need for updated terminology: "From the point of view of treatment . . . the separation of CPH from mild CAH is fundamentally unsound and ethically unacceptable; it betrays misunderstanding of the evolution of chronic viral hepatitis and may deprive patients of effective treatment."[5] Ishak's 1994 review[7] popularized the use of the more inclusive term *chronic hepatitis*, de-emphasizing the distinc-

tion between chronic persistent and chronic active hepatitis. In addition, the modified HAI published in 1995[8] introduced the term *interface hepatitis* in place of "piecemeal necrosis," to reflect the growing evidence that apoptosis, not necrosis, occurs at the limiting plate.[21]

The recommendation to include etiology in the classification of chronic hepatitis was one of the major contributions of a consensus conference held in 1994.[2] The diseases included were viral hepatitis B, C, and D, autoimmune hepatitis, drug-induced hepatitis, and cryptogenic hepatitis. Ludwig[6] and Batts and Ludwig[22] proposed systems of classification that subdivide chronic liver disease into nonbiliary or biliary categories. The former includes those listed above as well as α_1-antitrypsin deficiency and Wilson Disease. This has been endorsed by others,[7,23] because these entities have clinical and histological features in common with chronic viral hepatitis. However, the proposal to also include primary sclerosing cholangitis, primary biliary cirrhosis, and autoimmune cholangitis[6,22] has not been widely accepted. Although portal and lobular inflammation are seen in these disorders, other clinical and morphological features of chronic cholestasis are sufficiently distinctive usually to allow appropriate classification.[23]

GRADING AND STAGING THE LESIONS OF CHRONIC HEPATITIS: THE NEWER SYSTEMS

Since publication of the Knodell HAI, systems for grading and staging incorporate the view that necroinflammation is not only a measure of severity but also of ongoing disease activity and the parameter most potentially responsive to therapy. This is referred to as "grade." The lesions of fibrosis and parenchymal or vascular remodeling are referred to as "stage" and indicate long-term disease progression. Grade may fluctuate with disease activity or therapeutic intervention; stage is considered relatively constant. All systems report grade and stage, although they may arrive at a score using different criteria. The differences are subtle but potentially important when comparing clinical studies that have used 2 different systems. The Scheuer system[5] was described originally for chronic viral hepatitis but, like the Knodell HAI, is now applied to nonviral hepatitis as well. It is less complex than the HAI (Table 2), gives the portal and lobular components of activity equal weight, and groups the periportal and portal lesions into a single category. Some feel that this better reflects the lesions of significance in hepatitis C.[5,21,24] Ludwig's proposed system[6,22] is depicted in Figs. 1 and 2, and is similar to Scheuer's.

Ishak's 1994 review[7] promotes the use of descriptive terminology for activity and fibrosis, rating the different elements of activity as either present or absent; when present, a degree of severity is stated (Table 3). The French METAVIR Cooperative Study Group proposed a comprehensive but complex system for the histological evaluation of hepatitis C.[4] The final score reflects the combined ratings for focal lobular necrosis, portal inflammation, piecemeal necrosis, and bridging necrosis (Table 4). Finally, a recent modification of the Knodell HAI, commonly referred to as the Ishak system,[8] provides consecutive scores for well-defined lesions within 4 separate categories that are added together for the activity grade (Table 5). The lower end of the fibrosis scale (0-2) reflects the fact that not all portal tracts show similar amounts of portal and periportal fibrosis, and the assigned score is not based on the most advanced lesion but rather on the lesion affecting some or most of the portal tracts. Difficulties with the Ishak system have been noted.[18] Use of a $\times 10$ objective for the evaluation of necroinflammatory foci raises concerns of reproducibility, because the size of the field may vary among microscopes. In addition, definitions of a "focus" of lymphocytic aggregates, apoptotic hepatocytes, or confluent necrosis may vary among pathologists.

