

Evidence-based interpretation of liver biopsies

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‘Evidence based medicine’ is a paradigm introduced in the 1990s in which collection of clinical data in a reproducible and unbiased way is intended to guide clinical decision-making. This paradigm has been promulgated across the spectrum of medicine, but with more limited critical analysis in the realm of pathology. The ‘evidence base’ in support of our practices in Anatomic Pathology is a critical issue, given the key role that such diagnoses play in patient management decisions. The question is, ‘On what basis are diagnostic opinions rendered in Anatomic Pathology?’ The operative question becomes, ‘What is the published literature that supports our anatomic pathology interpretations?’ This second question was applied to the published literature in Hepatopathology, by identifying the ‘citation classics’ of this discipline. Specifically, the top 150 most-cited liver pathology articles were analyzed for: authorship; journal of publication; type of publication; and year of publication. Results are as follows. First, it is indeed true that the preeminent hepatopathologists of the age are the most cited authors in the ‘top 150’. Second, the most cited articles in hepatopathology are not published in the pathology literature, but are instead published in much higher impact clinical journals. Third, the pathology of viral hepatitis is demonstrated to be extraordinarily well-grounded in ‘evidence based medicine’. Much of the remainder of the hepatopathology literature falls into a ‘narrative based’ paradigm, which is the rigorous reporting of case experience without statistical clinical outcomes validation. Finally, the years of publication reflect, on the one hand, a vigorous recent literature in the pharmaceutical treatment of viral hepatitis, and on the other, a broadly distributed set of ‘narrative’ articles from the 1960s, 1970s, 1980s, and 1990s. In conclusion, the discipline of hepatopathology appears to be well-grounded in ‘evidence based medicine’ in the realm of viral hepatitis. The remainder of our discipline rests predominantly upon the time-honored identification of disease process through the publication of narrative case series.

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‘Evidence based medicine’ (EBM) is a term introduced in the early 1990s as a new paradigm for medical practice, whereby collection of clinical data in a reproducible and unbiased way is intended to guide clinical decision-making. To quote Sackett *et al*¹ in their seminal 1996 publication, ‘the practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence’. The justification for EBM includes the need to cope with information overload (particularly when it is anecdotal), the need to contain costs, and the need to supply information to a public impatient for the best in diagnostics and treatment. The EBM paradigm is challenged by those who claim that it is unscientific,

with instead a statistical and managerial approach to decision-making that undermines clinical expertise and clinical decision-making. EBM ostensibly requires large randomized controlled trials as the primary means of meeting rigid criteria on acceptable evidence, and hence connotes the demise of the expert opinion. ‘Two roads diverged in a yellow wood, And sorry I could not travel both...’. The critics note that when Frost pondered these two roads, he did not call for a randomized controlled trial.²

Evidence based medicine as a practice paradigm has had limited impact in the realm of Laboratory Medicine, over-and-above the use of laboratory values as read-outs for clinical trials. In the latter instance, Laboratory Medicine is bedrock data for determination of efficacy of pharmacologic therapies. Indeed, there is an implicit assumption that an evidence-based culture underpins the use of laboratory medicine. This is not necessarily a safe assumption.^{3,4} The evidence base supporting use of specific test procedures or technologies may be

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quite limited, and in many cases flawed. Test utilization may expand well beyond the evidence supporting its initial implementation. Moreover, a key deficiency in the published literature is the absence of a statement of specific need for a laboratory test, namely, the clinical or operational question that the use of the test is seeking to answer. In the first instance, there is an ongoing need for Medical Directors of Clinical Laboratories to evaluate the impact of laboratory tests on clinical outcomes. This includes relevance of the test to clinical management decisions, role of timeliness of result-ing (turnaround times), and the impact of test availability (or not). At the current time, analysis of such data has not kept pace with test implemen-tation and utilization patterns in clinical medicine. Evidence-based strategies will be critical to the future development of Laboratory Medicine, espe-cially with the profound appeal of new molecular tests.

