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# Are liver function tests outmoded?

The standard package of biochemical liver function tests offered by most laboratories in Britain consists of measurement of serum bilirubin, alkaline phosphatase, and aspartate or alanine aminotransferase. In these times of economic stringency it is important to ask whether clinicians find the results useful. Here we must remember that not only may an abnormality in liver function tests not be attributable to liver disease but that the pattern of disturbance in an individual patient may be atypical.

A slightly raised serum bilirubin concentration as an isolated abnormality is a common finding which often gives rise to alarm. The bilirubin is usually predominantly unconjugated (indirect reacting) and in the absence of haemolysis usually proves to be due to Gilbert's syndrome (constitutional hyperbilirubinaemia). The intravenous nicotinic acid test[1] is proving useful in establishing the diagnosis and often makes liver biopsy unnecessary.

Raised serum concentrations of alkaline phosphatase may be derived from bone or gut as well as liver; the source may be clarified by measuring the concentration of other enzymes affected in cholestasis, such as leucine aminopeptidase or 5-nucleotidase, or by examining the alkaline phosphatase electrophoretic pattern. Serum aminotransferase concentrations rise as a result of damage to muscle as well as to hepatocytes. In liver disease concentrations of alkaline phosphatase of over 30 King-Armstrong units tend to point to biliary obstruction and greatly raised aminotransferase to hepatocellular damage. Nevertheless, not only is the pattern of change often indeterminate but it may be frankly misleading. In one series[2] of patients with extrahepatic obstructive jaundice 20% had alkaline phosphatase concentrations below 30 KA units, and the serum aspartate aminotransferase was as high as 1000 IU 100 ml. In fulminant hepatic failure the serum aminotransferase concentrations may fall towards normal because there are virtually no hepatocytes remaining.

Additional tests of liver function often requested are the prothrombin time (after vitamin K treatment) and measurement of serum albumin and total protein concentrations. These results may be abnormal in patients with cirrhosis who have normal standard liver function tests. Protein electrophoresis (usually on cellulose acetate strips) is seldom of diagnostic value. Nevertheless, the alpha-1 globulin band may be absent and point to the possibility of alpha-1 antitrypsin deficiency[3]; a greatly increased gammaglobulin band suggests the possibility of chronic active hepatitis. Determination of individual immunoglobulins is of little value because of the large area of overlap among diagnostic groups.[4] Measurement of other plasma protein concentrations may indicate a specific diagnosis, examples being the low caeruloplasmin in Wilson's disease and raised alpha fetoprotein in primary hepatocellular carcinoma.[5]

New laboratory tests said to help in the diagnosis of liver disease are constantly appearing. One which seems to have established itself[6 7] is estimation of gamma glutamyltranspepidase (GGPT). This enzyme is not confined to the liver, and minor rises in the serum concentrations of GGPT have been found in patients with lobar pneumonia and inflammatory bowel disease and in those taking drugs such as anticonvulsants known to induce hepatic microsomal enzymes. Raised concentrations are found in most types of liver disease including acute and chronic hepatitis, cholestasis, and cirrhosis. The test seems a very sensitive indicator of alcohol-induced liver damage, and this is perhaps its greatest use.

Lipoprotein X (LPX) is an abnormal low density lipoprotein which appears in the serum of some patients with liver disease and is present almost invariably in patients with extrahepatic obstructive jaundice, when concentrations tend to be high. Nevertheless, LPX may also be present in intrahepatic disease, and measurement does not allow absolute differentiation.[8] A method of distinguishing between intrahepatic and extrahepatic causes of jaundice based on acrylamide gel electrophoresis of serum alkaline phosphatase has recently been reported by Warnes *et al.*[9] If a band of gut alkaline phosphatase is found the lesion is most likely to be intrahepatic. Further evaluation of this observation is needed.

From what has been said evidently biochemical assessment of liver function will rarely point unequivocally to a precise diagnosis. Liver function tests should be seen as an initial screening test, and there is now a wide range of ancillary investigations. Detection of hepatitis B surface antigen (HBsAg) in the serum suggests that the liver disease is either acute type B hepatitis or chronic liver disease due to the persistence of the virus. The presence of e antigen with persistent carriage of HBsAg usually (but not invariably)

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indicates serious chronic liver disease.[10] Autoantibodies to smooth muscle, nuclei, or mitochondria point to one of the autoimmune liver diseases, such as active chronic hepatitis or primary biliary cirrhosis. Liver scanning has become established as a safe and useful method of diagnosis, particularly for focal lesions such as metastatic deposits or abscesses. The scanning material generally used is $^{99m}$Tc sulphur colloid, which is taken up by the Kupffer cells. Additional information may be gained by using one of a number of other scanning materials such as $^{75}$Se selenomethionine (for primary hepatocellular carcinoma) or $^{67}$Ga citrate (for tumour or abscess). Grey scale ultrasound is proving a valuable complementary noninvasive technique, capable of showing dilated intrahepatic ducts, the gall bladder and any contained stones, and subphrenic abscesses. It seems to be less accurate than scanning in the diagnosis of cirrhosis and primary liver tumours.[11 12] The place of abdominal computerised axial tomography in the diagnosis of liver disease is still uncertain.

