will therefore end in complete refractoriness, at which stage only free folic acid will produce haematological benefit. Without doubt, however, other unknown factors are involved, for folic acid is not always completely successful in curing the anaemia.

Whatever the explanation, the beneficial clinical, nutritional, and haematological effect of folic acid in idiopathic steatorrhoea accompanied by megaloblastic anaemia makes accurate diagnosis a matter of great importance. It is all too easy, if anaemia is macrocytic and megaloblastic and associated with a histamine-fast achlorhydria, to diagnose Addisonian pernicious anaemia. In all such cases a careful assessment of the initial effect of parenteral liver extract or vitamin B_{12} is necessary, and, if not classical, a fat-balance test should be the next investigation irrespective of the gross appearance of the stools or a history of intestinal dysfunction. A positive result from this somewhat laborious procedure is an indication for vitamin B_{12} or liver to give place to folic acid.

Summary

Seven cases diagnosed as Addisonian pernicious anaemia before the age of 30, in the period 1937–49, were reinvestigated during 1950.

Alimentary symptoms were insignificant, but in three patients the initial response to parenteral liver was sub-optimal.

The diagnosis was confirmed in three patients; but four, including all three who responded poorly to liver in the beginning, were proved to be suffering from idiopathic steatorrhoea. These latter cases are described in detail, and their differentiation from Addisonian pernicious anaemia is discussed.

Various clinical, haematological, biochemical, and radiological features were suggestive of steatorrhoea; the demonstration of defective fat absorption was conclusive. No evidence of deficiency of the fat-soluble vitamins D and K was found.

The therapeutic importance of accurate diagnosis of occult steatorrhoea is stressed.

I wish to thank Professor Sir John McNee, in whose wards the patients were investigated and treated, for much encouragement and helpful advice in the preparation of this paper.

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The Royal Sanitary Institute has accepted an invitation from the Corporation of Hastings to hold the 1953 Health Congress in Hastings from Tuesday, April 28, to Friday, May 1, inclusive. Forty nations were represented at the 1952 congress, which was attended by 2,140 experts on health. Amongst them were five delegates from the Soviet Union specially charged with the mission of investigating British public health methods.

RISKS OF NEEDLE BIOPSY OF THE LIVER

BY

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Needle biopsy of the liver has now been adopted in many institutions throughout the world, but it is still regarded with misgiving by those who recall the frequent complications encountered by the pioneers of this procedure. Their doubts are not allayed by the high mortality figures mentioned in the literature, such as 1.0% by Snapper (1951), 0.93% by Kumpe (1949), 0.89% by Hoffbauer (1947), 0.60% by Webb and Werthammer (1949), 0.5% by Lichtman (1949), 0.3% by Sherlock (1949). The situation was in fact rather better than these figures suggested, for nearly three years ago there were records of 3,650 biopsies with seven deaths, a mortality rate of 0.19% (Terry, 1949b).

Mortality Rate

Over 10,000 liver biopsies have been reported in the literature since 1939, and it therefore seems an opportune moment to reassess the risks entailed. The various series are shown in Table I, which reveals that in 10,600 needle

 TABLE I.—Incidence of Deaths and Significant Complications in 10,600 Needle Biopsies of the Liver

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* Among 7,532 biopsies, or 0-32%.

biopsies of the liver performed by modern techniques there has been a mortality rate of 0.12% and a complication rate of 0.32%. It is instructive to analyse these 13 fatalities, details of which are given in Table II.

The 11 deaths from haemorrhage all occurred in patients of hopeless prognosis; in the remaining two there is no TABLE II.—Details of Deaths in Needle Biopsy of the Liver

