

Liver Biopsy Prognostication: The Clinical Perspective
Adrian Reuben, MBBS, FRCP, FACC
Medical University of South Carolina

U.S. and Canadian Academy of Pathology
Hans Popper Hepatopathology Society
Sunday, February 11, 2006

Introduction - Origins of the Practice:

Percutaneous needle core biopsy of the liver first became popular in the 1940s and 1950s, following the appearance of several publications that reported its successful application in a substantial number of patients. A “punch-aspiration” technique was described that was preferred in Europe¹⁻³ or, using the split-pronged Vim-Silverman needle and cannula⁴, a “punch-cutting” method was performed^{5,6} that was favored in the United States. Then, interest in liver histopathology was stimulated by the prevalence of epidemics of viral hepatitis⁷, which were especially common during the Second World War on both sides of the conflict⁸⁻¹¹, and by the need to investigate many non-fatal cases of viral hepatitis¹². Iversen’s and Roholm’s fatality-free record of success with liver biopsies in 160 patients³ (later extended to more than 600 biopsies¹³) was particularly persuasive in promoting punch-aspiration liver biopsy, although they had not originated the technique. But there were serious misgivings over performing liver biopsies because mortality rates ranging from 0.3 to 1.0% were reported in the literature between 1947 and 1951, as reviewed by Terry in 1952¹⁴. In this context, it is noteworthy that the performance of the first recorded percutaneous liver biopsies by Paul Ehrlich, - which was mentioned by Friedrich Theodor von Frerichs (in whose clinic he worked) in a footnote in his monograph on diabetes¹⁵, - was severely criticized as unethical by Wilhelm Ebstein, another illustrious graduate from Frerichs’ clinic¹⁶. Similarly, a correspondent to the editor of the *Lancet* in 1945 found it “startling” that Sheila Sherlock had performed liver biopsies in patients in whom a diagnosis of acute hepatitis might have been made without a biopsy¹⁷. In a detailed retrospective analysis of morbidity and mortality from 10,600 liver biopsies that were reported between 1939 and 1951¹⁴, Terry tabulated a complication rate of 0.32% (24 cases) and deaths in 13 patients (0.12%), with some overlap both with previous series and with the 12 deaths reviewed by Hoffbauer¹³. Terry reasoned that no more than 2 patients who had a good prognosis died as a result of the biopsy, as the other 11 deaths were in “hopeless cases” who should not have undergone biopsy in the first place, especially since an acceptable coagulation status and/or patient cooperation was not assured. Despite Terry’s optimistic conclusion and the publication of a report by Schiff the previous year¹⁸ of over 700 biopsies using a Vim-Silverman needle without fatality, it was not until Menghini eventually published in English his so-called one-second needle biopsy of the liver¹⁹, and later a detailed technical explanation²⁰, that percutaneous liver biopsy became widely practised. The endorsement by Sheila Sherlock²¹, Hans Popper²² and others ensured the universal acceptance of Menghini’s device and technique, which was obviously deserved because of its speed, simplicity, sample quality, relative freedom from morbidity and very low mortality. Gerald Klatskin modified Menghini’s needle and technique by leaving out the small loose-fitting obturator in the needle hub, and by changing the tip and having it sharpened to create an internal and external bevel²³. Hoffbauer’s article¹³ gave detailed descriptions of the various biopsy needles in use before Menghini’s invention appeared. Terry’s thorough account of the biopsy procedure and its complications¹⁴ is still largely applicable today, apart from his disdain for performing liver biopsies in the ambulatory setting, as was already advocated and practised 50 years ago by Wolff and Haythorn²⁴.

Modern Liver Biopsy Practice – An Evolution:

In the Lowell Lectures that he delivered in Boston, Massachusetts, in March 1947²⁵, Harold Himsworth emphasized the importance of appreciating the anatomical (i.e. microscopic) forms of different liver diseases to predict their outcomes. His view was that even though puncture biopsy of the liver was controversial and not without risk, its discriminative use was justified, especially to differentiate between parenchymatous hepatitis and obstructive jaundice. His second indication for liver biopsy was the need to demonstrate that viral hepatitis had *not* yet recovered histologically, in order to convince an otherwise well patient not to indulge yet “in a careless regime of life.” His third indication for liver biopsy was to be able to detect liver disease at a stage when corrective action was still feasible, such as the finding of fatty liver in alcoholic patients who can then be pressed “to reform their vicious habits and adhere to an appropriate dietary”.

In 1951, Schiff¹⁸ agreed with Himsworth about the value of liver biopsy to distinguish between so-called “medical” and “surgical” jaundice. Sheila Sherlock, in the third edition of her famous textbook of hepatobiliary diseases²¹, argued that biopsy was only needed to make a diagnosis in 15% of jaundiced patients. Schiff and Sherlock advocated liver biopsy in patients with hepatomegaly, and for the elucidation of metabolic diseases, hepatic malignancies and liver involvement in hematological diseases. Both favored liver biopsy for the diagnosis of sarcoidosis and other systemic granulomatous diseases, and for monitoring the responses of various liver diseases to therapy. Both recommended liver biopsy to follow the recovery of acute viral hepatitis, and whereas Sherlock proposed liver biopsy to confirm the presence of suspected cirrhosis and as part of the investigation of fever of unknown origin, Schiff also felt that liver biopsy could distinguish between intra- and extrahepatic portal hypertension. Based on such recommendations, the use of liver biopsy increased greatly until the 1970s. Liver biopsy use declined in the 1970s and 1980s with the introduction of reliable serological tests for viral hepatitis and other diffuse liver diseases, high resolution cross-sectional imaging with ultrasound and computerized tomography, and direct biliary imaging with endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography²⁶. In the 1990s and thus far in the 2000s, the pendulum has swung back towards liver biopsy use because of the high prevalence of chronic viral hepatitis C (and to some extent hepatitis B as well), the growth of liver transplantation and the need for a histological diagnosis of graft dysfunction, and because of the latest hepatopathy of the millennium, non-alcoholic fatty liver disease (NAFLD). Authors who write about liver biopsy nowadays often refer to the common theme of its evolution²⁷⁻³². We may now be poised for another downswing in the popularity of liver biopsy, if truly reliable noninvasive tests become available to estimate hepatic fibrosis, inflammation, steatosis and malignancy. Many thorough reviews of liver biopsy have been published over the past 4 years²⁸⁻³², which deal with the indications, contraindications, routes of access to the liver, choice of needle, complications and, to some extent, the diagnostic utility of the procedure³⁰.

