Diagnostic Approaches in Liver Disease,

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The photograph of William Wood Bradshaw (Fig. 1) shows him as a man of his time, a benign patriarch with an air of bland authority that is still instinctively sought by some patients, though a contemporary doctor’s training and the progressive medical education of the lay public militate against his being able to provide it.

The fashionable beard behind which he hides is part of the phenotype; it might conceal a Samuel Wilks, but in fact William Bradshaw was made of less unusual clay. Practising in Reading, he made frequent excursions to Andover where, in time, he found his wife, previously the widow of a wealthy jeweller whose estate (following certain legal transactions consequent on her re-marriage) allowed her to found this lecture. His obituary in the Reading Mercury and Oxford Gazette of 25th August 1866 noted him as ‘a kind and warm-hearted friend, ever ready to alleviate the sufferings of the poor by affording gratuitous relief’.

Nevertheless, the published trifles he left behind him provide too tenuous a connexion with today’s affairs: ‘cod-liver oil in chronic rheumatism’, ‘a case of chronic abdominal abscess’, and, more dramatically, ‘spontaneous cure of circocele’, in the course of which he records, with rather touching awe, in the correspondence column of Thomas Wakley’s Lancet, the unexpected disappearance of a hydrocele of ‘enormous’ proportions from the scrotum of a middle-aged shoemaker who was seized with an unusual urge to empty his bladder one dark October night in 1834. None of these concern liver disease, so I have to resort to a device to relate Dr William Bradshaw to my theme by calling on his namesake, George, who, though born in the same year of 1801, was probably unrelated.

George Bradshaw became a household name by publishing railway timetables. It is probable that Dr William Bradshaw had occasion to plough through this mass of data in the course of his earlier domestic life, and he might now sympathise with us as we struggle to find the optimum route to a diagnosis when faced with a problem in the hepatic area.
Quite apart from the undiminishing need to practise medicine against the clock, we have such a wide choice of approaches nowadays that we are obliged to consider their value and their cost in terms of effort to the doctor and discomfort, risk and time off work to the patient.

**HISTORY**

There is no doubt that the history can be very rewarding, quite apart from the value of spending some time with your patient in the early part of the relationship you are establishing. I would like to stress a few points, such as the extending range of hepatotoxic agents. Oxyphenisatin (McHardy and Balart, 1970; Reynolds et al., 1970; Reynolds et al., 1971) may not be too popular an aperient in Britain, but there is plenty of paracetamol about, and in a busy emergency department such as we have at University College Hospital it is difficult to ignore the comparative ease with which disturbed patients get hold of enough of this drug to produce severe liver damage.

We also need to take account of the large number of hepatiticomimetic viruses so ably documented by Zuckerman (1970). Herpes simplex has been identified as culpable in this sense in adults as well as infants (Lancet, 1973) but there is as yet no evidence on herpes zoster, though there seems to be no inherent reason why it might not behave in the same way. I keep an open mind, having recently seen two patients with severe hepatocellular jaundice occurring in close relation to an attack of shingles, one just before and one just after.

Though year by year we have to modify the somewhat rigid structure within which we take a history, and have to accept, for instance, that the incubation period of serum hepatitis may be as short as two weeks and that this disease may be transmitted by close intimate contact and by mosquitoes, the time devoted to history-taking is still well spent. It may not now be so important in the hepatic field to observe religiously the injunction of Bernardino Ramazzini, the father of occupational medicine, to ask one’s patient: ‘What do you do?’ but it is imperative not to forget Maegraith’s (1963) advice to enquire: ‘Where have you been?’ We may not find many cases of melioidosis, even in visitors from southern Burma, but this devastating systemic infection by *Pfeifferella Whitmori* must be considered in any patient from the Far East who has caseating abscesses in liver, and maybe in lungs, spleen and gut (Brundage et al., 1968).

More important, people continue to die in Britain of undetected infection with *Plasmodium falciparum*. The itinerant trend of contemporary humanity and the reappearance of malaria in many areas of the world from which, at one point, it had apparently been eradicated, coupled with the difficulty of
Fig. 1. Dr William Wood Bradshaw, M R C P 1862.
diagnosis in the initial attack, imply that we must not be too proud to make an empirical trial of chloroquine in cases of doubt. I am by nature antipathetic to empirical treatment, but I have always regretted not giving it to a 50-year-old man who had been selling cash registers all the way from New Delhi, across Asia Minor, and through Europe on his way back to Pennsylvania, getting more febrile, more jaundiced and more ill. He had accumulated no less than ten negative smears for malaria by the time I was asked whether he was fit to travel next day and if I had had the wit to fill him up with antimalarials he would have had a more comfortable journey. My colleague in Philadelphia was more active and had the courtesy to send me a detailed account of his satisfactory subsequent progress.

