Current Practice

DISEASE OF THE DIGESTIVE SYSTEM

Jaundice

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"*The physician makes the same mistake a thousand times and calls it experience.*"

Diagnosis of the cause of jaundice in most adult patients is not difficult. The ingredients of success are patience, persistence, and a modicum of self-doubt. These qualities are particularly necessary in the small but important group of patients in whom obstructive jaundice may be due to intrahepatic causes.

Clinical Features

Symptoms

Typical infectious hepatitis begins with a prodromal period of diagnostic symptoms, often labelled "gastric 'flu" before jaundice appears. Abdominal discomfort, sometimes over the liver, is accompanied by anorexia and severe nausea so that the thought, smell, and sight of food may cause revulsion. Vomiting and either diarrhoea or constipation may be present. If the patient smokes complete aversion to tobacco is characteristic. Fever and transient irritation of the skin are additional features. These symptoms seldom last longer than ten days and it is unwise to make a diagnosis of infectious hepatitis without them.

On occasion abdominal pain may be more severe, and I have seen one young boy operated on for acute appendicitis, fortunately without ill-effects. If pain rather than discomfort is a feature differentiation from gallstones is impossible in the early stages, but the latter is seldom accompanied by the constitutional ill-health of infectious hepatitis. Rigors are due to extrahepatic obstruction, commonly from gallstones or a carcinoma, and the patient should be closely questioned for this symptom. All too often jaundice due to gallstones is not accompanied by pain, there are no prodromal symptoms, and the problem is to distinguish it from other causes of cholestasis, both extrahepatic and intrahepatic.

Extrahepatic obstruction due to carcinoma is almost invariably insidious and painless unless complicated by cholangitis. Well-being is often preserved, and weight loss—being a feature of any type of jaundice—is an unhelpful symptom unless extreme. Pruritus is prominent but in extreme form suggests intrahepatic cholestasis.

Intrahepatic cholestasis is a relatively recent concept and implies that biliary obstruction occurs within the liver. There are many varieties,[1] some of which arise as complications of pregnancy, operation, severe infection, and haemolytic syndromes, or in association with alcoholic liver disease and portal and biliary cirrhosis. But the two commonest types are cholestatic hepatitis (a variant of infectious hepatitis) and drug-induced cholestasis; and since in each painless, progressive jaundice may arise in a previously healthy patient differentiation from extrahepatic obstruction is often extremely difficult.

For practical purposes jaundice associated with drugs can be divided into hepatic and cholestatic varieties. The former mimics closely infectious hepatitis. It is wise to suspect any drug which has been administered in the period immediately preceding the jaundice. Unfortunately it is not always easy to obtain information about possible hepatotoxicity, and there is a need for an authoritative check-list, kept regularly up to date, similar to the excellent series published by Dölle and Martini in West Germany.[2-5]

Signs

Examination of the jaundiced patient is often unrewarding, though a careful search should be made for the stigmata of liver disease, and specially spider naevi. Scratch marks and bruises are signs of obstructive jaundice. An enlarged lymph node may sometimes be felt in the right side of the neck in infectious hepatitis. The liver is tender in this disease and in gallstone jaundice, and is moderately enlarged in cholestasis from any cause. Irregularity suggests cirrhosis or carcinomatosis. A palpable gall bladder is rare but reassuring evidence of extrahepatic obstruction. The spleen is slightly enlarged in a proportion of patients with infectious hepatitis and with gallstones, especially when cholangitis has been a complication. More marked and firmer splenomegaly accompanies any variety of cirrhosis.

Investigation

Most of the investigations commonly employed in the diagnosis of jaundice have limited value, and may be frankly misleading.