Indications for Liver Biopsy:

These have already been given in an earlier talk in this symposium by Professor A.D. Burt, and can be summarized as follows:

- Diagnosis, grading and staging of alcoholic and non-alcoholic liver disease and autoimmune hepatitis
- Grading and staging of chronic hepatitis C and/or B
- Diagnosis of metabolic disorders, especially hemochromatosis and Wilson disease, with metal quantitation, specific compound assay or measurement of enzyme activity, etc., as appropriate
- Evaluation of the nature and severity of intrahepatic cholestatic liver disease
- Evaluation of elevated liver enzymes and/or bilirubin and/or hepatomegaly
- Monitoring of efficacy or toxicity of treatment regimens for liver or extrahepatic disorders
- Evaluation of systemic disorders with potential hepatic involvement, e.g. granulomatous disorders, hematological malignancies, unexplained pyrexia
- Evaluation of transplant recipients with graft dysfunction or of potential liver donors
- Diagnosis of a solid liver mass
- Determination of the presence of cirrhosis that could have an impact on other therapies.

Each of these broad categories requires further clarification that space and time do not permit in detail; the reader is referred to the reviews already cited²⁷⁻³². A few practical points are worth mentioning, however. In the evaluation of the alcoholic patient, the presence of active alcoholic hepatitis after 6 months or more of alleged abstinence can raise suspicion concerning the reliability of sobriety. This may be of great importance in assessing the patient’s transplant candidacy. In patients with fatty liver disease, the biopsy findings may be of more prognostic value than in some other liver disorders^{33,34}. Confirmation of the presence of alcoholic hepatitis is generally necessary before committing the patient to steroid therapy³⁵. Before the advent of serological markers for hepatitis C and other disorders, liver biopsy identified other causes of liver disease in 10-20% of alcohol abusers³⁶, but this is no longer particularly useful in the current era³⁷. In evaluating patients with hepatitis C and to a lesser extent with hepatitis B, the finding of trivial inflammation and minimal fibrosis may be used to postpone therapy, whereas seeing advanced fibrosis may be an added spur to starting it^{38,39,40}. In patients who are co-infected with HIV and/or hepatitis B, and in bone marrow transplantation, liver biopsy is especially helpful in management⁴¹⁻⁴³. In some cases in whom a liver diagnosis has already been established,

unexplained co-morbidities may be discovered, such as alpha-1-antitrypsin deficiency, granulomatous disease or steatohepatitis. It is not uncommon nowadays for superimposed steatosis to be found in any liver disorder, which can explain continuing liver enzyme elevations that would otherwise imply that the primary liver disease is not responding to therapy. The corollary to this statement is that there is still a role for diagnostic liver biopsy in the investigation of abnormal liver tests, especially when serological results are negative⁴⁴⁻⁴⁸. In autoimmune liver disease, the histologic appearance may be of a cholangiopathy when clinically and biochemically there is hepatitis and *vice versa*, or there may be an overlap of different autoimmune processes. In other disorders, such as hemochromatosis and primary biliary cirrhosis, some authors have shown that liver biopsy may not be necessary depending upon the clinical presentation and laboratory results^{49,50,51}. In other disorders, it may be valuable to prove or disprove the presence of cirrhosis where this diagnosis could affect the therapy of another disease process, e.g. the performance of renal transplantation or bariatric surgery. These and other similar nuances of the indications for liver biopsy are covered in detail (with appropriate literature references) in the several reviews already cited²⁷⁻³².

Contraindications to Percutaneous Liver Biopsy:

Contraindications to liver biopsy (shown below), relate to situations that increase the risk of the procedure unacceptably, in comparison to the benefit. It is here that the judgment of the physician performing or requesting the biopsy (when the procedure is delegated) is of the greatest importance, especially as some contraindications may be deemed relative:

- Uncooperative or non-comprehending patient.
- Bleeding risk or history of unexplained bleeding
 - Prothrombin time more than 3 seconds prolonged and not readily corrected with simple plasma infusion
 - Platelet count <60,000 and not readily corrected by platelet transfusion
 - NSAID use within 7 days
- Absence of prior liver imaging showing anatomical suitability for biopsy
- Presence of echinococcal cyst or surface hemangioma at proposed biopsy site
- Clinically detectable or significant ascites on imaging
- Right-sided pleural effusion or empyema
- Biliary obstruction or cholangitis
- Inability to identify a suitable biopsy site by percussion or by imaging, e.g. due to anatomical distortion, morbid obesity, chest hyperinflation, etc.

It should be self-evident that liver biopsy should only be done in facilities in which there are full resuscitation resources, interventional radiology and surgical expertise close-by, and where adequate post-biopsy surveillance can be done, including the safe transport of the patient to his/her residence with companionship for at least 24 hours. There are no data concerning the safety of biopsy in a patients taking NSAIDs, but generally aspirin is avoided for 7-10 days and other NSAIDs for 3-4 days. Patients with advanced renal failure may have platelet dysfunction that can be corrected by pre-biopsy treatment with estrogen for 2 to 3 days e.g. Premarin™ (conjugated estrogens) 10mg p.o. qd for 2 to 3 days or with intravenous desmopressin (DDAVP) 0.3µg/kg body weight within 60 to 90 minutes of the procedure. Otherwise the biopsy should be performed via the transjugular route.

Choice of Needle, Biopsy Guidance and Technique:

Most liver biopsies are done percutaneously via a transthoracic axillary approach either using percussion and palpation to locate optimal site – sometimes to referred to indelicately as a “blind” biopsy, when the term percussion-guided biopsy would be better – or using ultrasonography (US) or computerized tomography (CT) for guidance. Three similar hollow bore so-called “suction” needles are available, namely the Menghini, the Klatskin and the Jamshidi, which are entirely comparable in principle. The biopsy is actually obtained by the thrusting-cutting action of the sharpened tip of the hollow needle, and the specimen is retained on withdrawal by application of mild suction. The modern counterpart of the split-pronged Vim-Silverman is the so-called Tru-Cut needle, which is solid and has a side notch (usually 2cm in length) near the tip and a snug-fitting outer sheath that slides forward and actually cuts the tissue sample. Spring-loaded versions with a built-in triggering mechanism are used commonly

nowadays. There have been numerous comparisons of these needles with respect to sample size and quality (i.e. intact or fragmented^{52,53}) and patient safety⁵⁴. In general, aspiration needles are somewhat safer and yield larger specimens with a single pass, but give fragmented samples when there is advanced fibrosis. There may be a tendency for more bleeding with larger compared to smaller diameter needles, but this is not invariable. Ultimately, needle choice is a matter of training and personal preference.