The application of EBM to the practice of Surgical Pathology is an open question. One could argue that Surgical Pathology often operates in the realm of 'Eminence based Medicine', in which the profes-sional stature of the Pathologist rendering the opinion constitutes the basis for justifying the diagnostic interpretation.⁵ For some, 'clinical expe-rience' has been defined as 'making the same mistakes with increasing confidence over an im-pressive number of years'.⁶ Perhaps, a less whimsi-cal point of view is 'Narrative-based Medicine', whereby the art of selecting the most appropriate clinical decision is acquired largely through the accumulation of narrative 'case expertise'.⁷ This is distinct from 'evidence based medicine', in which the clinical decision is informed first by statistical evidence, and only then is tempered by judgement acquired through clinical experience. A maxim of my own is, 'You can gain a lifetime of experience with one case.' To wit, the Pathologist placed in the center of a whirling maelstrom of an exceedingly difficult case has to: become thoroughly familiar with all aspects of the specific case (clinical history, physical examination, laboratory findings, radio-graphic findings, current response-to-therapies, current dilemmas); study the world's literature carefully; consult with local Pathologist colleagues and with experts around the world as needed; render an interpretation; and then educate the clinical team in both the nature of the disease and the implications of the pathology interpretation. This is not EBM; it is bringing the entirety of medical knowledge and experience to bear upon one case. This process occurs with remarkable regularity in the practice of surgical pathology.

The central role of the Pathologist in managing patient information was articulated by Sinard and Morrow⁸ in a 2001 editorial. In the broadest sense, the Pathologist should manage *all* patient informa-tion, including incorporation of local patient popu-lation outcomes into the validation (or not) of

previous local clinical decisions. Our profession is, by nature, an information-management specialty. An information-based approach to Anatomic Pathology has been taken by Zarbo and co-workers, in which anatomic pathology databases have been analyzed to assess autopsy performance⁹ and quality of surgical pathology practice.¹⁰⁻¹³

There are few other critical appraisals of the evidence base upon which diagnostic interpreta-tions in Anatomic Pathology are rendered. Wright *et al*¹⁴ published the results of a 2001 Consensus Conference on Guidelines for the management of women with cervical cytological abnormalities. Recognizing that assessment of cytological abnor-malities of the uterine cervix for the amelioration and prevention of cervical cancer is one of the triumphs of 20th century medicine, these 121 experts re-viewed the published literature supporting the use of existing interpretive guidelines of cervical cytopathology specimens. The resulting clinical management recommendations derive from an out-standing 'evidence base', which links cytopathology interpretations to validated clinical outcomes. Marchevsky and Wick¹⁵ provide an excellent review of the broader role of 'evidence based medicine' and 'medical decision analysis' (whereby mathematical tools are used to 'reason with uncertainty') in the practice of pathology. They note that pathologists will be well served by becoming more familiar with the basic concepts of EBM and how pathology data can be better integrated into formal medical decision analysis.

In this paper the question asked was, 'What is the published literature that supports our interpreta-tions of liver pathology?' Textbooks were not used to answer this question, as these are compendiums written by experts on the basis of their experience and their knowledge of the literature. Rather, this question was addressed by identifying the 'Citation Classics' of our field. What can we learn from the most-cited (and presumably, most honored) pub-lications in this discipline? Moreover, what are the distinguishing features of these articles?

Citation classics in hepatopathology

The top 150 citations in hepatopathology were obtained through a search performed using the Thomson Science Citation Index[®], performed on 5 January 2006. Numerous terms pertaining to 'liver' and 'pathology', 'hepatopathology', 'hepatic' and 'pathology' were used, as were 'histology' and 'histopathology'. Based on foreknowledge of criti-cally important papers that were not identified through this mechanism, 'hepatitis' was searched without other qualifiers, as were 'liver' and 'cancer'. Lastly, the membership of the original International Liver Pathology Study Group, the 'Gnomes'¹⁶ was searched, owing to the fact that the field of hepatopathology was heavily influenced by the

publications emanating from these individuals. Papers selected were those that specifically featured liver pathology on human material. The Appendix A presented on p 332 gives the top 50 'citation classics'; the full citations (1–150) can be obtained on the journal web site <http://www.nature.com/labinvest/journal/v86/n4/full/3700343a.html>.

While this search strategy may inevitably lead to omission of articles, the purpose of this exercise was to identify the apparent operative principles of published hepatopathology. Hence, omission even of prominent publications (however unintentional) through this search strategy should not invalidate the effort to identify general principles. In addition, because this search strategy did not include the experimental literature derived from animal work or *in vitro* studies, critical analysis was not performed of how laboratory experimentation has informed diagnostic interpretation of human liver biopsies.