TABLE 2. The Scheuer System

A Simple System for Scoring Necroinflammatory Activity in Chronic Hepatitis*		
Grade	Portal/Periportal Activity	Lobular Activity
0	None or minimal	None
1	Portal inflammation (CPH)	Inflammation but no necrosis
2	Mild piecemeal necrosis (mild CAH)	Focal necrosis or acidophil bodies
3	Moderate piecemeal necrosis (moderate CAH)	Severe focal cell damage
4	Severe piecemeal necrosis (severe CAH)	Damage includes bridging necrosis

A Scoring System for Fibrosis and Cirrhosis†	
Grade	Fibrosis
0	None
1	Enlarged, fibrotic portal tracts
2	Periportal or portal-portal septa but intact architecture
3	Fibrosis with architectural distortion but no obvious cirrhosis
4	Probable or definite cirrhosis

*A score of 0 for portal activity and 2, 3, or 4 for lobular activity corresponds to the current category of chronic lobular hepatitis (CLH).

†Alternatively, cirrhosis can be separately scored from fibrosis, into the following categories: probably absent; developing; suspected; present; cannot be assessed.

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Studies to validate the most widely used systems have shown varying degrees of intraobserver and interobserver reproducibility.[3,18,24] In therapeutic trials for viral hepatitis, the 10 pathologists of the METAVIR group working in pairs and using either the METAVIR or Knodell systems were substantially in agreement in their fibrosis scores for 30 hepatitis C biopsies as well as in their assessment of cirrhosis, steatosis, and portal lymphoid aggregates.[3] There was less concordance in scoring necroinflammatory lesions. In a follow-up study by the same group using the METAVIR system (Table 4), agreement was good on the grading of 363 biopsy samples from patients with hepatitis C.[4]

Another study of reproducibility involved 5 hepatopathologists using Scheuer's system or the Knodell HAI to grade chronic hepatitis B and C (10 biopsies from each disease). Unlike the METAVIR group, they did not confer in advance on grading and staging, with the intent to model clinical practice in which biopsies are interpreted by pathologists at separate sites and whose understanding of the criteria are based on published information only. The results were similar: agreement was greatest for fibrosis assessment; the reading of necroinflammatory lesions was more reproducible with the Scheuer scale than with the Knodell HAI.[24] A separate study has shown the recent Ishak system to be reproducible.[18]

A final issue concerns sampling adequacy in liver biopsies. At the current time, while there is a recognized concern, there is no consensus on minimal adequacy, although criteria based