No.	Author	Cause of Death	Diagnosis	Comment	
1	Baron	Haemor- rhage	Diffuse liver sec- ondaries	Liver capsule torn. Prothrombin not estimated	
2	Buck	,,	Advanced cir- rhosis	Prothrombin level 50%. Too ill to co-operate	
3	Davis	,,	_ ,, ,, ,,		
4	Gillman et al.	,,	Gross hepatic	Aberrant artery	
5	(1945)		tuberculosis	punctured	
2	Moyer et al.	,,	-	Abnormal bleeding tendency; died of	
				coronary disease	
				during laparotomy	
6	Roholm et al.	·	Pancreatic car-	Prothrombin low	
			cinoma		
7	,, ,,		Malignant glands	,, ,,	
			in portal fissure		
8	Sherlock (1945)	,,	Subacute liver	Moribund with	
			necrosis	G.P.I. and rectal carcinoma	
9			Acute liver nec-	Prognosis considered	
1	,,	,,	rosis	hopeless	
10	Volwiler et al.		Hepatic amyloid-		
			osis	4.5 cm from sur-	
				face of liver	
11	White	,,	Advanced cir-	Prothrombin low	
10	TT	D'11	rhosis		
12	Hoffman et al.	Biliary peri- tonitis		-	
13	Schiff	Shock	jaundice Cholelithiasis:	Cause of shock not	
		SHOCK	Obstructive	revealed by nec-	
			iaundice	ropsy	

comment on this point. Thus at the most there have not been more than two deaths in patients of good prognosis in over 10,000 biopsies.

Biopsy should probably not have been carried out in Cases 2, 5, 6, 7, and 11, since the prothrombin levels were too low, while in Case 1 it was not estimated. Inability to co-operate was a further contraindication in Case 2. Several of the other patients appear to have been moribund at the time of biopsy, and many regard this state as a contraindication.

Case 12 is of particular interest, not only because it is the only recorded death from biliary peritonitis in these series but also because it has occurred so recently. It will be seen from Table III that this complication is more common than this isolated death might suggest.

Ultimate Mortality Rate

Five deaths from liver biopsy in England are known to me, all occurring in comparatively small series and none having been recorded in the literature. The causes were hepatic bleeding in three instances, haemorrhage into the abdominal wall, and suppurative peritonitis in a patient with pyelophlebitis. Isolated deaths are occasionally referred to in the literature. However, the high mortality rates of these small series are probably more than balanced by the large series yet to be published by various writers.

Most procedures in medicine carry a mortality rate, and with every precaution liver biopsy will never be free from risk. Coincidental deaths will doubtless form a proportion of these irreducible complications, since liver biopsy is so often performed in ill patients suffering from obscure disorders. I have experience of four patients who died unexpectedly before liver biopsy could be carried out, including the following:

Two biopsies were arranged for the same morning. The first, on an infant aged $3\frac{1}{2}$ months, lasted longer than anticipated. The second, on a man with phthisis and hepatomegaly, had to be postponed. Next morning I learned that this man had died during the night. Necropsy revealed hepatic amyloidosis.

The death reported by Schiff (1951), and ascribed to shock of unknown cause, may well have been a coincidental death.

This mortality rate of 0.12%, the continued improvement in technique and selection of cases, and the freedom from complication in the larger series indicate that the mortality of needle biopsy of the liver will settle at 0.10% or less.

Complications

Articles on liver biopsy often fail to mention or to analyse complications, and their true incidence cannot yet be assessed. In the present survey 24 significant complications are recorded among 7,532 biopsies, an incidence of 0.32%. Further details are shown in Table III.

Haemorrhage.—Significant bleeding has occurred on 16 occasions, an incidence of 0.20%; it was subcutaneous in one and into the peritoneal cavity in the rest. Laparotomy was necessary in four patients, transfusion alone in three, and expectant treatment in nine. The underlying disorders included cholangiolitic hepatitis, congestive heart failure with hepatosplenomegaly, Hodgkin's disease, and, in two patients, Weil's disease. No diagnosis was mentioned in the other reports. No other clinical or laboratory details are available, and it is not possible to assess the factors contributing to haemorrhage in these 16 patients. Sherloek (1945) stated that in a total of 264 biopsies, of which 157 had been on jaundiced patients, signs of bleeding had been noted only in those with jaundice.

Biliary Peritonitis.-This complication occurred in seven patients, three of whom required laparotomy. Four other instances have been recorded, one proving fatal, but they are not included in Table III, since the corresponding number of biopsies is not mentioned (Gallison and Skinner, 1950; Kleitsch and Kehne, 1950; Reynolds, 1950). Obstructive jaundice existed in 10 of these 11 patients and had recently been present in the eleventh. Since biliary peritonitis apparently occurs only in the presence of biliary obstruction, the incidence of this complication should be assessed in relation to patients with jaundice rather than to liver biopsy as a whole, but such an assessment is not yet possible. Liver biopsy should probably not be undertaken in undoubted cases of obstructive jaundice, unless secondary deposits or some other feature are being sought. However, neither Sherlock (1945) nor Weisbrod et al. (1950) mentioned this complication, though each had performed 157 biopsies on patients with jaundice.