Results

The top 150 citations in Hepatopathology—our 'citation classics'—exhibited a range of citations per paper from 1921 down to 40. The publication years of cited papers were 1948 to 2002. Only the top 150 were examined, because there was an extreme 'flattening of the curve' below 40 citations per paper.

Authorship (Table 1)

Although the search strategy may be somewhat self-predicting, in point of fact the 'Gnomes' search turned up few articles that had not already been found by the topical search strategy. Hence, the first conclusion is that the publications that serve as the foundation for our subspecialty are contributed in a

substantial fashion by those hepatopathologists whom we hold in the highest regard. Over the course of the 1940s to 1980s, this original generation of hepatopathologists shaped our subspecialty in a profound fashion, not only through their teachings but through publication of their experience from case material and writing about the implication of such diagnostic findings for clinical management.

One may also observe that a younger generation of hepatopathologists (now not-so-young) can be found among the 'citation classics'. I am glad, however, that being a highly cited author is not a requirement for officership in the Hans Popper Hepatopathology Society (an official companion society of the United States and Canadian Academy of Pathology)!

Journal of Publication (Tables 2a and b)

A very striking finding is that the best in the hepatopathology literature is published, not in pathology journals, but in major journals of clinical medicine: *Hepatology*, *Gastroenterology*, *New Eng J Med*, *Lancet*, *J Hepatology*. These data are given both for the top 50 cited articles (Table 2a), and the top 150 articles (Table 2b). It seems fair to say that hepatopathologists strive to have their best work published in the major clinical journals (especially *Hepatology*). This raises a critical dilemma: how do practicing rank-and-file pathologists gain access to the best publications in hepatopathology? To the extent that pathologists in the private sector do not have electronic journal subscription access to clinical journals, as would be true through an academic medical center, *Hepatology* and *Gastroenterology*, in particular, will not be available to them. What remains is for the super-subspecialists—the declared hepatopathologists who assiduously subscribe to the sub-specialty clinical journals—to educate the general pathology community through their extended efforts: presentations at national and

Table 1 Multiple publications by Pathologists (includes multiple authorships), top 150 most-cited hepatopathology articles

Ishak K	33	Ferrell LD	7
Popper H ^a	21	Desmet VJ	6
Scheuer PJ	21	Bianchi L	4
Portmann BC	17	Neuberger J	4
Goodman ZD	13	Phillips MJ	4
Batts KP	12	Poulson H	4
Demetris AJ	11	Thung SN ^b	4
Wanless IR ^b	9	MacSween RNM	3
Ludwig J	9	Charlotte F	3
Nakanuma Y	8	Bedossa P	3

Authors with two publications: Anthony PP, Baptista A, Chapman RW, Crawford JM,^b DeGroot J, Dhillon AP, Gerber M,^b Hubscher S, Lee RG, Lefkowitz JH, Lewin K, Petrovic LM, Rodes J, Schmid M, Snover D, Sobin LH, Theise ND and Yano M.

^aNamesake of the Hans Popper Hepatopathology Society (an official companion society of the United States and Canadian Academy of Pathology).

^bPresidents of the Hans Popper Hepatopathology Society.

Table 2 Publication journals

<i>(a) Top 50 most-cited hepatopathology articles^a</i>			
Hepatology	18	Cancer	2
New Eng J Med	8	Am J Pathol	2
Lancet	5	J Am Med Assoc	2
Gastroenterology	4	J Clin Pathology	1
Ann Int Med	3	Human Pathology	1
J Hepatology	3		
<i>(b) Top 150 most-cited hepatopathology articles^b</i>			
Hepatology	44	Cancer	7
Gastroenterology	16	Ann Int Med	7
Lancet	11	Arch Pathol	6
New Eng J Med	10	Am J Pathol	3
Am J Surg Pathol	9	Am J Clin Pathol	3
J Hepatology	7	Liver	3

^aNumber of articles published in Pathology journals: 4/50.

^bSingle and double publications in journals not shown. Number of articles published in Pathology journals: 20/150.

regional meetings; lower impact articles published in the traditional surgical pathology journals. There is no easy answer to this question. This is, in fact, an issue for the breadth of academic pathology. For the first half of 2005, at least, fully half of 'human pathology' articles were published in clinical journals of higher Impact Factor than pathology journals.¹⁷ For many organ systems or tissues (especially liver, alimentary tract, and brain), the highest impact and most cited pathology articles are published in the respective clinical journals, not in the pathology literature. This raises the question of whether these publication practices by academic pathology properly foster the broader education of the practicing pathology community.