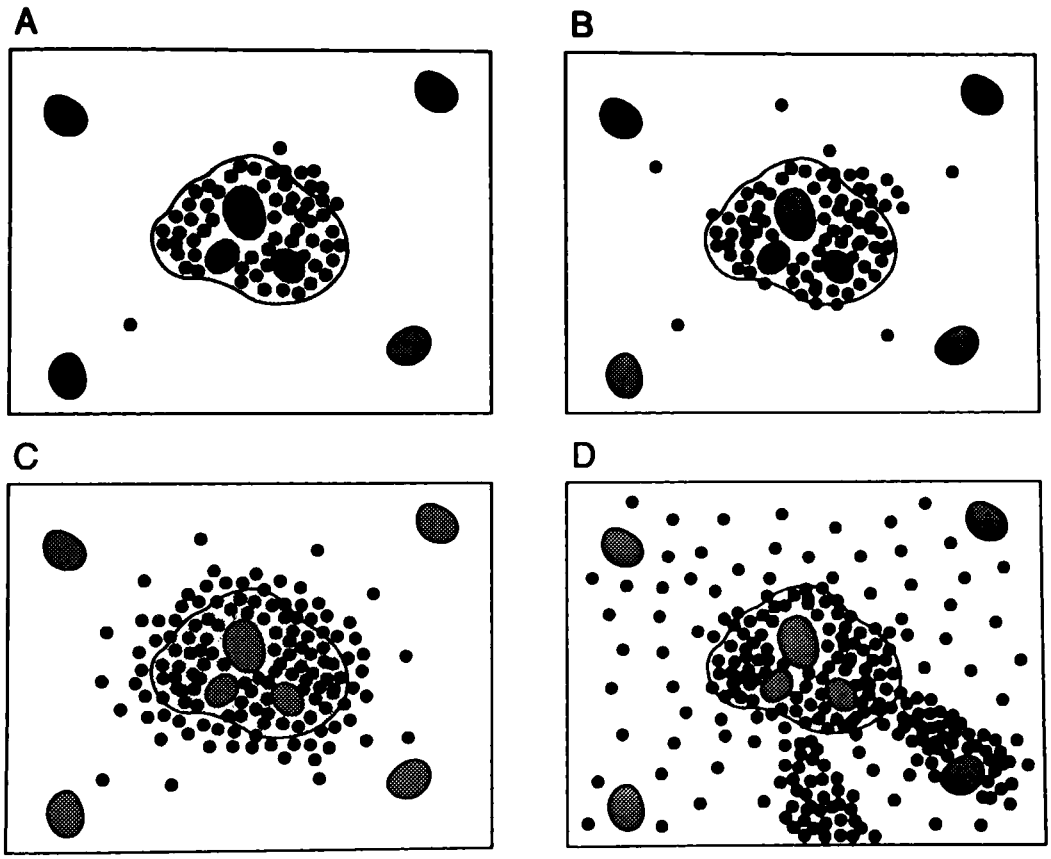

FIG. 1. In these four panels, the increasing severity of portal inflammation, interface hepatitis, and lobular necroinflammatory lesions in chronic hepatitis are shown. Reprinted with permission from Batts KP, Ludwig J. Chronic hepatitis. An update on terminology and reporting. Am J Surg Pathol 1995;19:1409-1417.[22]