The technique of percussion-guided percutaneous liver biopsy has been described graphically recently^{28,55}, but there is no substitute for a good apprenticeship. Supervising a fellow in the performance of a liver biopsy can be nerve-racking. To paraphrase Einstein in his explanation of relativity, “When you are courting a nice girl an hour seems like a second. When you are supervising a liver biopsy a second seems like an hour”⁵⁶. Concern over the risk or failure of performing a so-called “blind” liver biopsy has led to the increasing use of imaging-assistance, especially US-guidance. To be sure, it is critical to know that there is no anatomical lesion present that could complicate the liver biopsy⁵⁷. Yet whereas the results of several studies have suggested that image-guidance leads to increased safety and higher tissue yields, this comes at a substantial monetary cost, it is still debatable whether the routine use of US truly reduces complications, provides better diagnostic material or is cost-effective⁵⁷⁻⁶⁴. The incremental cost to avoid one complication was estimated to be \$2,731.00 in 1998⁶¹. The author of this review is skeptical that having a sonographer mark the site for a proposed liver biopsy ahead of time²⁹, offers any more than psychological reassurance to the operator.

Several large surveys of biopsy practice have been reported over the past 12 years from Switzerland⁶⁵, England and Wales⁶⁶, France⁶⁷, United States^{68,69,70} and Italy⁷¹. Collectively the results of these studies showed that although liver biopsy continues to be performed in substantial numbers, there is considerable regional and individual variation in practice, with an increasing use of ultrasound guidance and/or delegation/abandonment of the procedure to radiologists. There is ambivalence to biopsy of patients with hepatitis C in some centers, and wide variation in the time periods recommended for post-biopsy observation of the patient. The use of daycare facilities varies too. Outpatient liver biopsy, which was performed at least 55 years ago²⁴, was rediscovered in the mid-1960s⁷¹ but only became popular from the late 1970s onwards⁷³⁻⁷⁶. It is surprising that there are few definite guidelines on the use of liver biopsy in clinical practice⁷⁷ and only one from the Patient Care Committee of the American Gastroenterological Association (AGA) that addresses undertaking it in the outpatient setting⁷⁸. The AGA Committee recommended a minimum of 6 post-biopsy hours observation⁷⁸, but since then this period has become eroded in some centers to as little as 1 hour^{79,80}, seemingly without misadventure. One would have thought that, by now, more than 120 years since the first core percutaneous biopsy was performed and more than 40 years after the procedure became widespread, questions of how to, where to, and who should do the biopsy, would have been answered. Yet these are still concerns for editorial comment⁸¹⁻⁸⁵, including a debate concerning the training of physician extenders to do the job, as the Mayo Clinic have demonstrated successfully⁸⁶.

Pitfalls to Liver Biopsy - Safety, Sampling and Spread:

The two major pitfalls of liver biopsy that have dogged the practice since its inception, are safety and sampling error. After Terry's 1952 assessment of morbidity and mortality over the previous 13 years of liver biopsy performance, four huge retrospective analyses were published of liver biopsy safety that included approximately 23,000⁸⁷, 20,000⁸⁸, 79,000⁸⁹ and 68,000⁵⁴ procedures. Lesser sized but still substantial series from various countries (1978-2004) were presented, containing anywhere from 117 to 12,750 biopsies (median approximately 1,000)^{54,90-96}, which included inpatient and outpatient procedures, biopsies performed by a physician assistant⁵⁴ and other operators with varying levels of experience⁹⁶, biopsies performed without or with ultrasound guidance, and liver transplant recipients⁹¹. Prompted by the publication of the outcome of patients hospitalized for complications after outpatient liver biopsy⁹², Garcia-Tsao and Boyer penned an editorial in the same journal issue⁹⁷, in which they carefully analyzed the results described in published series and their own experience of outpatient liver biopsy performed at Yale University. Overall the outpatient procedure is safe although both inpatient and outpatient biopsies in the modern era appear to have a higher complication rates (approximately 3%) compared to the much older series (approximately 0.3%), probably because of more liberal definitions of complications nowadays, such as hospitalization for pain. Deaths are rare but unfortunately do occur (0.009-0.12%) and are always a regrettable outcome of a purely diagnostic procedure. This emphasizes the need for close adherence to accepted indications and contraindications, with scrupulous attention to detail in patient assessment and conduct of the procedure. Of the complications reported, pain at the biopsy site or referred to the shoulder (sometimes due to a subcapsular

hematoma), bleeding, non-hemorrhagic hypotension, perforation of an adjacent organ (gallbladder, lung or intestine), cholangitis and bacteremia, were the most common, sometimes requiring surgical intervention or interventional radiology attention. Hematomas may be found more frequently if sought by imaging after liver biopsy but are less often a cause of morbidity^{98,99,100}. The risk of complications rises with the severity of liver disease, the presence of cirrhosis, the degree of coagulopathy and jaundice, the number of passes that are made into the liver, and with the presence of AIDS or sickle cell disease. Again, there does not seem to be an absolute requirement for imaging assistance to reduce or avoid complications. In the author's 30-year experience of percussion-guided performance of liver biopsy, including many thousands of patients, there have been 7 episodes of significant bleeding requiring admission to the hospital (3 of which were treated with blood transfusion and 2 of which were intrabiliary), 17 episodes of "bile peritonitis" that is attributed to leakage from the liver surface puncture site but not major bile duct or gallbladder perforation (as judged by rapid spontaneous resolution and the absence of any abdominal imaging abnormality) and 1 simple pneumothorax that required chest tube placement but not surgery. One death occurred in an inpatient transplant recipient with severe graft dysfunction and renal failure. The literature is replete with other rare complications of liver biopsy, such as liver abscess, biliary ascites, subcutaneous emphysema, pneumoperitoneum, pneumoscrotum, portobiliary fistula, arteriportal fistula, hepatic artery pseudoaneurysm and even retention of a broken needle. Patients with post-biopsy pain who "splint" their breathing on the right side can develop hypostatic pneumonia because of poor lung expansion, and this can be avoided by use of adequate analgesia and encouragement to breathe deeply.