In jaundiced patients the distinction between intrahepatic cholestasis and extrahepatic obstruction may be extremely difficult on the basis of clinical and biochemical data, and cholecystography and intravenous cholangiography frequently fail to show the relevant structures when the serum bilirubin concentration is over 34-51 μmol/l (2-3 mg/100 ml). Percutaneous transhepatic cholangiography has become easier and safer since the introduction from Japan of a fine flexible (skinny) needle, and dye can often be injected to outline the normal biliary tree. In cases of extrahepatic obstruction there is a small risk of septicaemia or biliary peritonitis, and it is probably wise to proceed to laparotomy on the same day.[13] Endoscopic retrograde cholangiopancreatography offers an alternative means of obtaining cholangiograms,[14] but as the technique is technically demanding it is less generally applicable. Its advantages include the facility of outlining the pancreatic ducts, and it can be combined with sphincterotomy and removal of common bile duct stones. Nevertheless, percutaneous cholangiography will probably be the procedure of choice in most hospitals in the investigation of patients with cholestasis.

Needle biopsy of the liver is safe in expert hands. The diagnostic accuracy may be increased when the specimen is taken under direct vision from abnormal areas of the liver at laparoscopy. Valid interpretation requires much experience.

Conventional liver function tests still have a valuable part to play in the detection and assessment of liver disease when taken in conjunction with a careful history and the results of physical examination. Advances in treatment have made precise diagnosis more than ever important, however, so that there is now justification for using the range of non-biochemical investigative techniques as well.


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# Childhood hypertension

Should measurement of blood pressure be included in the routine examination of schoolchildren, and, if so, when? As with any other screening procedure, this question has to be answered by analysis of the cost and time required, of the side effects induced by screening, of the likelihood of finding disease, of the chance of this disease being treatable, of the relative dangers of the treatment and the disease, and of the advantages gained by presymptomatic diagnosis.

Measurement of blood pressure is certainly cheap by comparison with, say, mammography, but it may be time-consuming in fretful children. Because the dimensions of the cuff are so critical a variety of sizes must be available, such that the width of the cuff bladder is at least 20% (and preferably 30%) greater than the diameter of the upper arm and that the bladder encircles the arm.[1] The mercury column must fall less than 5 mm Hg each minute. Any screening programme in which these simple rules are ignored is quite valueless.

The rest of the questions cannot be answered without confronting the fundamental problem that hypertension is a unique disease, in that it forms but one end of a more or less normal distribution.[2] Because of this distribution and its variation with age hypertension must be defined arbitrarily in terms of expected percentiles for a given age (and probably for sex, after puberty[3]). The intrinsic importance of hypertension is, firstly, as a clue to underlying disease (raising the question of whether screening for that disease, rather than hypertension, might not be more effective) and, secondly, as a predictor of future complications.

In 1967 Still and Cottom[4] claimed that the chances of finding a remediable cause for hypertension in children were greater than in adults—a view strengthened by a recent publication from Guy's Hospital,[5] but challenged from America.[3 6] Indeed, Londe[3] has bluntly stated that "when the paediatrician routinely takes blood pressure measurements in all his patients, secondary hypertension ceases to be the chief cause of juvenile hypertension." If there are genetic or environmental differences then British standards need to be established for normal blood pressure in large populations of schoolchildren, as they have been in Iowa.[7] If, on the other hand, the different findings in America are due to patient selection, then the first result of universal screening for blood pressure in British schoolchildren would be a large increase in the rate of diagnosis of essential hypertension.

Almost nothing is known of the value of detecting mild essential hypertension in childhood. We do not even know for certain whether an abnormally high pressure in childhood is predictive of hypertension in adolescence, let alone whether it foretells serious complications in later life. In one series of 80 clearly hypertensive children followed from three to nine years, only 65% had raised blood pressures at their last examination; none had received treatment.[3] This rate of apparent spontaneous regression underlines the need for controlled trials of medical treatment. Since familial clustering may include children,[8] such trials might well be started in the hypertensive children of families already afflicted by the complications of hypertension. For there is no question that severe hypertension in children or adolescents may have serious, even lethal, consequences.[9 10] In deciding how far to pursue investigation in a hypertensive child measurement of the plasma renin activity is useful: if it is normal this goes a long way towards excluding an underlying renal lesion.[11]

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