Publication Type (Table 3)

The crux of our discussion is whether the types of publication meet criteria for 'Evidence based Medicine'. Table 3 gives a classification of publication types.

The first remarkable finding is that clinical studies of viral hepatitis that include histopathological information are the strongest group of 'top 50' hepatopathology citation classics. As will be discussed below, these articles are recent (within the past 10 years), and attest to a vigorous clinical literature addressing the clinical course and pharmacological treatment of chronic viral hepatitis (Citation Classics 2,3,5,9,10,11,13,16,27,33,37,41,44,46,47). The fact that pathologists are frequent co-authors is both reassuring and essential. These articles represent, perhaps, the strongest case that

can be made for hepatopathology truly having entered into the realm of 'Evidence based Medicine'.

A second finding is that strictly pathology-oriented articles on chronic viral hepatitis, written by pathologists for pathologists, also are highly represented among 'top 50' citation classics. Chronologically starting with DeGroote *et al* in 1968 (7) and including revisions and re-revisions of the classification of viral hepatitis (Citation Classics 1,4,7,8,18,19,20,22,32,35,38), these articles are the bedrock upon which the aforementioned clinical studies are performed. An additional 20 of the articles in the 'top 51-150' also are in support of histopathological interpretation of chronic viral hepatitis (with one additional 'viral hepatitis, clinical with pathology' paper). I therefore conclude that it is the *aggregate* of these articles, 10 of the top 10, 26 out of the 'top 50', and 47 out of the 'top 150' that clearly demonstrate that hepatopathology is a well-established evidence-based subspecialty when it comes to viral hepatitis.

The emergence and reporting of non-alcoholic fatty liver disease (NAFLD, five articles in the 'top 50') and drug toxicities (two articles in the 'top 50') are important contributions by pathologists. The characterization of these important human conditions permits all practicing physicians to adapt their clinical management accordingly. A superb and rigorous literature has emerged for the recognition of hepatocellular carcinoma and its variants (three articles in the 'top 50'), and interpretation of post-transplant liver biopsies (five articles in the 'top 50'). These consist primarily of 'narrative' articles, either on the basis of case series (eg Citation Classics 15,23,42) or comprehensive consensus statements (eg Citation Classic 42).

Table 3 Publication types, top 150 most-cited hepatopathology articles

	1-10	11-20	21-30	31-40	41-50	51-100	101-150	Total 1-50	Total 1-150
Viral hepatitis, clinical with pathology	5	4	1	3	3	2	0	16	18
Viral hepatitis, pathology	5	2	2	2	1	11	7	12	30
NAFLD, clinical with pathology	0	0	1	3	1	3	0	5	8
HCC and other liver tumors, pathology	0	0	3	0	0	9	8	3	20
Liver Transplantation, pathology	0	2	0	0	3	7	11	5	23
Drug Toxicity, pathology	0	0	2	0	0	5	1	2	8
Autoimmune hepatitis, clinical with pathology	0	1	1	0	0	0	0	2	2
NRH, FNH ^a	0	0	0	1	1	1	2	2	5
Primary biliary cirrhosis, pathology	0	0	0	1	0	3	1	1	5
Stem cell biology, human liver	0	1	0	0	0	1	0	1	2
Cirrhosis, pathology	0	0	0	0	1	1	6	1	8
Hemochromatosis, pathology						2	1		3
Alcoholic liver disease, pathology						2	1		3
Cholestasis, pathology						0	3		3
Microanatomy of the human liver						0	3		3
Liver disease of pregnancy, pathology						2	1		3
Wilson's disease, pathology						0	2		2
Agonal changes of liver, pathology						0	1		1
Bone marrow transplantation, pathology						1	0		1
Alpha-1-antitrypsin deficiency, pathology						0	1		1
Sarcoidosis, pathology						0	1		1

^aHCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; NRH, nodular regenerative hyperplasia; FNH, focal nodular hyperplasia.

Declarations of consensus among clinicians and pathologists also have been a theme for autoimmune hepatitis (Citation Classics 14,29).

