The Value of Liver Biopsy

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We have tried to determine whether it is still true that an accurate hepatological diagnosis can only be achieved with liver biopsy, or if the information from a liver biopsy could be obtained using other simpler, non-invasive techniques. The value of a test, in the medical context, implies more than just accuracy.

A test result is of value if the information so obtained can enable the doctor to improve the patient's existing state of health. Thus, liver biopsy data are valuable if of help in classifying patients in such a way that treatment is improved.

One of the most important effects of a test result is the degree of confidence that it gives to a doctor when evaluating the problem in hand. Confidence is reflected in a number of ways. The accuracy of liver biopsy data in discriminating between different diseases can be easily assessed for conditions in which the true diagnosis can be established by alternative techniques. For example, in assessing jaundiced patients with suspected extrahepatic biliary obstruction, the true diagnosis can be obtained using cholangiographic techniques such as endoscopic retrograde cholangiopancreatography and percutaneous cholangiography, which give direct visualisation of the biliary tree. The discriminating ability of liver biopsy can then be tested by comparing the biopsy data with those obtained from cholangiography. This is, of course, not possible in conditions such as chronic active hepatitis where liver biopsy is the main yardstick available for evaluation.

However, irrespective of its discriminating ability, the value of liver biopsy will also depend on the competence of the histopathologist in producing an accurate histological report, thus the observer's error should be low. But, to determine the 'truth' is also crucial to the evaluation of observer error. Again, for conditions where alternative approaches to diagnosis are available, the 'truth' can be determined and, hence, the histopathologist's accuracy or error checked. However, in the absence of alternative diagnostic criteria, all we can do is to make estimates of the truth; for example by taking the consensus opinion as the truth and then calculating how far the reported observation differed from the estimate. At this stage we must take into account the reliability or reproducibility of liver biopsy data, i.e. the degree of observer agreement or variation; for observer agreement and error, although fundamentally different in nature, are in fact intimately related. If a number of observers cannot agree about a certain feature, observer agreement will be low and this will most certainly result in observer error.

The cost of obtaining liver biopsy data includes both the financial cost to the NHS and the cost to the patient in terms of taking time off work and the associated morbidity and mortality of the procedure. The cost to the NHS is approximately £30, but this does not include the cost of the patient's overnight stay in hospital. However, a patient need not necessarily take much time off work to have a liver biopsy, as the technique has now been reported[1] to be a successful and safe procedure for outpatients. The overall morbidity and mortality is very low[2, 3] and the incidence of bleeding, one of the most serious complications of liver biopsy, may well be reduced in selected cases with the more widespread use of the transvenous liver biopsy technique[4, 5].

When characterising different diseases with liver biopsy data, the histological features themselves are useful the more frequently they are found; for example, bile lakes are held to be pathognomonic of large bile duct obstruction and as such are a valuable marker for this condition. However, the rarity of bile lakes may prevent them from being as useful as if they were more commonly encountered.

Clinical Studies Relating to the Value of Liver Biopsy

Schiff and his associates[6] reported that out of 1455 liver biopsies undertaken for various hepatological problems, 75 per cent were of significant aid in establishing the diagnosis and 24 per cent of these led to a change in the original clinical opinion. However, 16 per cent were non-contributory, 3 per cent were misleading and failure to obtain an adequate specimen occurred in 6 per cent of cases. Morris and co-workers[7] in evaluating jaundiced patients with possible extrahepatic biliary obstruction, found that of 127 liver biopsies, 81 per cent were important in diagnosing the presence of large duct obstruction. But the liver biopsy data showed evidence of cholestasis alone in 12 per cent, were misleading in 5 per cent and biopsy failed in 2 per cent. Complications, which did not include any deaths, occurred in 6 per cent.

Sampling Error and Observer Variation for a Single Observer

Soloway and his colleagues[8] assessed observer variation by comparing the paired reports from one observer who interpreted the same 12 biopsies 'blind', with an interval of several months between the two readings. Full agreement between the two sets of reports occurred in 73 per cent of the total comparisons, minor disagreement occurred in 24 per cent, and marked disagreement in 3 per cent. Sampling error, in the sense of whether or not the specimen was representative of the whole liver, was assessed in 13 living patients with chronic active liver disease. Two or three specimens were obtained from each patient from the same biopsy site on the same occasion by varying the angle of the needle by at least 30 degrees between each biopsy. For the presence of hepatitis, the sampling error was 19 per cent, but for the presence of cirrhosis it was 57 per cent.