 TABLE III.--Details of 24 Complications in 7,532 Needle Biopsies

 of the Liver

Author		Complications	6	
Autnor	No.	Nature	Comment	
Caravati et al. Clay et al Davis Haex Moyer et al. Sanes et al Schiff Store et al Torp et al Topp et al Webb et al	* 1 2 5 1 1 1 1 1 2 4 1 1	Haemorrhage Biliary peritonitis Haemorrhage Biliary peritonitis """ Subcutaneous haemorrhage Haemorrhage "" "Acute abdomen" Biliary peritonitis Haemorrhage Biliary peritonitis	Hodgkin's disease of liver Plasma transfusion needed Both mild Laparotomy in 4; suture in 3 Obstructive jaundice present Obstructive jaundice with Bact. coli cholangitis Weil's disease. Laparotomy needed Cholangiolitic hepatitis. Trans- fused Both associated with obstructive jaundice. One needed laparo- tomy Severe bleeding. Weil's disease Pancreatic carcinoma. Laparo-	

Penetration of Abdominal Viscera.—The series under review does not contain any such complication, but a few authors refer to cases within their knowledge (Hoffbauer, 1947; Reynolds, 1950). The discovery of intestinal, pancreatic, or renal tissue in the histological preparation was usually the only evidence of this happening, though death followed one instance of puncture of the colon.

Tumour Seeding.—Snapper (1951) refers to a patient with cirrhosis and malignant hepatoma, in whom biopsy revealed only the cirrhosis. Six months later a metastasis appeared in the biopsy track. This appears to be the only example of this complication. Other Complications.—Pneumothorax occurred five times without causing anxiety. This complication would probably be discovered more often if routine chest x-ray films were taken, but it does not seem to be a significant complication except in the presence of emphysema. There was one case of "acute abdomen" and one of "febrile reaction" five hours after biopsy; both responded to conservative measures.

Prevention of Complications

Among the precautions to be taken the following appear to be the most important:

1. Observance of Recognized Contraindications, particularly: (a) haemorrhagic states failing to respond to treatment, including prothrombin levels below 70%, thrombocytopenia, polycythaemia vera, and Weil's disease; (b) pyogenic infection in the liver; (c) inability of the patient to co-operate; (d) absence of superficial liver dullness; and (e) moribund, senile, and anaemic patients.

2. Choice of Operator.—Few will agree with the view of Meredith and Hicks (1950), who regard liver biopsy as "a relatively simple and safe procedure that can be performed by the average house-officer." The complications recorded in the literature have mostly occurred among the earlier cases while the authors concerned were still inexperienced, and it is apparent that the casual performance of liver biopsy by the untrained must lead to disaster. Furthermore, the nature of the indications, contraindications, and actual technique suggests that liver biopsy is best performed by a physician rather than a surgeon, while the numerous clinical aspects render it an unsuitable procedure for the pathologist. It is in fact clear from the literature that liver biopsy is almost entirely carried out by physicians.

3. Size of Needle .- After several severe haemorrhages for which there seemed to be no very good reason, a physician known to me abandoned liver biopsy, and nearly 10 years passed before it was pointed out to him that such haemorrhages were the natural consequences of using a needle of 3 mm. bore (7.1 mm.² cross-section). Raby (1944) recorded two deaths in 28 biopsies, using a 2.23-mm. needle (4.1 mm.). Sherlock (1945), after experiencing two deaths from haemorrhages and three cases of haemorrhage requiring transfusion in 126 biopsies, changed from a 2-mm. needle (3.1 mm.²) to a 1-mm. needle (0.78 mm.²). I used a 2.1-mm. needle (3.5 mm.²) without trouble, but changed to a 1.8-mm. needle (2.5 mm.³) after realizing the critical importance of the size of the needle. A needle of less than 1.5 mm. bore often fails to obtain a specimen, and, even when successful, the pathologist is often dissatisfied with the scanty material. The Vim-Silverman needle with its split inner needle of only 1.2 mm. bore is usually successful, since it grips the specimen between the two halves of this inner needle, but many find the specimen too small. A needle whose bore lies between 1.5 and 1.8 mm. seems to be both safe and satisfactory.