The reporting of extensive case series, and interpretation thereof by highly experienced pathologists, is perhaps the most-traveled form of surgical pathology scholarship. Over-and-above the case series mentioned above in the 'top 50' (Citation Classics 23,40,43), case series are very well-represented among the 'top 51–150' citation classics (57 out of 100 articles, not shown). On the one hand, these are the articles which every practicing hepatopathologist should know by heart, as they form the basis for interpretation of liver biopsies. On the other hand, these articles enable pathologists to serve as the 'gold standard' for evidence-based clinical studies, simply by declaring what disease process is actually occurring in the liver. Whether surgical pathology can truly serve as a 'gold standard', or is instead a 'tin standard' (since we are not obliged to correlate our interpretations with clinical follow-up in order to publish), is a topic beyond the scope of this review.

What remains to be determined is if reporting of case series, or deriving consensus among pathologists (or among clinicians and pathologists), has been adequately validated for each given disease category. There are occasional but important forays into this arena. In the top 150 hepatopathology citation classics, one article in particular stands out: a 1995 report by Demetris *et al.*¹⁸ (Citation Classic 137 out of 150, 46 citations) on the reliability and predictive value of a nomenclature and grading system for cellular rejection of liver allografts. The validation of a rigorous scoring system for assessment of cellular rejection in relation to its predictive value of clinical outcomes served as the foundation

principle for subsequent interpretation of liver allograft biopsies.

Years of Publication (Table 4)

Final thoughts pertain to the years of publication for our citation classics. Over half of the top 50 articles were published in the decade 1996–2005 (to be exact, 1996–2002; 27/50). 1998 and 1999 were particularly strong years (6 and 5 'top 50' publications, respectively), and almost all of these articles are clinical histories of viral hepatitis therapeutics that include histopathology data. These years are strong publication years for the outcomes of randomized clinical trials for interferon-alpha and ribavirin treatment of Hepatitis C viral infection.

The remarkable number of citations per article for 'top 10' articles (ranging from 1921 down to 762) may reflect in part the extraordinary facility for medical literature searches now made possible by electronic databases available worldwide. It may also reflect the fact that the older non-electronic literature, which cannot be down-loaded from electronic databases, is overlooked. It may simply be that there are more recent publications to cite. The exponential growth over the years of the medical literature has already been noted in a pair of somewhat whimsical letters-to-the-editor in the *New England Journal of Medicine*, whereby the pre-electronic Index Medicus volumes were weighed for each year and plotted as a function of their weight.^{19,20} However, I ultimately believe that the high citation rates for the 'top 10' are a 'true' reflection of their medical importance, owing to the fact that they support clinical practice for a vast number of hepatitis patients worldwide.

Table 4 Years of publication

	1–10	11–20	21–30	31–40	41–50	51–100	101–150	Total 1–50	Total 1–150
2005								0	0
2004								0	0
2003								0	0
2002	0	1	0	0	0	0	0	1	1
2001	1	0	0	0	1	4	1	2	7
2000	0	1	1	0	0	2	1	2	5
1999	0	0	2	2	1	1	0	5	6
1998	4	0	0	0	2	1	3	6	10
1997	1	0	0	1	1	0	2	3	5
1996	0	2	2	1	0	0	6	5	11
1991–1995	2	5	2	2	0	6	8	11	25
1986–1990	0	1	0	1	1	10	7	3	20
1981–1985	1	0	1	2	2	8	3	6	17
1976–1980	0	0	1	1	2	7	4	4	15
1971–1975	0	0	0	0	0	7	3	0	10
1961–1970	1 ^a	0	1 ^b	0	0	4	5	2	11
1951–1960						0	4	0	4
1941–1950						0	2	0	2

^aDeGroote J *et al.* A classification of chronic hepatitis. *Lancet* 1968; 2: 626–629.

^bIshak KG, Glunz PR. Hepatoblastoma and hepatocarcinoma in infancy and childhood—report of 47 cases. *Cancer* 1967; 20: 396–405.