There is no doubt that liver biopsy size matters, but the pathologists' insatiable desire for bigger samples must be tempered with the safety of the "tissue donor". There have been many studies of sampling variation and error over many decades¹⁰¹⁻¹⁰³, especially recently in patients with chronic hepatitis C¹⁰⁴⁻¹⁰⁷ in whom up to 30% false-negativity rates for cirrhosis have been reported¹⁰⁶. Whereas even the most clinician-friendly hepatopathologist will not commit himself^{107,108} to an exact biopsy size, it seems that he would be reasonably content with a 2cm long x 1.4mm wide specimen that preferably contains 11, but certainly not less than 6 portal tracts^{107,108}. Smaller but focally accurate samples from liver tumors, and even fine-needle aspiration cytology, might suffice in this special situation. With respect to liver cancer histopathological diagnosis, there is the continuing concern over tumor seeding even with fine needle aspiration sampling. In one study¹⁰⁹ of 150 patients who underwent 1-3 passes of tumor sampling with 18-20 gauge needles, 4 (2.7%) suffered subcutaneous metastasis at the needle insertion site. A similar experience from Honolulu¹¹⁰ of 3/59 (5%) patients who developed needle-tract implantation from hepatocellular carcinoma, reinforces the current growing grassroots consensus to only biopsy liver tumors when the diagnosis cannot be made with certainty by a combination of imaging and circulating tumor marker measurements, especially in transplant candidates.

Alternative Routes to the Liver - Transvenous and Intraabdominal:

For patients in whom percutaneous liver biopsy is contraindicated, has failed or is otherwise not feasible, the liver may be accessed transvenously, usually via the jugular vein, or per-abdominally by laparoscopy or laparotomy. Once the feasibility of the transvenous route was confirmed in dogs¹¹¹ and applied to humans¹¹², transjugular liver biopsy was taken up in many liver centers worldwide¹¹³⁻¹¹⁶. The transjugular approach is particularly applicable²⁹ to patients with:

- Severe coagulopathy
- Massive ascites
- Massive obesity
- Suspected vascular liver lesions
- The need for additional hepatic venous access, for hepatic venous pressure measurements or placement of a transjugular intrahepatic portosystemic shunt.

About 10 years ago, technical improvement of the transjugular biopsy needle, which is of the side-notch cutting type, and its delivery system, led to improved sample sizes that are now usually adequate for histological assessment¹¹⁷. The complication rates are higher than for percutaneous biopsies¹¹⁸⁻¹²⁰, as to be expected in this sick patient population. Adverse events are usually related to the site of access in the neck, the adjacent structures, and perforation of the liver capsule, especially in patients with small livers. On the other hand, transjugular liver biopsy is particularly applicable to patients with congenital bleeding disorders, as shown recently from Canada, in the largest series yet reported in such patients¹²¹.

Laparoscopy comes into its own when it is desirable to view the liver grossly, looking for lesions that might not otherwise be apparent by cross-sectional imaging, or to stage their extent, notably in liver cancer. Laparoscopy allows several biopsies to be taken from different regions and lesions within the liver, especially if combined with laparoscopic US. Laparoscopy also allows examination of the peritoneal cavity and intraabdominal masses. Severe cardiopulmonary disease, intestinal obstruction, and peritonitis are absolute contraindications to laparoscopy, which may also be compromised by massive obesity or a large ventral hernia. There are now only a few dedicated hepatological aficionados of this technique, which is reputed to provide definitive diagnosis in 98% of patients with chronic liver disease, at the modest cost of 0.45% complications¹²². For the rest of the hepatology community, when there is a call for laparoscopic liver biopsy, the surgeon is called.

Alternatives to Liver Biopsy - Serology and Sound:

For some liver diseases, parameters have been defined from clinical and laboratory variables that permit estimation of the state of liver injury and scarring without needing to resort to liver biopsy. This is the case with hemochromatosis, primary biliary cirrhosis^{49,50,51} and perhaps some instances of non-alcoholic fatty liver disease. The goal may yet be realized, to perfect the serological diagnosis of fibrosis in other liver diseases too¹²³, and this topic will be reviewed by Dr. Bedossa. Another approach that has promise, is the measurement of liver stiffness non-invasively by so-called transient elastography (Fibroscan®, EchoSENS, Paris, France)¹²⁴. The method uses both US (5 MHz) and low-frequency elastic waves (50 Hz) whose propagation velocity is related directly to elasticity. Thus far this painless, speedy, objective and apparently reproducible technique has been applied to patients with chronic hepatitis C and has been compared with liver biopsy and serological markers^{125,126}. Confirmation of its objectivity and validity is awaited.

Conclusion:

Biopsy is still referred to as the “gold standard” for the diagnosis of liver disease, but this may now be a somewhat tarnished metaphor. A gold standard test should be definitive in determining whether an individual has a disease process or not, with 100% sensitivity and specificity. In practice this is not practicable, and even a so-called gold standard test may have false-positives and false-negatives. For liver biopsy, the result must be interpreted in the context of the history, physical findings and results of other investigations. For cirrhosis, for example, the diagnosis may seem obvious clinically, such as in the patient with jaundice, hepatomegaly, ascites, leg edema, low albumin, elevated liver enzymes and coagulopathy – unless, of course, this syndrome results from constrictive or restrictive cardiac disease, or another primary non-hepatic disorder. It is easy to be fooled by one disease masquerading as another. By the same token, a negative liver biopsy does not necessarily exclude cirrhosis and an apparently positive one may be misleading too. In some patients it may not be justified to perform a liver biopsy, by any method, because of risk or because the result will not alter management or even the psychological care of the patient. It should be remembered that in financial terms a gold standard meant that gold is held to backup bank notes or other legal tender. This practice, which started in 1871 in the newly-united Germany following the Franco-Prussian War, was slowly adopted by other nations and only became law in the United States in 1900. The international gold system, as it was then, more or less collapsed in 1933 after the Depression, with financial convulsions through the Second World War and afterwards, until it really died in 1971. Perhaps we should not use this obsolete and confusing analogy for liver biopsies. Notwithstanding, it will be difficult for dyed-in-the-wool hepatologists to think of abandoning their most prized stock-in-trade investigation. Or perhaps, as psychologist Abraham Maslow reasoned, it is simply the case that “when the only tool you own is a hammer, every problem begins to resemble a nail.” Despite some gastroenterologists railing against it¹²⁷, it seems highly likely, however, that irrespective of exciting developments in non-invasive testing in liver disease, hepatologists will continue to *hammer* away at liver biopsies (whether they wield the needle or appoint a surrogate) and pathologists will still be needed to *nail* the diagnoses, for a long time yet.