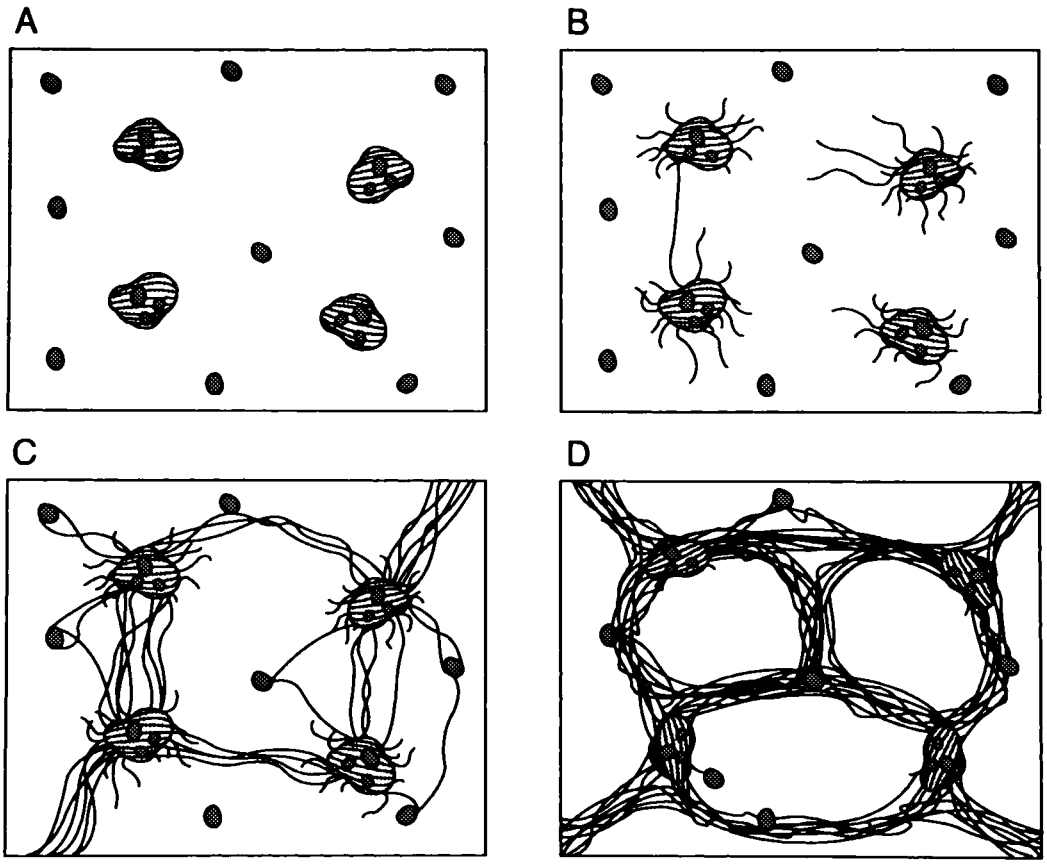

FIG. 2. These panels graphically portray the progression of fibrosis from portal expansion (A) through septal fibrosis (B and C) to complete cirrhotic remodeling (D). The distinction between the lesions of panels C and D in liver biopsy material are acknowledged by all investigators as an area of potential difficulty. Reprinted with permission from Batts KP, Ludwig J. Chronic hepatitis. An update on terminology and reporting. Am J Surg Pathol 1995;19:1409-1417.[22]

TABLE 3. Ishak's System From 1994

	Degree of Activity in Chronic Hepatitis Lesions and Degree of Injury			
Category	Portal Area Inflammation	Piecemeal Necrosis	Spotty Necrosis	Bridging and/or Multi-Acinar Necrosis
Mild	Mild, patchy	Absent or mild	Mild	Absent
Moderate	Moderate	Moderate	Moderate	Absent
Marked	Marked	Marked	Marked	Absent
Very marked	Marked	Marked	Marked	Present

	Degree of Fibrosis in Chronic Hepatitis Component Lesions		
Category	Fibrous Expansion of Portal Areas	Bridging Fibrosis*	Bridging With Nodules (cirrhosis)
Mild	Absent or mild	Absent	Absent
Moderate	Moderate	Absent†	Absent
Marked	Marked	Marked	Absent‡
Very marked	Marked	Marked	Present

*Bridging can be portal to portal, portal to zone 3 (central), or zone 3 to zone 3.

†Occasional bridging may be present.

‡Occasional nodule may be present ("incomplete cirrhosis").

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on the number of portal tracts in the specimen or its total length are frequently applied.

REMAINING QUESTIONS AND THE FUTURE

Although scoring systems are now in widespread use, Scheuer[25] and Ishak et al.[8] have suggested that these are not necessarily appropriate for clinical practice, noting that the scores are not to be considered the equivalent of quantitative laboratory tests but rather are indicative of relative severity. Perhaps these issues are the basis for a situation that has been referred to as "the scoring jungle."[26] In addition, an abundance of work details the histopathologic differentiation of the various forms of chronic hepatitis based on findings by routine histochemical and immunohistochemical stains.[7,16,17,21,23,27-30] Therefore, is it reasonable to expect a single system of grading and staging to adequately address all of the more subtle lesions that may distinguish various forms of chronic hepatitis? Also, is it correct to apply a system designed for viral hepatitis to all forms of chronic liver

TABLE 4. The METAVIR System

Algorithm for Evaluation of Histological Activity*				
Piecemeal Necrosis	+	Lobular Necrosis	=	Histological Activity Score
0 (none)		0 (none or mild)		0 (none)
0		1 (moderate)		1 (mild)
0		2 (severe)		2 (moderate)
1 (mild)		0, 1		1
1		2		2
2 (moderate)		0, 1		2
2		2		3 (severe)
3 (severe)		0, 1, 2		3