Observer Variation Between Several Observers

The aim of our study[9] was to determine the degree of agreement when six histopathologists reviewed the same 60 biopsies 'blind'. Three of these observers were experienced consultant general histopathologists, one a trainee with a special interest in liver disease and two of them specialist consultants with several additional years' experience in liver disease. Twenty-one of the biopsies came from patients with hepatitis, 19 from patients with extrahepatic biliary obstruction and 20 from patients with alcoholic liver disease. The final diagnoses were made by the consultant in clinical charge of the patient on the basis of all available information, including clinical findings and follow-up and, where appropriate, laparotomy or autopsy findings. Each histopathologist completed a biopsy coding form for every slide. The form comprised 18 different hepatocyte features and eight different portal tract features. For every feature there were four possible grades of change, from which the histopathologist had to choose one. Grade 1 was no change, grade 2 doubtful change, grade 3 mild to moderate change, and grade 4 was severe change. In addition, the histopathologist gave his opinion as to the final histopathological diagnosis.

The agreement rates between the observers were critically evaluated by Kappa statistics. These quantities measure the agreement obtained between observers in excess of that which is expected by chance agreement. However, to show that the agreement measures so obtained are indeed significantly greater than chance agreement, separate tests of significance must be carried out. Table 1 shows how some of the histological features have been classified according to the significance of their respective Kappa values. Group A includes features such as Mallory's hyaline and portal tract oedema with high Kappa values indicating significant agreement. The middle column shows their respective percentage agreements of 78 per cent and 60 per cent and both these features show an agreement measure that is significantly greater than chance agreement. Group B includes features such as confluent necrosis and bile duct pericholangitis which have insignificant and low Kappa values, indicating agreement to be no greater than that expected by chance agreement.

Table 1. Classification of features based on significance of Kappa values.

A. *Features with Significant Agreement*		
Features	% Agreement	Significance
1. Mallory's hyaline	78	0.01
2. Portal tract oedema	60	0.01
B. *Features without Significant Agreement*		
1. Confluent necrosis	89	N.S.
2. Pericholangitis	58	N.S.

With regard to calculating the agreement rates for the final histopathological diagnoses, the six observers gave rise to 15 observer pairs. The pair of observers comprising the two specialist consultants agreed on 84 per cent of the 60 biopsies. This was found to be significantly better than any of the remaining 14 pairs of observers, who showed a range of agreement between 27 per cent and 53 per cent.

Usefulness of Liver Biopsy Data in a Liver Unit

In a separate study[10] to evaluate the usefulness of liver biopsy data, each of eight doctors (one consultant, two senior registrars and five registrars) working on the Liver Unit at King's College Hospital independently assessed 75 case histories. The data from the patients was introduced sequentially as 'blocks' of information and a diagnosis was requested from each doctor after each block. These comprised clinical, biochemical, ultrasound and, finally, liver biopsy data. In this study each diagnosis was considered at three levels. This was done for two main reasons: first, so that the patients could be classified to obtain better treatment results, and second, to facilitate the assessment of the accuracy of the reported diagnoses by the doctors. The first level classified the patients into medical and surgical categories. Clearly this is of major importance, as patients with hepatocellular disease do

badly following surgery, while patients with extrahepatic biliary obstruction will not improve unless the obstructing lesion has been removed by surgery. The second level classified patients into 12 categories of major pathological change, and the third level classified the patients according to their final specific clinical diagnosis.

Thus, a doctor who made a diagnosis of primary biliary cirrhosis in a patient who had a true diagnosis of cirrhosis due to chronic active hepatitis would be correct at the medical-surgical level. He would also be correct at the second level, as the patient was suffering from chronic liver disease rather than acute liver disease, but he would be incorrect at the specific final diagnosis level. The data from this study is being evaluated, but Table 2 shows some preliminary results. The table represents the diagnostic accuracy achieved by the doctors. Any percentage result represents the overall percentage of accuracy in correctly classifying the patients into a particular diagnostic level and following a particular block of information. As might be expected, the diagnostic accuracy increases with the accumulation of more and more data, but at the same time the diagnostic accuracy is seen to decrease as the classification of the patients becomes more and more specific. The most striking finding is seen at the third level where, up to and including ultrasound data, the overall diagnostic accuracy was 25 per cent, and this increased to 52 per cent following liver biopsy data.

Table 2. Accuracy of diagnosis (%).

	Clinical	Biochemical	Ultrasound	Liver Biopsy
1st Level	63	73	80	89
2nd Level	42	54	62	81
3rd Level	14	21	25	52

Discussion

The main aim of a diagnostic test should not be simply to make the diagnosis. The information obtained should also enable the doctor to improve the patient's existing state of health, but it is still necessary to classify the patients in some way so that better results from treatment can be obtained[11]. Liver biopsy is important in identifying treatable conditions such as chronic active hepatitis and Wilson's disease. It is equally important in making a positive diagnosis such as acute unresolved hepatitis as the cause of cholestatic jaundice. This kind of positive information greatly increases the confidence of the clinician and prevents him from doing any unnecessary investigations in evaluating a jaundiced patient, which could include an unnecessary laparotomy.