I would like to comment on the advantages of taking a holistic view of a patient’s medical life, despite the increasing frequency of the multiple diagnoses we have to make in an ageing population. Perseverance with the past history may throw up interesting and informative patterns. Let me give three examples.

When a 31-year-old West Indian, whom I had known on account of recurrent leg ulcers due to homozygous sickle cell disease, became pregnant for the third time, it seemed likely that the attacks of severe abdominal pain and jaundice that plagued her last trimester were due to haemolytic crises. But there was bilirubin in the urine, conjugated bilirubin in the blood, and a raised plasma alkaline phosphatase. After spontaneous delivery of another sickler, X-ray confirmed the presence of gallstones. Cholecystectomy was technically easy but her postoperative course was extended by severe infection and, later, by a liver abscess.

The second example is provided by a woman who died at the age of 62, 45 years after the first appearance of anaemia and leg ulcers shown to be associated with microspherocytosis, from which her brother also suffered. Splenectomy kept her going till she was 43, when her gallstones first made themselves felt. Recurrent attacks of obstructive jaundice followed cholecystectomy, and cirrhosis was confirmed by biopsy at the age of 59, at which time an operative cholangiogram showed a tapered narrowing of the upper part of the common bile duct. Various antibiotics failed to prevent a spasmodic downhill course, eventually terminating in deep jaundice and hepatocellular failure in 1972. Autopsy showed a large hepatocarcinoma, a known, though rare, complication of biliary cirrhosis (and of biliary atresia) (Okuyama, 1965; Fish and McCary, 1966; Deoras and Dicas, 1968).

The third example is a man who lived to be 64, having had a total colectomy for intractable ulcerative colitis 20 years previously. He was admitted on account of bleeding round the edge of his ileostomy; his liver was palpable,
as was his spleen, and oesophageal varices were shown on X-ray. He died, within a week, of massive gastrointestinal haemorrhage followed by coma, and autopsy showed a large hepatocarcinoma in a liver that was the seat of macronodular cirrhosis (Ross et al., 1966; Eade, 1970).

This sequence of events is probably quite different from that described by Ritchie and Hawley (1972) and by Ross and Braasch (1973) who noted the increased incidence of cholangiocarcinoma in the biliary tract in patients with chronic ulcerative colitis, even after proctocolectomy.

EXAMINATION

The diagnostic information provided by the various stigmata of hepatocellular failure and by the tell-tale lymph node in the left posterior triangle of the neck is well known. In the abdomen, the presence of a small liver in a jaundiced patient shows that we are not dealing with extrahepatic obstruction. A palpable spleen may also be reassuring, but not always. The splenic vein shares the convoluted course of its arterial companion, dipping and weaving behind the upper border of the pancreas on its way to the porta hepatis, and, falling an easy prey to the advancing pancreatic carcinoma, becomes obstructed, to produce congestive splenomegaly. This is especially likely to occur with those carcinomas arising in the body and tail of the gland, which are so much more difficult to diagnose.

We should not forget to take account of signs in other parts of the body (Stokes, 1972). The skin, for instance, quite apart from affording much superficial evidence of hepatocellular failure, may, as Sarkany (1966) has pointed out, give a clue to the presence of active chronic hepatitis in the shape of allergic vasculitis. The skin may also give a heavy-handed hint as to the reason for an enlarged liver in urticaria pigmentosa, the carcinoid syndrome, and in mycosis fungoides.

Examination of the joints may be rewarding; arthropathy is always suggestive of chronic hepatitis which is probably still under-diagnosed. A troublesome feature of haemochromatosis may be joint pain from chondrocalcinosis due to intra-articular deposition of calcium pyrophosphate. Hamilton et al. (1968) speculated as to how far this change might be due to previous damage to cartilage caused by excessive deposits of iron.

BLOOD INVESTIGATIONS

Most patients with a hepatic problem have plenty of blood tests made, though some laboratories, appreciating the dangers of the AA positive status, are reluctant to undertake anything that cannot be automated, and thus may deprive us temporarily of the differential white cell count and ESR.
A big leucocytosis of up to 30,000 white cells per mm$^3$ may be found in alcoholic cirrhosis, and I have recently seen a patient whose baffling PUO proved to be due to a pancreatic carcinoma with diffuse small hepatic metastases, who had a consistent and rising white cell count of over 50,000.

The differential pattern of raised serum enzymes that should theoretically help to distinguish primary hepatocellular disease from extrahepatic biliary obstruction leaves us in the air with uncomfortable frequency. The general physician has difficulty in keeping pace with enzymes that leak into the blood as a result of swelling of liver cells. No sooner has he got used to the transaminases than they change their name to aminotransferases and their unit of measurement from Karmen to International Units, at which we must hope they will stick. But this is only the start of it, and Coodley (1971), for instance, tells us that ‘commonly employed liver enzymes may not be sufficiently specific in differentiation of viral hepatitis from active cirrhosis or related conditions’ and recommends the use of serum guanase, isocitric dehydrogenase, leucine aminopeptidase, alcohol dehydrogenase, and aldolase. It is a case of every man for himself, and we can only be mindful of Tom Stoppard’s (1972) comments in a different context: ‘How do I know what I believe? Credibility is an expanding field . . . sheer disbelief hardly registers on the face before the head is nodding with all the wisdom of instant hindsight’.