Fibrosis Scoring†	
Score	Description
0	No fibrosis
1	Stellate enlargement of portal tract but without septa formation
2	Enlargement of portal tract with rare septa formation
3	Numerous septa without cirrhosis
4	Cirrhosis

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†Modified and reprinted with permission.[3]

TABLE 5. The Ishak Modified HAI

Modified HAI Grading: Necroinflammatory Scores*	Score
A. Periportal or periseptal interface heptatitis (piecemeal necrosis)	
Absent	0
Mild (focal, few portal areas)	1
Mild/moderate (focal, most portal areas)	2
Moderate (continuous around <50% of tracts or septa)	3
Severe (continuous around >50% of tracts or septa)	4
B. Confluent necrosis	
Absent	0
Focal confluent necrosis	1
Zone 3 necrosis in some areas	2
Zone 3 necrosis in most areas	3
Zone 3 necrosis + occasional portal-central (P-C) bridging	4
Zone 3 necrosis + multiple P-C bridging	5
Panacinar or multiacinar necrosis	6
C. Focal (spotty) lytic necrosis, apoptosis and focal inflammation†	
Absent	0
One focus or less per 10× objective	1
Two to four foci per 10× objective	2
Five to ten foci per 10× objective	3
More than ten foci per 10× objective	4
D. Portal inflammation	
None	0
Mild, some or all portal areas	1
Moderate, some or all portal areas	2
Moderate/marked, all portal areas	3
Marked, all portal areas	4
Maximum possible score for grading	18

Modified Staging: Architectural Changes, Fibrosis, and Cirrhosis‡	
Change	Score
No fibrosis	0
Fibrous expansion of some portal areas, with or without short fibrous septa	1
Fibrous expansion of most portal areas, with or without short fibrous septa	2
Fibrous expansion of most portal areas with occasional portal to portal (P-P) bridging	3
Fibrous expansion of portal areas with marked bridging (P-P) as well as portal-central (P-C)	4
Marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis)	5
Cirrhosis, probable or definite	6
Maximum possible score	6

**Additional features that should be noted but not scored:* bile-duct inflammation and damage; lymphoid follicles; steatosis, mild, moderate, or marked; hepatocellular dysplasia, large- or small-cell; adenomatous hyperplasia; iron or copper overload; intracellular inclusions (*e.g.* PAS-positive globules, Mallory bodies); and *immunohistochemical findings.* Information on viral antigens, lymphocyte subsets, or other features, when available, should be recorded and may be semi-quantitatively expressed.

†Does not include diffuse sinusoidal infiltration by inflammatory cells.

‡*Additional features that should be noted but not scored:* intra-acinar fibrosis, perivenular ("chicken-wire" fibrosis); phlebosclerosis of terminal hepatic venules.

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disease? Finally, an exclusive focus on the global or summary score for a biopsy may lead one to overlook the contribution of individual components with clinical significance; indeed, it has been shown that different patterns of activity can produce the same final score.[21]

In conclusion, for a system to be effective in everyday diagnostic practice, it must be simple to understand and to apply, it must communicate effectively to the treating clinician, and it must be clinically relevant. The system that is most appropriate for clinical practice may not be the most informative for investigative work. The development of separate systems tailored to clinical use or research may be warranted if such a goal can be accomplished without imposing unnecessary difficulty on the pathologist or imparting confusion to the clinical audience.

As documented in this review, it is to the credit of many dedicated pathologists that liver biopsy continues to have a central role in clinical evaluation and diagnosis; indeed biopsy evaluation remains the "gold standard" for many of the current clinical investigations in chronic hepatitis. Popper's insightful statement of nearly 30 years ago remains true at the start of the 21st century: "The pathology of viral hepatitis has practical significance in diagnosis and prognosis and elucidates its evolution."[9] Building on the background reviewed herein and in the spirit of the contributions of last 50 years, pathologists will continue the efforts to participate in the expanding clinical and scientific knowledge of chronic hepatitis.

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