References

1. Huard P, May JM, Joyeux B. La ponction biopsie du foie et son utilité dans le diagnostic des affections hépatiques. *Ann. Anat. Path. Anat. Norm. Méd.-chir.* 1935;12:1118-1124.
2. Baron E. Aspiration for removal of biopsy material from the liver. *Arch. Intern. Med.* 1939;63:276-289.
3. Iversen P, Roholm K. On aspiration biopsy of the liver, with remarks on its diagnostic significance. *Acta Med. Scandinav.* 1939;102:1-16.
4. Silverman I. A new biopsy needle. *Am. J. Surg.* 1938;40:671-672.
5. Tenophr J, Silverman I. The importance of biopsy in tumor diagnosis. *Radiology* 1941;36:57.
6. Tripoli C, Fader D. The differential diagnosis of certain diseases of the liver by means of punch biopsy. *Am. J. Clin. Path.* 1941;11:516.
7. Roholm K, Iversen P. Changes in the liver in acute epidemic hepatitis (catarrhal jaundice) based on 38 aspiration biopsies. *Acta Path. et Microbiol. Scandinav.* 1939;16:427.
8. Axenfeld H, Brass K. Klinische und biopische Untersuchungen über den sogenannten icterus catarrhalis. *Frankfurt Z. Path.* 1942;57:147-236.
9. Dible JH, McMichael J, Sherlock SPV. Pathology of acute hepatitis – Aspiration biopsy studies of epidemic, arsenotherapy and serum jaundice. *Lancet* 1943;2:402-408.
10. Mallory TB. The pathology of epidemic hepatitis. *JAMA* 1947;134:655.
11. Krarup NB. The development of cirrhosis of the liver after acute hepatitis, elucidated by aspiration biopsy. *Acta. Med. Scandinav.* 1941;108:48.
12. Volwiler W, Elliot JA. Late manifestations of epidemic infectious hepatitis. *Gastroenterology* 1948;10:349.
13. Hoffbauer FW. Needle biopsy of the liver. *JAMA* 1947;134:666-670.
14. Terry R. Risks of needle biopsy of the liver. *Brit. Med. J.* 1952;1:1102-1105.
15. Frerichs FT. Über den Diabetes. Berlin. A. Hirschwald 1884, page 272.
16. Ebstein W. Die Zuckerharnruhr ihre Theorie und Praxis. Wiesbaden. Verlag von JF Bergmann 1887.
17. Levy H. Liver biopsy. *Lancet* 1945;2:480.
18. Schiff L. The clinical value of needle biopsy of the liver. *Ann. Intern. Med.* 1951;34:948-967.
19. Menghini G. One-second needle biopsy of the liver. *Gastroenterology* 1958;35:190-199.
20. Menghini G. One-second biopsy of the liver – problems of its clinical application. *N. Eng. J. Med.* 1970;283:582-585.
21. Sherlock S. Diseases of the liver and biliary system. 3rd Edition. Oxford. Blackwell Scientific Publications. 1963.
22. Perez V. Chapter 29. In: Berk PD, Schaffner F, Schmid R eds. Hans Popper: A tribute. New York. Raven Press 1992. page 121.

23. Klatskin G, Conn HO. Histopathology of the liver. Volume 1. Chapter 1. Techniques. New York. Oxford University Press 1993. Pages 4-5.
24. Wolff RA, Haythorn SR. The liver biopsy in the diagnosis of liver disease. Pa. Med. 1950;53:344-348.
25. Himsworth HP. Puncture biopsy of the liver. Chapter VI. The syndrome of hepatic failure. In: Lectures on the liver and its diseases, comprising the Lowell Lectures delivered at Boston, Massachusetts in March 1947. Oxford UK. 1947, pages 137-138.
26. Reuben A. A tree grows in the liver, and now we can see it. HEPATOLOGY 2005;41:1201-1206.
27. van Leeuwen DJ, Wilson L, Crowe DR. Liver biopsy in the mid-1990s: Questions and answers. Seminars in Liver Disease 1995;15:340-359.
28. Adams TL, Lewis JL. Percutaneous liver biopsy. Clinical Perspectives in Gastroenterology 2002;March/April:117-121.
29. Bravo AA, Sheth SG, Chopra S. Liver biopsy. N. Engl. J. Med. 2001;344:495-500.
30. Campbell MS, Reddy KR. Review article: the evolving role of liver biopsy. Aliment Pharmacol. Ther. 2004;20:249-259.
31. Siegel CA, Silas AM, Surlawinata AA, van Leeuwen DJ. Liver biopsy 2005;When and how? Cleveland Clinic Journal of Medicine 2005;72:199-224.
32. Sheela H, Seela S, Caldwell C, Boyer JL, Jain D. Liver biopsy. Evolving role in the new millennium. J. Clin. Gastroenterol. 2005;39:603-610.
33. Matteoni CA, Younossi ZM, Gramlich T, Bopari N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999;116:1413-1419.
34. Teli MR, James OF, Burt AD, Bennett MK, Day CP. The natural history of nonalcoholic fatty liver disease: a follow-up study. HEPATOLOGY 1995;22:1714-1719.
35. O'Shea RS, McCullough AJ. Treatment of alcoholic hepatitis. Clinics in Liver Disease 2005;9:103-134.
36. Levin DM, Baker AL, Riddell RM, Rochman M, Boyer JL. Nonalcoholic liver disease. Overlooked causes of liver injury in patients with heavy alcohol consumption. Am. J. Med. 1979;66:429-434.
37. Talley NJ, Roth JA, Hench WV. Diagnostic value of liver biopsy in alcoholic liver disease. J. Clin. Gastroenterol. 1988;10:647-650.
38. Dienstag JL. The role of liver biopsy in chronic hepatitis C. HEPATOLOGY 2002;36:S152-S160.
39. Pradat P, Alberti A, Poynard T, Esteban J-I, Weiland O, Marcellin P, Badalamenti S, Trépo C. Predictive value of ALT levels for histologic findings in chronic hepatitis C: A European collaborative study. HEPATOLOGY 2002;36:973-977.
40. Herrine SK, Friedman LS. Divining the role of liver biopsy in hepatitis C. J. Hepatol. 2005;43:374-376.
41. Ma SY, Au WY, Ng IO, Lie AK, Leung AY, Liang RH, Lau GK, Kwong YL. Role of liver biopsy in the management of liver dysfunction after hematopoietic stem-cell transplantation in a hepatitis B virus-prevalent patient population. Transplantation 2003;15:169-176.