Biochemical Tests

It is usual to perform a number of so-called liver-function tests, but the usefulness of this practice is questionable in view of the increasing work-load on biochemistry departments. Estimation of the serum bilirubin is valuable as a guide to progress, and the proportion of conjugated to unconjugated pigment may help in assessing the type of jaundice. The level of serum alkaline phosphatase is a quite unreliable guide to diagnosis,[6] and should in my view be abandoned until suitable methods are available for estimating its isoenzymes. Flocculation tests are rarely of help, and when they are positive there is frequently other evidence of hepatocellular damage. Filter paper electrophoresis of plasma proteins may serve to distinguish obstructive jaundice, in which there is an increase in alpha and beta globulins, from hepatocellular jaundice, where gammaglobulins are raised. Perhaps the aminotrans-

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ferases are the most valuable diagnostic aid, since figures in the hundreds and more imply hepatocellular jaundice, but even these, as do other enzymes, fail to distinguish extrahepatic from intrahepatic cholestasis. The very number of liver function tests that have been advocated testifies to their ineffectiveness, and the differentiation of cholestasis remains the outstanding biochemical challenge.

Radiology

A straight *x*-ray film of the gall bladder region should always be taken, but it is surprising how seldom radio-opaque stones are seen. Cholecystography at the time of jaundice is likely to reveal "a non-functioning gall bladder," and is best left till after the jaundice has cleared in those patients in whom gallstones are suspected. Barium-meal examination with special attention to the duodenal loop may sometimes confirm the presence of a carcinoma. I am not convinced that percutaneous transhepatic cholangiography is a justifiable procedure, since if no diagnosis has been reached at the stage when it is contemplated laparotomy is probably preferable.

Liver Biopsy

There is an increased risk of complications following liver biopsy in the jaundiced patient, particularly from haemorrhage and leakage of bile. It has no place as a casual procedure by the inexperienced. It may be of value in the diagnosis of hepatocellular jaundice and in drug-induced cholestasis, particularly of the phenothiazine variety. There is considerable discussion, however, as to whether liver biopsy can distinguish between extrahepatic and intrahepatic cholestasis,[7] and satisfactory interpretation depends on close collaboration between physician and pathologist.

Therapeutic Trial of Corticosteroids

Administration of A.C.T.H. or corticosteroids has been used to differentiate intrahepatic from extrahepatic cholestasis.[8] Complete relief may be expected if the jaundice is due to cholestatic hepatitis, but not with other types of intrahepatic cholestasis. Little or no effect is usual in the patient with a carcinoma, though the test may coincide with the spontaneous disappearance of jaundice due to an ampullary neoplasm or gallstones. Results must therefore be interpreted with caution, but the test is occasionally valuable and carries no danger if operation subsequently becomes necessary.

Management

With the possible exception of those with cholangitis no patient with jaundice should be operated on for at least two weeks after the onset, however certain the diagnosis appears to be. There is a body of opinion that deplores inactivity and maintains that the risk of operation is small.[9] The physician who has been called to treat a patient (often young) with irreversible liver failure following precipitate laparotomy may well remain sceptical. Is it better to delay operation in an elderly patient with a carcinoma or to operate early on a young person with intrahepatic cholestasis? There have been, for example, an alarming number of deaths from chlorpromazine jaundice, usually regarded as a benign condition. How many of these followed operation? It is a mistake to think that because the jaundice is due to intrahepatic biliary obstruction there is no interference with liver cell function. "The arbitrary period of study and medical treatment constitutes a hardship for the patient who ultimately proves to have a surgical lesion. However, it is likely to be life-saving for the patient with medical jaundice in whom early surgical intervention is not only unrewarding but actually dangerous."[10]

I am in complete agreement with those who advocate operation if the jaundice shows no signs of diminishing after six weeks, but only if every effort has been made to establish a diagnosis.

A young woman of 28 was admitted to hospital for laparotomy after eight weeks of unremitting jaundice. A few spider naevi were noted, and while awaiting operation she was given injections of A.C.T.H. The jaundice cleared in two weeks.

The difficulty, of course, is that intrahepatic cholestasis can be a prolonged disease, and diagnosis needs to be firmly established so as to avoid recurring doubts in the minds of the patient and his medical attendants. I have seen three young women who developed intrahepatic cholestasis while taking contraceptive pills, and in each case the jaundice took two to three months to disappear.

Laparotomy should not be regarded as the easy way out from laborious investigation. I would prefer to see much closer co-operation between physician and surgeon in the pre-operative (or non-operative) diagnosis of jaundice.