Both Schiff's and Morris's studies suggested that liver biopsy data were of great importance in determining the diagnosis in patients with hepatological problems. However, newer diagnostic techniques have become available since their studies were undertaken, including percutaneous and retrograde cholangiography and, in particular, ultrasound and computer-aided diagnosis [12, 13], which are non-invasive techniques.

Similarly, others[14, 15] have reported the value of ultrasound in assessing jaundiced patients. Although both liver biopsy and ultrasound have a high accuracy in establishing the presence of biliary obstruction, neither technique is as accurate as detailed cholangiography in determining the nature and site of the obstruction, which is necessary if optimum therapeutic surgical results are to be obtained. Nonetheless, Wessely and his co-workers (1977)[16] have reported that liver biopsy data and the information obtained from percutaneous cholangiography are complementary in evaluating jaundiced patients. There are several other hepatological problems for which liver biopsy is essential to establish the diagnosis and thus determine management. These include the investigation of patients with portal hypertension and unexplained hepatomegaly, and the differentiation of chronic from acute liver disease. In alcoholics, liver biopsy is essential for assessing the presence, type and severity of liver damage. The finding of granulomas may help in the investigation of pyrexias and suspected sarcoidosis. The presence and nature of primary and metastatic tumours can also be established[17].

Our study of the usefulness of liver biopsy data in a liver unit clearly showed that the information obtained in liver biopsies, which is required to classify correctly some patients into diagnostic groups, does not appear to be available from easier, non-invasive techniques. But our study was purely to assess diagnostic accuracy. It is now necessary to assess the value of liver biopsy, taking into account the cost, the associated morbidity and mortality of the procedure and the expected gains for the patient. This will involve making estimates in terms of probabilities of the likely sequelae if liver biopsy is or is not carried out and attaching some form of value to the outcomes.

The observer variation study[9] revealed that many histological features obtained from liver biopsy have an agreement measure that is significantly better than chance agreement. Thus, they are reliable in the sense of being accurately reproducible. If a separate study can also show that these same features are good discriminators between different diseases, then they are valuable features on which further action, either investigatory or therapeutic, can be confidently based. On the other hand, we recommend that, when classifying patients using liver biopsy findings, less weight should be attached to those features shown by Kappa statistics to have an agreement measure no better than that expected by chance.

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Book Review

Topics in Therapeutics 5. Edited by D. M. Davies and M. D. Rawlins. Pitman Medical for the Royal College of Physicians 1979. 182 pages. Price £7.50.

This book is an account of the proceedings of the fifth annual Topics in Therapeutics Conference held at the Royal College of Physicians in November 1978. These conferences have become popular and the reason for this is evident in this well produced and edited version of the proceedings. The list of eminent contributors is an indication of the growing importance of a sound knowledge of clinical pharmacology and therapeutics in medical practice today.

The items chosen for review reflect current interests and range widely throughout therapeutics. Emphasis is placed on the scientific approach to pharmacology in medicine, but there is a need for a little more practical therapeutics in a book aimed at general physicians.

The contents of the book are divided into seven parts covering different topics. The first six each consist of two or three chapters, and the final part is devoted to a clinico-pharmacological conference. The first part gives a concise and useful account of prostaglandins in clinical medicine. The next part deals with the progress made in anti-rheumatic and immunosuppressive therapy. The rheumatology chapter provides an interesting discussion on the pharmacology of the long-acting anti-rheumatic drugs such as gold, penicillamine and levamisole. The third part considers the causes of the variability in response to drugs, and surveys such factors as patient compliance, pharmacokinetics and pharmacodynamics. These are educational chapters worthy of reading by all physicians who wish to understand the principles behind safer prescribing. In the fourth part an excellent chapter on the drug treatment of gallstones is followed by an evaluation of fibre as a modulator of gastrointestinal function. Next there are three chapters highlighting some hazards associated with modern therapeutics. A well-balanced and thought-provoking review of menopausal hormone replacement therapy precedes an informative article on the hazards of parenteral nutrition. In a chapter entitled 'Hazards of Drug Masking' the author considers some historical and present day diagnostic pitfalls that drugs, for example steroids and antibiotics, may cause. In the penultimate part of the book there is a discussion of the relative merits of drugs available for the prevention of arrhythmias that is followed by a comprehensive but rather involved chapter on new approaches to the treatment of heart failure including vasodilator therapy. The clinico-pharmacological conference is an innovation which is to be encouraged and hopefully extended in future issues.

I found an abundance of interesting and useful therapeutics in this edition and there should be something of interest to most doctors. The chapters are of a high standard with, as expected, up-to-date references and a comprehensive index. This series of books certainly deserve to stand proudly alongside the Advanced Medicine publications, their stable companions from the Royal College of Physicians, and likewise should be readily available in hospital libraries to all who prescribe drugs.

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