4. Anaesthesia.—Many accept local and referred pain and an accompanying sharp inspiration as inseparable features of liver biopsy. Such incidents are not merely unpleasant for the patient but are also dangerous, since the liver capsule may well be torn during the sharp descent of the diaphragm. They are also unnecessary, for, with adequate infiltration of the diaphragm and Glisson's capsule, the patient feels no discomfort and not infrequently remains unaware that the biopsy has been performed. General anaesthesia is preferred by some, but I do not recommend it, since deep anaesthesia is needed to produce apnoea and the postoperative state is difficult to assess, while post-anaesthetic vomiting hinders haemostasis.

5. Duodenal Intubation.—Whenever there is any possibility of active cholangitis, particularly in the presence of jaundice, duodenal intubation should be performed and the specimen examined for pus and organisms. If these are present, liver biopsy should not be carried out. It should be remembered that *Bact. coli* cholangitis may cause neither fever nor leucocytosis. 6. Selection of Route.—The intercostal route was condemned by Davis et al. (1946) and others, who noted that most complications had occurred when this route had been used, but failed to perceive that this association merely reflected the almost universal preference for the intercostal to the subcostal route. It is now becoming generally accepted that there is no inherent danger in the intercostal route. The subcostal route is applicable only to cases of gross and undoubted hepatomegaly, but even under these circumstances some prefer the intercostal approach, since it permits better appreciation of the position and progress of the needle.

7. Pseudo-hepatomegaly.—Tumours of the colon, stomach, kidney, or suprarenal may become attached to the liver and mimic hepatomegaly. Under such conditions, direct biopsy of the mass may lead to peritonitis. Unless the physical signs of hepatomegaly are clear-cut, it is wiser to avoid the subcostal route.

8. Bleeding from Skin Incision.—The skin incision usually stops bleeding in 5 to 10 minutes. If there is no sign of haemostasis after this time, the biopsy should be postponed and the haemorrhagic state reinvestigated.

9. Interposition of Gut Between Liver and Diaphragm.— Varying degrees of this condition are not uncommon (Simon and Terry, 1952), and liver biopsy is contraindicated in their presence. The disorder is sometimes intermittent, and the operator should therefore never depend on an area of liver dullness delineated at some prior visit, but should always confirm the presence of dullness at the time of biopsy.

10. Depth of Puncture.—The deeper the liver is penetrated the greater the risk of damaging vessels of significant size. Volwiler and Jones (1947) punctured a large hepatic vein 4.5 cm. from the surface of the liver and fatal haemorrhage ensued. If a guard is mounted on the needle and adjusted to a distance of 5.5 to 6.5 cm., an adequate specimen will be obtained and penetration of the liver will be limited to about 3.5 cm.

11. Deep Pressure Over the Biopsy Site.—Immediately the biopsy is completed, firm pressure should be applied to the biopsy site in order to control bleeding or leakage from the wound in the liver. It should be maintained for 15 minutes in the routine case and for 30 minutes in cases of jaundice or if any cause for concern exists. This simple and obvious manœuvre is barely mentioned in the literature, but I think it is of fundamental importance in the prevention of complications. It should also be used in the treatment of bleeding.

12. A Ward Procedure.—The biopsy is best performed in the ward, with the patient lying comfortably on the edge of his bed, and it is then possible to restrict movement to a minimum and thus promote haemostasis. After the biopsy he remains on the edge of the bed during the 15 to 30 minutes of deep pressure on the biopsy site and is then gently lifted back into the centre of the bed. If the biopsy is carried out in an operating theatre, haemostasis is not assisted by the disturbances associated with returning him to the ward, even if a pressure pad or other device is employed. The practice of Wolff and Haythorn (1950), who perform many of their liver biopsies in the out-patient department, has little to recommend it.

13. Local Application of Haemostatic Agents.—Friedrich and Policzer (1948-9) and Clay and Dickinson (1949) advocate the injection of thrombin into the puncture wound on completion of the biopsy. The absence of bleeding in most biopsies does not seem to justify a procedure which itself introduces a hazard by prolonging the duration of the intrahepatic manipulation.

14. Post-operative Management.—The patient should remain flat in bed for six hours and at rest in bed until the next day. It seems wise not to discharge him for a further 24 hours. He should be closely watched and his pulse and blood pressure recorded at frequent intervals. Evidence of haemorrhage indicates the use of deep pressure for a prolonged period and perhaps a blood transfusion. Compatible blood should always be available, though in fact it will scarcely ever be used. If peritoneal irritation appears antibiotics should be used early, and, if not quickly effective, surgical advice should be obtained.