During the period of observation the physician has two important tasks. The first is to assess the progress of the jaundice. A note should be made of the colour of the stools whenever they are passed (and they should occasionally be tested for the presence of occult blood). The urine should be tested daily for the presence of bilirubin and urobilinogen. If possible the serum bilirubin should be estimated twice weekly because it is difficult to assess changes in the depth of jaundice by examining the patient. A careful watch should be kept for bruising, which indicates hypoprothrombinaemia, and for signs of hepatic failure.

The second task of the clinician is to ask repeated questions not only of himself but of the patient, his relatives, and other medical attendants. It is perhaps not surprising that a history of alcoholism may be concealed, but the patient can hardly be expected to know that hepatitis can be transmitted by serum inoculated up to six months previously. It is sometimes important to know whether cases of infectious hepatitis are occurring in the locality.

During a local outbreak of hepatitis a young woman of 24 was admitted with a recurrence of jaundice. A diagnosis of gallstones was considered until her mother told the ward sister that a brother had just become jaundiced.

The most important question, however, concerns drugs. Few drugs are entirely free from the risk of producing jaundice, and every new compound should be viewed with suspicion. The difficulty very often is to discover what the patient has been taking, and this, as Professor Sherlock has pointed out, may require skills usually more appropriate to the expert detective.

An elderly woman of 79 with obstructive jaundice denied that she had received any drugs in the recent past, and investigations failed to reveal a cause for the jaundice. Laparotomy was advised, but she maintained that she was "too old for that sort of thing." A few weeks after her discharge a letter was received from the general practitioner to say that the jaundice had disappeared, and enclosing a report from a hospital in the south of England where she had been admitted while on holiday the previous summer after a fall. Chlorpromazine had been prescribed to combat restlessness and confusion.

Painless jaundice which clears fairly rapidly is likely to be attributed to infectious hepatitis, and if it recurs a diagnosis of subacute hepatitis may be made. I have seen a man who had repeated attacks of jaundice for fifteen years before pain finally led to the correct diagnosis of gallstones. It cannot be emphasized too strongly that cholecystography should be carried out at least six weeks after an attack of jaundice in any patient in whom there is the slightest doubt that the original episode was due to infectious hepatitis. As a corollary, it is necessary to point out that hepatitis not uncommonly relapses,

and thoughtless operation under such circumstances may well prove disastrous.

If laparotomy has to be undertaken as a diagnostic measure the possibility must be faced that no extrahepatic obstruction will be found. In such circumstances the surgeon has an obligation to take a liver biopsy and to perform some form of cholangiogram. The cause is likely to be intrahepatic cholestasis or biliary cirrhosis, but a hepatic duct carcinoma can easily be overlooked. This tumour can mimic hepatocellular jaundice, both in the histological changes produced in the liver and in its clinical course,[11] and since it is slow-growing and may be amenable to treatment it is important that the correct diagnosis should be made.

Envoi

It requires time and thought to collect and assess the evidence in patients with jaundice. Frequently there is no difficulty in diagnosis, but because of this very fact one should be constantly on the look out for the rare exception where a mistake may cost the patient his life. In spite of pathological and radiological advances, the clinician still bears the main responsibility for diagnosis. I know that I am not alone in finding jaundice an increasingly difficult diagnostic challenge, and I look forward to the day when this onerous burden will be taken over by the computer.

REFERENCES

1 *Brit. med. J.*, 1964, **1**, 196.
2 Dölle, W., and Martini, G. A., *Acta hepato-splenol (Stuttg.)*, 1959, **6**, 138.
3 —— —— ibid., 1959, **6**, 225.
4 —— —— ibid., 1962, **9**, 74.
5 —— —— ibid., 1964, **11**, 355.
6 Paton, A., *Midl. med. Rev.*, 1962, **2**, 26.
7 Shorter, R. G., Paton, A., and Pinniger, J. L., *Quart. J. Med.*, 1959, **28**, 43.
8 Johnson, H. C., Jr., and Doenges, J. P., *Ann. intern. Med.*, 1956, **44**, 589.
9 Bourke, J. B., Cannon, P., and Ritchie, H. D., *Lancet*, 1967, **2**, 521.
10 Hoffbauer, F. W., *J. Amer. med. Ass.*, 1959, **169**, 1453.
11 Klatskin, G., *Amer. J. Med.*, 1965, **38**, 241.

