Evidence-Based Interpretation of Liver Biopsies

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Introduction: Evidence-Based Medicine

'Evidence based Medicine' (EBM) is a term introduced in the early 1990's 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. 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. 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 the bedrock for determination of efficacy of pharmacologic therapies. 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 timeliness of resulting (turnaround times), test availability, and evaluation of test utility. At the current time, analysis of such data is an under-developed skill in Medical Directorship. Evidence-based strategies will be critical to the future development of laboratory medicine.

The application of Evidence based Medicine as a paradigm for Surgical Pathology is quite unclear. One could argue that Surgical Pathology operates in the realm of 'Eminence-based Medicine', whereby the stature and experience of the Pathologist rendering the opinion constitutes the basis for justifying the diagnostic interpretation (1,2). With regards to publications, an appropriate term might be 'Narrative-based Medicine', whereby the art of selecting the most appropriate clinical decision is acquired largely through the accumulation of narrative "case expertise" (3). 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, radiographic 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 pathological interpretation. This is not Evidence-based Medicine; 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.

A question that does not appear to have been asked in the 'Evidence based Medicine' age is, "On what basis are diagnostic opinions rendered in Surgical Pathology?" For the purposes of this discussion, the question becomes, "What is the published literature that supports our surgical pathology interpretations?" I applied the second question to the published literature in Hepatopathology, by identifying 'Citation Classics' of our field. What can we learn from the most-cited (and presumably, most honored) publications in our field? Moreover, what are the distinguishing features of these articles?

Citation Classics in Hepatopathology

The italicized references in the bibliography are the top fifty citation classics in hepatopathology. These citations were obtained by a PubMed search performed on January 5, 2006, using numerous terms pertaining to 'liver' and 'pathology', 'hepatopathology', 'hepatic' and 'pathology', and likewise

‘histology’ and ‘histopathology’. Based on foreknowledge of critically important papers which were not identified through this mechanism, ‘hepatitis’ was searched without other qualifiers, as were ‘liver’ and ‘cancer’. Lastly, the membership of the ‘Gnomes’ was searched, owing to the fact that the field of hepatopathology was heavily influenced by the publications emanating from these individuals. All searches were limited to human studies. While this search strategy may inevitably lead to omission of articles, the purpose of this exercise was identify the apparent operative principles of published hepatopathology. Hence, omission even of prominent publications through this search strategy should not invalidate the effort to identify general principles.

Some interesting data pertain.

Table 1. Publications by Authors; includes multiple authorship – TOP 150 articles (numbers 51-150 not shown in bibliography):

Author	Count	Author	Count
Ishak K	31	Ferrell LD	5
Popper H*	22	MacSween RNM	3
Scheuer PJ	22	Thung SN**	3
Portmann BC	17	Desmet VJ	3
Goodman ZD	14	Gerber M**	2
Demetris AJ	11	Dhillon AP	2
Chapman RW	11	Crawford JM**	2
Ludwig J	9	Lefkowitch J	1
Wanless IR**	8	Theise ND	1
Nakanuma Y	8	Petrovik L	1
Batts KP	7		

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Table 2A. Publication Journals, TOP 50 articles:

Journal	Count	Journal	Count
Hepatology	18	Cancer	2
New Eng J Med	8	Am J Pathol	2
Gastroenterology	5	J Am Med Assoc	2
Lancet	5	J Clin Pathology	1
Ann Int Med	3	Human Pathology	1
J Hepatology	3		

(number of articles published in Pathology journals: 4/50)

Table 2B. Publication Journals, TOP 150 articles:

Journal	Count	Journal	Count
Hepatology	40	Cancer	7
Gastroenterology	15	Ann Int Med	7
Lancet	11	Arch Pathol	6
New Eng J Med	10	Am J Pathol	3
J Hepatology	9	Am J Clin Pathol	3
Am J Surg Pathol	9	Liver	3

(number of articles published in Pathology journals: 21/150)

Table 3. Publication Types, TOP 150 articles:

	1-10	11-20	21-30	31-40	41-50	Total	51-100	101-150
Viral hepatitis, clinical with pathology	6	3	0	3	2	*14*	1	0
Viral hepatitis, pathology	4	2	2	0	1	*9*	10	9
NAFLD, clinical and pathology	0	1	0	4	3	*9*	1	0
HCC, other liver cancer, pathology	0	1	3	0	1	*5*	11	6
Liver Transplantation, pathology	0	1	0	2	1	*4*	7	11
Drug Toxicity, pathology	0	0	3	0	0	*3*	5	1
Autoimmune hepatitis	0	1	1	0	0	*2*	0	0
NRH, FNH	0	0	0	1	1	*2*	2	1
Primary biliary cirrhosis, pathology	0	0	1	0	0	*1*	3	1
Stem cell biology, human liver	0	1	0	0	0	*1*	1	0
Cirrhosis, pathology	0	0	0	0	1	*1*	1	6
Hemochromatosis, pathology							2	2
Alcoholic liver disease, pathology							2	1
Agonal changes of liver, pathology							0	2
Cholestasis, pathology							0	3
Microanatomy of the human liver							0	3
Wilson's disease, pathology							1	1
Liver disease of pregnancy, pathology							2	1
Bone marrow transplantation, pathology							1	0
Alpha-1-antitrypsin deficiency, pathology							0	1
Sarcoidosis, pathology							0	1

Table 4. Years of Publication:	1-10	11-20	21-30	31-40	41-50	Total	51-100	101-150
2005								
2004								
2003								
2002	1			1		*2*		
2001	1			1		*2*	3	1
2000		1	1		1	*3*	2	1
1999		1	2	1	1	*5*	1	
1998	4				2	*6*	1	3
1997	1			2		*3*		2
1996		2	2			*4*	1	5
1991-1995	2	5	1	1		*9*	5	10
1986-1990		1		2	3	*6*	8	7
1981-1985			2	1	1	*4*	8	2
1976-1980			1	1	2	*4*	9	4
1971-1975						*0*	7	3
1961-1970	1*		1**			*2*	5	5
1951-1960								4
1941-1950								3

DeGroote J et al. A classification of chronic hepatitis. Lancet 1968: 2: 626-629.