42. Quereda C, Moreno S, Moreno L., Moreno A, Garcia-Sanmiguel L, Perez-Elas MJ, Navas E, Dronda F, Morena A, Casado J, Antela A, Lopez-San Roman A. The role of liver biopsy in the management of chronic hepatitis C in patients infected with the human immunodeficiency virus. *Human Pathology* 2004;35:1083-1087.
43. Crockett SD, Keffe EB. Natural history of treatment of hepatitis B virus and hepatitis C virus coinfection. *Annals of Clinical Microbiology and Antimicrobials* 2005;4:13. DOI:10.1186/1476-0711-4-13
44. Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *N. Engl. J. Med.* 2000;342:1266-1271.
45. Moix FM, Raufman JP. The role of liver biopsy in the evaluation of liver test abnormalities. *Clinical Cornerstone* 2001;3:13-23.
46. Skelly MM, James PD, Ryder SD. Findings on liver biopsy to investigate abnormal liver function studies in the absence of diagnostic serology. *J. Hepatol.* 2001;35:195-199.
47. Blanchi L. Liver biopsy in elevated liver function tests? An old question revisited. *J. Hepatol.* 2001;35:290-294.
48. Sprycher C, Zimmermann A, Reichen J. The diagnostic value of liver biopsy. *BMC Gastroenterology* 2001;1:12. <http://www.biomedcentral.com/1471-230X/112>.
49. Guyader D, Jaquelinet C, Moirand R, Turlin B, Mendler MH, Chaperon J, David V, Brissot P, Adams P, Deugnier Y. Noninvasive prediction of fibrosis in C282Y homozygous hemochromatosis. *Gastroenterology* 1998;115:929-936.
50. Beaton M, Guyader D, Deugnier Y, Moirand R, Chakrabati S, Adams P. Noninvasive prediction of cirrhosis in C282Y-linked hemochromatosis. *HEPATOLOGY* 2002;36:673-678.
51. Zein CO, Angulo P, Lindor KD. When is liver biopsy needed in the diagnosis of primary biliary cirrhosis. *Clinical Gastroenterology and Hepatology* 2003;1:89-95.
52. Bateson MC, Hopwood D, Duguid HLD, Bouchier IAD. A comparative trial of liver biopsy needles. *J. Clin. Pathol.* 1980;33:131-133.
53. Colombo M, del Ninno E, de Franchis R, de Fazio C, Festorazzi S, Ronchi G, Tommasini MA. Ultrasound-assisted percutaneous liver biopsy: superiority of Tru-cut over the Menghini needle for the diagnosis of cirrhosis. *Gastroenterology* 1982;83:338-340.
54. Piccino T, Sagnelli E, Pasquale G, Giusti G. Complications following percutaneous liver biopsy. A multicenter retrospective study on 68,276 biopsies. *J. Hepatol.* 1986;2:165-173.
55. Kugelmas M. Liver biopsy. *Am. J. Gastroenterol.* 2004;99:1416-1417.
56. Reuben A. Just a second. *HEPATOLOGY* 2003;38:1316-1320.
57. Riley TR III. How often does ultrasound marking change the liver biopsy site? *Am. J. Gastroenterol.* 1999;94:3320-3322.
58. Vautier G, Scott B, Jenkins D. Liver biopsy: blind or guided. *Brit. Med. J.* 1994;309:1456-1455.
59. Caturelli E, Giacobbe A, Facciorusso D, Bisceglia M, Villani MR, Siena D, Fusilli S, Squillante MM, Andriulli A. Percutaneous biopsy in diffuse liver disease: increasing diagnostic yield and decreasing complication rate by routine ultrasound assessment of puncture site. *Am. J. Gastroenterol.* 1996;91:1318-1321.