TODAY'S DRUGS

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Debrisoquine

This drug is marketed by Roche Products Ltd. under the name Declinax.

There are two broad categories of drugs used to treat hypertension. Diuretics, exemplified by chlorothiazide, have a mild pressure-lowering action which does not change much with posture and rarely gives rise to symptoms of hypotension. The second group consists of drugs which interfere with transmission in sympathetic adrenergic nerves and may also have effects within the brain. This group includes reserpine, guanethidine, methyldopa, bethanidine, and debrisoquine. These drugs are potent hypotensive agents which interfere with sympathetically mediated vascular reflexes and so may lead to postural and exercise hypotension.

Pharmacology

In animals debrisoquine blocks sympathetic adrenergic nerves but does not deplete noradrenaline from tissues. In this respect it resembles bethanidine more closely than guanethidine.

Intravenous debrisoquine causes a sharp rise in blood pressure, which may be sustained for more than an hour. In consequence the drug is not suitable for use in hypertensive emergencies. Oral doses reduce the blood pressure for about 12 hours, the maximum effect being about two hours after the dose. The drug is well absorbed from the gut and about 80% appears in the urine, part as unchanged debrisoquine and part as metabolites.

The fall in blood pressure is greatest on standing and after exercise and least in the supine position. The effect is potentiated by a warm environment (warm weather, a hot bath, etc.) and by loss of salt and water (diuretics, vomiting, or diarrhoea). The response to noradrenaline is increased by debrisoquine, presumably owing to denervation hypersensitivity, and the response to tyramine is increased because debrisoquine does not deplete noradrenaline from tissue stores.

Therapeutic Use

Debrisoquine is marketed as white 10 mg. tablets and pale-blue 20 mg. tablets. The usual starting dose is 10 mg. twice daily, and this can be increased every day or two until a satisfactory value of standing blood pressure is reached. Doses used range from 20–400 mg. daily, the average being about 70 mg. daily.[1 2] After initial control of blood pressure is achieved a moderate increase in dose may be required to maintain the effect over a long period.

The side-effects described are those which would be expected from the drug's mode of action. Postural and exercise dizziness and muscular weakness are manifestations of hypotension, and nasal stuffiness, failure of ejaculation, and diarrhoea probably result from sympathetic adrenergic blockade.[1 2] These effects are similar to those observed with guanethidine and bethanidine (except that bethanidine rarely causes diarrhoea), and the incidence depends in part upon the enthusiasm with which the dose is pressed to achieve maximum effect.

No serious toxicity has been reported.

Which Adrenergic Blocking Drug ?

No formal comparative clinical trial between debrisoquine and guanethidine or bethanidine has been carried out. The published evidence suggests that debrisoquine very closely resembles bethanidine in its potency, duration of action, side-effects, and tolerance. There is some advantage in having more than one such drug available, because resistance or intolerance to one does not necessarily occur with another. However, results with these powerful drugs depend much more upon the patience and skill of the doctor than on small differences in pharmacological action. It is best to learn how to use one drug in the group rather than ring the changes between them every time a patient runs into difficulties. Debrisoquine will find a place among the drugs used to treat moderate and severe hypertension, but this place will probably not be a large one, because it does not offer any substantial advantages over drugs already in use.

The basic N.H.S. cost of 100 tablets of 10 mg. is 16s. 8d. ; 100 tablets of 20 mg. cost 24s.

REFERENCES

1 Athanassiadias, D., Cranston, W. I., Juel-Jensen, B. E., and Oliver, D. O., *Brit. med. J.*, 1966, **2**, 732.
2 Kitchen, A. H., and Turner, R. W. D., ibid., 1966, **2**, 728.