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

Discussion

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 1940's to 1980's, this generation of hepatopathologists shaped our subspecialty in a profound fashion, not only through their teachings but through their examination of case material and the implication of diagnostic findings for clinical management.

One may also observe that a younger generation of hepatopathologists (now not-so-young) can be found amongst 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!

Journal of Publication (Tables 2A and 2B).

A very striking finding is that the best in the hepatopathology literature is published, not in pathology journals, but in the 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 private pathologists do not have electronic subscriptions 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 regional meetings; occasional articles published in the traditional pathology journals. One could argue that this paradigm is not optimal.

Publication type (Table 3).

The crux of our discussion is whether the type 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' 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 (*1,2,4,8,9,10,12,15,24,30,34, 37,40,42,43,49*). The fact that pathologists are listed co-authors is both reassuring, and essential. These articles represent, perhaps, the strongest case that can be made for surgical pathology truly having entered into the realm of 'Evidence based medicine'.

A second finding is that it is the strictly pathology-oriented articles on chronic viral hepatitis, written by pathologists for pathologists, that also are highly represented among 'top 50' citation classics. Starting with DeGroote et al. in 1968 (*6*) and including revisions and re-revisions of the classification of viral hepatitis (*3,5,7,17,18,19,29,32*), these articles are the bedrock upon which the aforementioned clinical studies are performed. An additional 19 of the articles '51-150' also are in support of histopathological interpretation of chronic viral hepatitis. I therefore conclude that it is the *aggregate* of these articles, 10

of the top 10, and 25 out of the ‘top 50’, that clearly demonstrate that hepatopathology is a well-established evidence-based subspecialty in the realm of viral hepatitis.

The emergence and reporting of non-alcoholic fatty liver disease (NAFLD, 9 articles in the ‘top 50’) and drug toxicities (3 articles in the ‘top 50’) are important contributions of 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 (5 articles in the ‘top 50’), and interpretation of post-transplant liver biopsies (5 articles in the ‘top 50’). These may include more descriptive articles, either on the basis of case series (e.g., *21,36,39*) or comprehensive consensus statements (e.g., *38*). Consensus among clinicians and pathologists also has been a theme for autoimmune hepatitis (*13,26*).

The reporting of extensive case series, and interpretation 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’ (*21,36,39*), case series are very well-represented among the ’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 are how pathologists 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 whether it is more of 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 whether reporting of case series, or deriving consensus among pathologists, or among clinicians and pathologists, has been adequately validated. 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 on the reliability and predictive value of a nomenclature and grading system for cellular rejection of liver allografts, by Demetris et al. (4; #134 out of the ‘top 150’, 46 citations). The validation of a rigorous scoring system for assessment of cellular rejection in relation to predictive value and clinical outcomes serves as the foundation principle for interpretation of liver allograft biopsies in the clinical setting.

Years of Publication (Table 4).

Final thoughts pertain to the years of publication for our citation classics. Exactly half of the top 50 articles were published in the decade (1996-2002, to be exact; 25/50). 1998 and 1999 are particularly strong years (6 and 5 ‘top 50’, respectively), and almost all of these articles are clinical studies of viral hepatitis therapeutics that include pathology data. These years are strong publication years for the outcomes of randomized clinical trials for interferon-alpha and ribavirin for treatment of Hepatitis C viral infection. These high citation rates most likely reflect the fact that they support a clinical literature much larger than the rather focused pathology literature.

Of particular note are two 1960’s articles in the ‘top 50’. The 1968 *Lancet* article by DeGroote et al. reporting ‘A classification of chronic hepatitis’ is 6th 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 system 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 21st in the rankings, and has 337 citations. This is a superb example of utilizing case material to map out the spectrum of human disease.

The remaining 25 articles of the 'top 50' are well-distributed through the 20 years spanning 1976-1995. 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 non-alcoholic fatty liver disease.

The publication years of articles 51-150 are listed in the last two columns of Table 4. These articles represent the length-and-breadth of our subspecialty. There is a reassuring broad spread of citation classics from the 1960's, 1970's, 1980's, and 1990's. 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 as the foundations for our discipline.

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 ground. Second, the time-honored identification of disease process through the publication of case series constitutes the other bedrock upon which we practice. Many of these case series are authored by the preeminent hepatopathologists of our age, thereby serving both the 'evidence' and 'narrative' strengths of medical knowledge. Certainly, there is room – and ongoing need – for high quality publications from pathologists worldwide. This is a necessity not only for the continued vitality of our discipline, but also for access to case material worldwide. Third, our subspecialty should be well-suited for rigorous use of molecular techniques to assess liver disease and drive clinical decision-making. Time will tell whether we take suitable advantage of this opportunity. Lastly, 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.

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