Present Series

Over 200 needle biopsies of the liver have been carried out in the past four years, using the combined syringe, trocar, and needle technique already described (Terry, 1949a). This series is too small to merit full analysis, and only the ill effects will be discussed.

Pain.-During the biopsy there was no pain in 85% of cases, and only trivial pain in the remainder, with the exception of a few early biopsies performed before the importance of thorough anaesthesia was realized. Following the biopsy there was no pain whatever in 28%, trivial pain in 54%, moderate pain (requiring aspirin) in 12.5%, and marked pain (requiring pethidine or morphine) in 5.5%.

Complications.—There were no deaths and no instances of haemorrhage. The only complications were two cases of biliary peritonitis, one mild and the other severe. These two cases occurred among 25 patients with obstructive iaundice.

Case 1. Mild Biliary Peritonitis .- A man aged 21 developed jaundice 60 days after partial gastrectomy. There was neither fever nor leucocytosis. The prothrombin level was 100%. A diagnosis of homologous serum jaundice seemed likely. Two hours after biopsy moderate right upper abdominal pain and splinting developed, accompanied by a temperature of 102.4° F. (39.1° C.) and a leucocytosis of 10,600. The episode quickly subsided and he was quite well after four days.

The biopsy revealed obstructive jaundice and cholangitis. At laparotomy a traumatic stricture of the common bile duct was found. A cholecyst-enterostomy was performed and recovery was uneventful. Bact. coli was isolated from the bile.

Case 2. Severe Biliary Peritonitis.-A man aged 63 had been suffering from recurrent bouts of abdominal pain and vomiting for five years and from remitting jaundice for 16 months up to two months before the biopsy. Immediately after the biopsy he experienced an unusual amount of pain in the right shoulder, and two hours later developed central abdominal pain and vomiting in every way similar to the attacks of the preceding five years. There was no abdominal rigidity, and only minimal tenderness on palpation, but morphine, $\frac{1}{2}$ gr. (16 mg.), one hour before biopsy may well have been responsible for this absence of physical signs. Low-grade fever, varying abdominal pain, and frequent vomiting continued for six days, after which he appeared to be well. On the twelfth day, however, his condition rapidly deteriorated and there was a large mass in the right iliac fossa. On the thirteenth day 8 pints (4.5 litres) of bilestained pus was evacuated at laparotomy. After a stormy post-operative course he made a full recovery. Unfortunately I was unaware of the result of duodenal intubation performed before the biopsy, which showed "a fair amount of pus and scanty Bact. coli in one specimen.' This finding would have been a contraindication to liver biopsy in the first place and an indication for early and energetic antibiotic therapy once abdominal symptoms had developed.

Both these instances of biliary peritonitis occurred before I adopted the use of deep pressure over the biopsy site.

Discussion

Those who wish to have the assistance of liver biopsy in the investigation of their patients are naturally anxious to know the risks involved. The foregoing survey of the literature reveals an overall mortality of 0.12% and a complication rate of 0.32%, and is reassuring so far as it goes, but it now seems desirable to obtain more detailed information.

It is clear that in young or middle-aged patients without jaundice or specific contraindication the risks are virtually non-existent. However, in the presence of jaundice there is a small but definite risk of biliary peritonitis and haemorrhage, and it is obviously important to assess the magnitude of this risk. This assessment can be made only if future publications on liver biopsy furnish more exact analysis of the disorders involved and the complications incurred.

Those who wish to practise liver biopsy should bear in mind that its present satisfactory status has been achieved only by careful attention to technique and the selection of cases, and that most complications reported in the literature have occurred in the first 100 cases.

Summary

A survey of the literature reveals that over 10,000 needle biopsies of the liver have been performed with modern techniques, with a mortality of 0.12% and an incidence of major complications of 0.32%.

The more important precautions are discussed.

Personal experience of 207 liver biopsies is noted, including two instances of biliary peritonitis.

A plea is made for a full analysis of cases in future publications, for only then will it be possible to assess the risk of specific complications in various disorders, particularly the risk of biliary peritonitis and haemorrhage in obstructive and parenchymatous jaundice.

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