It is good to be able to rely on the alkaline phosphatase, which, quite apart from leaking, is manufactured and delivered to the blood in increased amounts by the liver faced with obstruction of the biliary tract (Warnes, 1972). The problem is to be sure that the phosphatase is hepatic and not due to bone disease such as osteitis deformans which is so often present and symptomless in older patients. A parallel rise in 5-nucleotidase helps to resolve this issue. With this proviso, an isolated high alkaline phosphatase spells obstruction and, if accompanied by a high ESR, spells trouble.

Early hopes that immunoglobulin patterns in the blood might correlate with different types of liver disease were soon dispelled, but it is thought that more information may result from a search for circulating antibodies. On the whole, the presence of smooth muscle antibodies usually connotes active chronic hepatitis, and mitochondrial antibodies connote primary biliary cirrhosis; but things do not always work out tidily and it is better to regard these two diseases as distinct clinical syndromes that share a common immunological basis (Gips, 1971).

Sherlock (1970) has suggested that the chief use of a test for mitochondrial antibodies is to distinguish primary biliary cirrhosis from ‘surgical’ obstruction to the main bile ducts, but Lam et al. (1972) reported the presence of mitochondrial antibodies in 16 out of 21 cases of extrahepatic biliary obstruction
in which the jaundice had been present for more than three months. This makes for special difficulties in the case of a carcinoma of the bile duct which so often runs an indolent course.

The presence of alpha feto-protein may suggest the diagnosis of hepatocarcinoma, more often in non-Caucasian races, but Ramalingaswami (1972, personal communication) has found it in many cases of juvenile cirrhosis in Delhi, so it may not give specific information. Again, Geffroy et al. (1971) reported a positive result in patients suffering from hepatic metastases from gastric carcinoma (and in one case of viral hepatitis) in the course of a routine survey of over 200 cases of liver disease. It may be that we shall have to take into account both the age of the patient and the method used for detecting alpha feto-protein (radioimmunoassay is, for instance, much more sensitive than diffusion or electrophoretic techniques) and make a quantitative evaluation before we can use this test to its best advantage.

All this has cost the patient one prick in the arm, and we now find ourselves with an unresolved problem which demands a choice of direction depending on whether we think we are dealing with diffuse or with focal disease of the liver.

**Diffuse disease**

Diffuse disease demands an approach by needle biopsy, a reasonably safe procedure, although Menghini (1970) felt the need to reiterate the rules that must be observed, having been alarmed by the rising morbidity and even mortality of some series. He stressed particularly the need to use a small, 1-mm bore needle in borderline risk cases, for example, obstructive jaundice, superficial metastases, liver congestion, and a barely acceptable prothrombin time.

Biopsy will confirm that the enlarged liver of the alcoholic is not due to fatty infiltration but to cirrhosis. It will distinguish alcoholic cirrhosis from active chronic hepatitis and from haemochromatosis. It will sometimes produce a surprising reason for hepatomegaly, in the shape of primary or secondary amyloidosis. But it cannot be expected to be reliable in the presence of focal liver disease. We may pick up diffusely scattered granulomas, monuments to the eventual settlement of prolonged negotiation with a wide variety of invading organisms, but these usually have no diagnostic features and it is only too rarely that we chance on the pathognomic evidence provided by sarcoidosis, tuberculosis, or Hodgkin’s disease. Metastases are more elusive, though encouragement of the histologist to take further sections deeper in the block may bring to light a small but significant lesion. The position may be improved by making a biopsy under direct vision (McBrien, 1970; *Lancet*, 1971).
FOCAL DISEASE

The search for focal disease is best initiated by a scan, or by gamma photos that give an easy view of the liver from several angles but lack the resolution of the scan. The difficulties of interpretation have been well reviewed by Covington (1970) but I believe that the best information is gained from any scan when the clinician who is familiar with the patient and his diseased organ sits down and makes a joint report with the physician or physicist who has the technical expertise.

In focal disease, ultrasound gives the same sort of information as scanning, with the additional advantage of distinguishing between a solid lesion and one filled with fluid (McCarthy et al., 1970) by appropriate manipulation of the gain setting on the instrument. This adjustment varies from one apparatus to another and needs to be controlled by an individual, preferably a doctor, which increases its cost. Ultrasound pictures are quite difficult to read but are likely to improve (Leyton et al., 1973). Meanwhile, angiography gives more precise information in terms of the vascularity of the tumour. A retrograde Kifa catheter lodged in the coeliac axis via the femoral artery is useful, if local perfusion of a hepatoma with 5-fluorouracil is contemplated (Provan et al., 1968) and it may also reveal lesions not demonstrated by scanning techniques.