Of particular note are two 1960s articles in the 'top 50'. The 1968 *Lancet* article by DeGroot *et al* reporting 'A classification of chronic hepatitis' is 7th in the rankings (883 citations), and is the seminal article for rigorous histological evaluation of hepatitis. While this article did not link the pathology 'interpretation' to clinical outcomes, it declares that such a classification approach may be of value for future clinical work. This hope has certainly been realized. The 1967 *Cancer* article by Ishak and Glunz describes hepatoblastoma and hepatocellular carcinoma in infancy and childhood. It is 23rd in the rankings, and has 337 citations. This is a superb example of utilizing case material in a 'narrative' fashion to map out the spectrum of human disease.

The remaining articles of the 'top 50' are well distributed through the 25 years spanning 1976–2001. These articles would truly qualify as the 'classics' of our subspecialty, as they address the key morphological findings pertinent for the diagnostic evaluation of chronic viral hepatitis, hepatocellular carcinoma and other liver neoplasms, liver transplantation, drug toxicity, and NAFLD.

The publication year frequencies of articles 51–150 are listed Table 4 as well; the extended bibliography may be accessed through the journal website. These articles represent the length-and-breadth of our subspecialty. There is a reassuringly broad spread of citation classics from the 1960s, 1970s, 1980s and 1990s. This finding supports the concept that steady effort on the part of pathologists worldwide has enabled the continued advance of our diagnostic and interpretive skills. Moreover, these articles continue to 'live on' in the published literature—a testament to their importance for our discipline.

The future of hepatopathology

It is too soon to know which articles published in 2001–2005 will become 'citation classics', and an attempt to make predictions would surely make strategic omissions. It is certainly reasonable to posit that a superb new generation of hepatopathologists will emerge, in part on the basis of the rigorous original work that they are currently performing. Articles published in 2005 that fall into an 'evidence-based' paradigm include studies of hepatocellular carcinoma staging^{21,22} and treatment,²³ and studies of the value of hepatic histologic findings in predicting the clinical outcomes of steatohepatitis²⁴ and graft-versus-host disease.²⁵ There is a healthy discussion of how to use the liver biopsy as a 'gold standard'.²⁶ Looking forward, there is eager anticipation of the publication of results for rigorous testing of histologic classification system(s) for NAFLD. The critical importance of molecular diagnostics in tissue pathology has been emphasized by ourselves¹⁷ and others. Genomic and proteomic characterization of human liver tissue is

in progress,^{27,28} and it will be critical to link these molecular data to clinical outcomes in order to fully realize the future value of liver tissue assessment. Taken collectively, there is every reason to expect that exceedingly important 'evidence based' articles will emerge in the 2001–2010 time frame.

Conclusion

This literature analysis reasonably establishes that hepatopathology, and pathologists interpreting liver biopsies, are well plugged in to efforts to use rigorous evidence to guide treatment of patients with liver disease. Both through stringent refinement of histologic classification systems, and rigorous utilization of these systems in randomized clinical controlled trials, the discipline of hepatopathology appears to stand on firm 'evidence based' ground. Second, the time-honored identification of disease process through the publication of case series constitutes the other foundation upon which we practice. Many of these case series are authored by the preeminent hepatopathologists of our age, thereby serving both the 'eminence' and 'narrative' strengths of medical knowledge. Certainly, there is room—and ongoing need—for high-quality publications from hepatopathologists worldwide. This is a necessity not only for the continued vitality of our discipline, but also for learning from case material worldwide. Third, our subspecialty should be well-suited for rigorous use of molecular techniques to assess liver disease and help drive clinical decision-making. Time will tell whether we take suitable advantage of this opportunity. Fourth, we should celebrate the worldwide community of hepatopathologists. This may be our greatest strength, in that we have opportunity to collaborate with one another, and work with our clinical colleagues worldwide. Lastly, I invite others to conduct similar analyses of their surgical pathology subspecialties, as an exercise in critically appraising the basis upon which we conduct our surgical pathology practices.

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Appendix A

Citation Classics in Hepatopathology, top 50 (as of 5 January 2006).

The full list of citations 1–150 is available on-line at <http://www.nature.com/labinvest/journal/v86/n4/full/3700403a.html>. The number in parentheses following the reference is the number of cites.

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Note added in proof: One additional paper on ‘steatohepatitis’ in NAFLD should be noted: Brunt EM, Janney CG, Di Bisceglie AM *et al.* Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. *Am J Gastroenterol* 94:2467–2474. (284)

Supplementary Information accompanies the paper on the Laboratory Investigation website (<http://www.nature.com/labinvest>).