60. Lindor KD, Bru C, Jorgensen RA, Rakela J, Bordas JM, Gross JB, Rodes J, McGill DB, Reading CC, James EM, Charboneau JW, Ludwig J, Batts KP, Zinsmeister AR. The role of ultrasonography and automatic-needle biopsy in outpatient percutaneous liver biopsy. *HEPATOLOGY* 1996;23:1079-1083.
61. Pasha T, Gabriel S, Therneau T, Dickson ER, Lindor KD. Cost effectiveness of ultrasound-guided liver biopsies. *HEPATOLOGY* 1998;27:1120-1126.
62. Younossi ZM, Teran C, Ganiats TG, Carey WD. Ultrasound-guided liver biopsy for parenchymal liver disease: an economical analysis. *Dig. Dis. Sci.* 1998;43:46-50.
63. Farrell RJ, Smiddy PF, Pilkington RM, Tobin AA, Mooney EE, Temperley IJ, McDonald GS, Bowmer HA, Wilson GF, Kelleher D. Guided versus blind liver biopsy for chronic hepatitis C: clinical benefits and cost. *J. Hepatol.* 1999;30:580-587.
64. Almad M, Riley TR. Can one predict when ultrasound will be useful with percutaneous liver biopsy? *Am. J. Gastroenterol.* 2001;96:547-549.
65. Froehlich F, Lamy O, Fried M, Gonvers JJ. Practice and complications of liver biopsy. Results of a nationwide survey in Switzerland. *Dig. Dis. Sci.* 1993;38:1480-1485.
66. Gilmore IT, Burroughs A, Murray-Lyon IM, Williams R, Jenkins D, Hopkins A. Indications, methods, and outcomes of percutaneous liver biopsy in England and Wales: an audit by the British Society of Gastroenterology and the Royal College of Physicians of London. *Gut* 1995;36:437-441.
67. Cadranet J-F, Rufat P, Degos F. Practices of liver biopsy in France: Results of a prospective nationwide survey. *HEPATOLOGY* 2000;32:477-481.
68. Mayoral W, Lewis JH. Percutaneous liver biopsy. What is the current approach? Results of a questionnaire. *Dig. Dis. Sc.* 2001;46:118-127.
69. Muir AJ, Trotter JF. A survey of current liver biopsy practice patterns. *J. Clin. Gastroenterol.* 2002;35:86-88.
70. Angtuaco TL, Lal SK, Banaad-Omiotek GD, Zaidi SSA, Howden CW. Current liver biopsy practices for suspected parenchymal liver diseases in the United States: The evolving role of the radiologist. *Am. J. Gastroenterol.* 2002;97:1468-1471.
71. Almasio PL, Niero M, Angioli D, Ascione A, Guillini S, Minoli G, Oprandi NC, Pinzello GB, Verme G, Andriulli A. Expert opinions on the role of liver biopsy in HCV infection: A Delphi survey by the Italian Association of Hospital Gastroenterologists. *J. Hepatol.* 2005;43:381-387.
72. Frank H, Leodolter I. Praktische Erfahrungen mit der ambulanten Leberbiopsie. *Wien Klin. Wschr.* 1966;78:756-758.
73. Knauer CM. Percutaneous biopsy of the liver as a procedure for outpatients. *Gastroenterology* 1978;74:101-102.
74. Perrault J, McGill DB, Ott DM, Taylor WF. Liver biopsy complications in 1000 inpatients and outpatients. *Gastroenterology* 1978;74:103-106.
75. Westaby D, MacDougall BRD, Williams R. Liver biopsy as a day-care procedure – selection and complications in 200 consecutive patients. *Brit. M. J.* 1980;281:1331-1332.
76. Judmaier G, Kathrein H. Ultraschallunterstützte perkutane Leber ‘blind’-Punktion. *Ultraschall* 1983;4:81-84.

77. Grant A, Neuberger J. Guidelines on the use of liver biopsy in clinical practice. *Gut* 1999;45 (Suppl.V);IV1-IV11.
78. Jacobs WH, Goldberg SB. Statement on outpatient percutaneous liver biopsy. *Dig. Dis. Sci.* 1989;34:322-323.
79. Bicknell SG, Richenberg J, Cooper PL, Tiwari P, Halperin L. Early discharge after core liver biopsy: is it safe and cost-effective. *Can. Assoc. Radiol. J.* 2002;53:205-209.
80. Firpi RJ, Soldevila –Pico C, Abdelmalek MF, Morelli G, Judah J, Nelson DR. Short recovery time after percutaneous liver biopsy: should we change our current practices? *Clin. Gastroenterol. Hepatol.* 2005;3:926-929.
81. Schiff ER. Should liver biopsies be relegated to the radiology suite? *Gastrointestinal Endoscopy* 1987;33:330.
82. McGill DB. Liver biopsy: When, how, by whom and where? *Curr. Gastroenterol. Rep.* 2001;3:19-23.
83. Griffiths A, Viñala CH, Olynyk JK. Liver biopsy in the 21st Century: where and why? *Med. J. Aust.* 2002;176:52-53.
84. van Leeuwen DJ. Liver biopsy: who should do it... and who will show up in court? *Am. J. Gastroenterol.* 2002;97:1285-1288.
85. Friedman LS. Controversies in liver biopsy: who, where, when, how, why? *Current Gastroenterology Reports* 2004;6:30-36.
86. Gunneson TJ, Menon KV, Wiesner RM, Daniels JA, Hay JE, Charlton MR, Brandhagen DJ, Rosen CB, Porayko MK. Ultrasound-assisted percutaneous liver biopsy performed by a physician assistant. *Am. J. Gastroenterol.* 2002;97:1472-1475.
87. Thaler H. Über Vorteil und Risiko der Leberbiopsiemethode nach Menghini. *Wien Klin. Wochenschr.* 1964;76:533-538.
88. Wildhirt E, Moller E. Experience with nearly 20,000 blind liver punctures. *Med. Klin.* 1981;76:254-255.
89. Lindner H. Grenzen und Gefahren der perkutanen Leberbiopsie mit der Menghini-Nadel. Erfahrungen bei 80,000 Leberbiopsien. *Dtsch. Med. Wochenschr.* 1967;39:1751-1757.
90. Sherlock S, Dick R, Van Leeuwen DJ. Liver biopsy today. The Royal Free Hospital experience. *J. Hepatol.* 1984;1:75-85.
91. van Thiel DM, Gavalier JS, Wright H, Tzakis A. Liver biopsy: Its safety and complications as seen at a liver transplant center. *Transplantation* 1993;55:1087-1090.
92. Janes CH, Lindor KD. Outcome of patients hospitalized for complications after outpatient liver biopsy. *Ann. Int. Med.* 1993;118:96-98.
93. Al Omair A, Al Bakr F, Al Traif I. Outpatient percutaneous blind needle liver biopsy: safety and cost analysis. *Ann. Saudi Med.* 1997;17:503-505.
94. Vivas S, Palacio MA, Rodriguez M, Lomo J, Cadenas F, Giganto F, Rodrigo L. Ambulatory liver biopsy: complications and evolution in 264 cases. *Rev. Esp. Enferm Dig.* 1998;90:175-182.