In difficult cases of jaundice, endoscopy and retrograde choledochopancreatography have been recommended by Blumgart et al. (1972), while from the other side of the Atlantic, an integrated procedure for the rapid diagnosis of biliary obstruction, portal hypertension and liver disease of uncertain aetiology is advocated by Strack et al. (1971) who make a 5-cm sub-xiphoid incision under local anaesthesia, through which they undertake open transhepatic cholangiography, open Vim-Silverman needle biopsy with suture, open gastro-epiploic vein catheterisation with portography, with or without peritoneal biopsy, ‘various cultures’ and ascitic fluid analysis.

Clearly, the patient is at some risk of technological overkill when it comes to investigation and this is heightened if a member of the team caring for him thinks that he might one day make a good clinico-pathological conference. A wish to outdo the pathologist sometimes clouds judgement.

THE USE OF COMPUTERS

Small wonder, then, that Knill-Jones et al. (1973) feel that the time has come to try to find out just what factors are helpful in reaching a high probability of a diagnostic or, more important, a treatment class. He has analysed for me a handful of cases, three of which illustrate the uses of the computer. The first (Fig. 2) shows how far one can get with as few as three indicants; this is
Fig. 2. Computer-derived probability of diagnosis: final diagnosis of primary biliary cirrhosis (PBC). AP = alkaline phosphatase. AP/SG = alkaline phosphatase/SGOT ratio.

Fig. 3. Computer-derived probability of diagnosis: final diagnosis of cirrhosis. CAH = chronic active hepatitis.
the woman with the clinical picture of primary biliary cirrhosis (PBC), whom I have already mentioned. Starting with a prior probability of zero (derived from the bank of patients analysed and, of course, likely to vary as the number of cases, at present 390, increases) three bits of information—the alkaline phosphatase/SGOT ratio (AP/SG), the duration of the itching, and the actual level of the alkaline phosphatase (AP)—take primary biliary cirrhosis up to a probability of 0.98. The odds on primary biliary cirrhosis are 120 to 1, with 9,000 to 1 against a carcinoma and 14,000 to 1 against stones. Figure 3 shows the pattern usually obtained in alcoholic cirrhosis, which rarely provides a serious problem.

Some cases take longer to work out, as in the case of a 90-year-old man who was known to have had gallstones for many years before he developed obstructive jaundice (Fig. 4). Cancer initially headed the list of probabilities, but only reached a probability of 0.76 after the use of a dozen indicants,
though stones were the only other serious contender. We ended with a probability of 0.90, 8 to 1 on cancer, 8 to 1 against stones. The effect of 45 further indicants was not great. The indicants were all simple ones derived from clinical contact or the laboratory, involving the patient in little discomfort. Extension of this work should be most rewarding and helpful in choosing the most advantageous investigations. Some workers (Bégon and Dhumeaux, 1971) advocate the use of laboratory data alone, finding it difficult at times to formulate the lines of the physician’s reasoning’. This is understandable, but it should be noted that the clinical symptom of duration of itching produced the greatest reduction in total uncertainty in the first case mentioned.

The other area in which the computer has been pressed into service is taking the history, in an effort to save the doctor’s time. Mayne et al. (1972) recently reported on the result of applying the questionnaire they had shown in 1969 to be feasible and acceptable to the patient. They analysed their results under six headings—

1. The urgency of the patient’s need for medical attention. (This was slightly underestimated.)
2. The basic nature of the health problem. (There was a disappointingly low correlation between organic and functional disorders.)
3. The complexity of the problem.
4. The time probably required for the initial consultation.
5. The medical subspecialty that might best handle the problem. (None of these gave a correlation greater than +0.6.)
6. The type of laboratory tests probably needed. (These proved a great deal more difficult to forecast.)

‘These findings’, they conclude, ‘strongly suggest that it is the nature rather than the quantity of information in the available medical history that determines its usefulness to the clinician.’

This is not surprising. It is difficult to imagine a questionnaire which would, at a follow-up session, elicit from a girl with anorexia nervosa who has made an unexpected improvement, the crucial information that last week she had eaten the whole of her sister’s wedding cake the night before the ceremony.

We must continue to take our own histories for the time being. And, when making a diagnostic and treatment plan for our patients, we should bear in mind that their time is limited and deploy it as well as we can.

I have said nothing new but invited a closer look at what is already known. What Dr Bradshaw would have made of all this is a matter for conjecture,
but I am sure that the fact that we have speculated on his reaction would give pleasure to his devoted wife who endowed this lectureship.

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