95. Montalto G, Soresi M, Carroccio A, Bascone F, Tripli S, Aragona F, di Gaetano G, Notarbartolo A. Percutaneous liver biopsy: A safe outpatient procedure? *Digestion* 2001;63:55-60.
96. Chevalier P, Ruitort F, Denys A, Staccini P, Saint-Paul MC, Ouzan D, Montamedi JP, Tran A, Schnyder P, Bruneton JN. Influence of operator experience on performance of ultrasound-guided percutaneous liver biopsy. *Eur. Radiol.* 2004;14:2086-2091.
97. Garcia-Tsao G, Boyer JL. Outpatient liver biopsy: How safe is it? *Ann. Int. Med.* 1993;118:150-153.
98. Minuk GY, Sutherland LR, Wiseman DA, MacDonald FR, Ding DL. Prospective study of the incidence of ultrasound-detected intrahepatic hematomas in patients randomized to 6 or 24 hours of bed rest after percutaneous liver biopsy. *Gastroenterology* 1987;92:290-293.
99. Sugano S, Sumino Y, Hatori T, Mizugami H, Kawafune T, Abei T. Incidence of ultrasound-detected intrahepatic hematomas due to Tru-cut needle liver biopsy. *Dig. Dis. Sci.* 1991;36:1229-1233.
100. Glaser J, Mann O, Siegmüller M, Pausch J. Prospective study of the incidence of ultrasound-detected hepatic hematomas due to percutaneous Menghini needle liver biopsy and laparoscopy-guided Silverman needle biopsy. *Ital. J. Gastroenterol.* 1994;26:338-341.
101. Abdi W, Millan JC, Mezey E. Sampling variability on percutaneous liver biopsy. *Arch. Intern. Med.* 1979;139:667-669.
102. Hølund B, Poulsen H, Schichting P. Reproducibility of liver biopsy in relation to the size of the specimen. *Scand. J. Gastroent.* 1980;15:329-335.
103. Maharaj B, Leary WP, Naran AD, Maharaj RJ, Coopan RM, Pirie D, Pudifin DJ. Sampling variability and its influence on the diagnostic yield of percutaneous needle biopsy of the liver. *Lancet* 1986;1:523-525.
104. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, Feng Z-Z, Reddy KR, Schiff ER. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am. J. Gastroenterol.* 2002;97:2614-2618.
105. Colloredo G, Guido M, Sonzogni A, Leandro G. Impact of liver biopsy size on histological evaluation of chronic viral hepatitis: the smaller the sample, the milder the disease. *J. Hepatol.* 2003;39:239-244.
106. Bedossa P, Dargère D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *HEPATOLOGY* 2003;38:1449-1457.
107. Scheuer PJ. Liver biopsy size matters in chronic hepatitis: Bigger is better. *HEPATOLOGY* 2003;38:1356-1357.
108. Demetris AJ, Ruppert K. Pathologist's perspective on liver needle biopsy size? *J. Hepatol.* 2003;39:275-277.
109. Chapoutot C, Perney P, Fabre D, Taourel P, Bruel JM, Larrey D, Domergue J, Ciurana AJ, Blanc F. Needle-tract seeding after ultrasound-guided puncture of hepatocellular carcinoma. A study of 150 patients. *Gastroenterol. Clin. Biol.* 1999;23:552-556.
110. Takamori R, Wong LL, Dang C, Wong L. Needle-tract implantation from hepatocellular cancer: is needle biopsy of the liver always necessary? *Liver Transpl.* 2000;6:73-75.
111. Dotter CT. Catheter biopsy: experimental technique for transvenous liver biopsy. *Radiology* 1964;82:312-314.

112. Rosch J, Lakin PC, Antonovic R, Dotter CT. Transjugular approach to liver biopsy and transhepatic cholangiography. *N. Engl. J. Med.* 1973;289:227-231.
113. Lebrec D, Buyschaert M, Dégott C, Rueff B, Benhamou JP. Hepatic puncture biopsy by the transjugular route. *Nouv. Presse Med.* 1976;5:2135-2137.
114. Gilmore IT, Bradley RD, Thompson RP. Transjugular liver biopsy. *Brit. Med. J.* 1977;2:100-101.
115. Goldman ML, Gonzalez AC, Galambos JT, Gordon IJ, Oen KT. The transjugular technique of hepatic venography and biopsy, cholangiography, and obliteration of esophageal varices. *Radiology* 1978;128:325-331.
116. Gamble P, Colapinto RF, Stronell RD, Colman JC, Blendis L. Transjugular liver biopsy: a review of 461 biopsies. *Radiology* 1985;157:589-593.
117. Chan T-N, Tong S-W, Li T-M, To H-T, Lee K-C, Lai J-Y, Lai S-T, Yuen M. Transjugular liver biopsy with an automated trucut type needle: comparative study with percutaneous liver biopsy. *Eur. J. Gastroenterol. Hepatol.* 2002;14:19-24.
118. Lebrec D, Goldfarb G, Degott C, Rueff B, Benhamou JP. Transvenous liver biopsy; An experience based on 1000 hepatic tissue samplings. *Gastroenterology* 1982;83:338-340.
119. McAfee JH, Keefe EB, Lee RG, Rosch J. Transjugular liver biopsy. *HEPATOLOGY* 1992;15:726-732.
120. Garcia-Compean D, Cortes C. Transjugular liver biopsy. An update. *Ann. Hepatol.* 2004;3:100-103.
121. Shin JL, Teitel J, Swain MG, Bain VG, Adams PC, Croitoru K, Peltkekian K, Schweiger F, Simons ME, Heathcote EJ. A Canadian multicenter retrospective study evaluating transjugular liver biopsy in patients with congenital bleeding disorders and hepatitis C. Is it safe and useful? *Am. J. Hematol.* 2005;78:85-93.
122. Vargas C, Jeffers LJ, Bernstein D, Reddy KR, Munnangi S, Behar S, Scott C, Parker T, Schiff ER. Diagnostic laparoscopy: a 5 year experience in a hepatology training program. *Am. J. Gastroenterol.* 1995;90:1258-1262.
123. Afdhal NH, Nunes D. Evaluation of liver fibrosis: A concise review. *Am. J. Gastroenterol.* 2004;99:1160-1174.
124. Sandrin L, Fourquet B, Hasquenoph J-M, Yon S, Fournier C, Mal F, Christidis C, Ziol M, Poulet B, Kazemi F, Beaugrand M, Polau R. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med. Biol.* 2003;29:1705-1713.
125. Ziol M, Handra-Luca A, Kettaneh A, Christidis C C, Mal F, Kazemi F, de Ledinghen V, Marcellin P, Dhumeaux D, Trinchet JC, Beaugrand M. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. *HEPATOLOGY* 2005;41:48-54.
126. Castero L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, Darriet M, Couzigon P, de Ledinghen V. Prospective comparison of transient elastography, Fibrotest, APRI and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005;128:343-350.
127. Andriulli A, Annese V, Facciorusso D, Giacobbe A. First, do no harm: Power, oppression and violence of liver biopsy. *Gastroenterology* 2003;125:272-284.