ASPIRATION BIOPSY OF THE LIVER.

A CLINICAL EVALUATION.

Being a Thesis for the Doctorate

Of Medicine

by

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The purpose of this thesis is to evaluate the technique of aspiration liver biopsy. With this objective in view the relevant literature is reviewed and personal experience in the field is presented.

C O N T E N T S.

Introductory and Historical.

From time to time in the history of aspiration biopsy of the liver fatalities have occurred which have been attributed to the performance of the biopsy. This has deterred many physicians from adopting the procedure as a diagnostic measure even in obscure cases. That other clinicians have accepted the risk involved is an indication of the dissatisfaction frequently experienced in attempting accurate diagnosis of many maladies of the liver. It is generally agreed that an understanding of the natural history of any disease is of great value in assisting diagnosis. Appreciation of the pathogenesis of certain liver diseases was described a century ago by Rokitansky as a subject of great difficulty, the difficulty appearing to Boyd (1944) not to have grown materially less with the passage of the years. In 1939 Iversen and Roholm were able to write that "Considering the size and importance of the liver, our knowledge of its pathology is rather limited. From autopsy we are acquainted with many, particularly chronic, changes in the liver, but we do not know much concerning why and how these changes develop".

Introduction of an exploring needle into the liver is a procedure of by no means recent origin. In 1833 Roberts reported the cure of a patient suffering from a pus-containing hydatid cyst by means of drainage through a silver cannula and several other papers appeared in the nineteenth century dealing with the location and drainage of liver abscesses and cysts. In modern tumour diagnosis, aspiration biopsy plays an increasingly important role (Blinkenberg, 1938) and it seemed obvious that this technique should be applied to the liver. It is true that histological examination of aspirated liver tissue had been attempted by Lucatello as early as 1895 and his method was well-known in France and Italy. He used a fine needle and made smears of the aspirated blood in which isolated liver cells were sometimes to be found. In recent years Emile-Weil et al. (1938) and Fiessinger (1938) speak of elaborating "hepatograms" by this method which, however, never became popular and Frola (1935), in an exhaustive monograph, concluded that it was of little value.

Wider cannulae were employed by Snupfer (1907), Bingel (1923), Olivet (1926), Scalabrino (1928) and Huard et al. (1935). The varying technique used by these workers yielded only small fragments of liver tissue. No real advance in knowledge of hepatic pathology accrued from their studies which did not attract much attention.

A new phase was opened by Iversen and Roholm in 1939 when they described an original method whereby a solid core of liver substance was removed by biopsy. This enabled histological sections to be made which provided a more coherent picture of the state of the organ than was possible with the fragments of tissue obtained by the

earlier techniques. Since 1939 publication of work dealing with general aspects of liver aspiration biopsy by this new technique has been made by Tripoli and Fader (1941), Hatieganu et al. (1943), van Beck and Haex (1943), Hoffbauer (1945) and Sherlock (1945) among others. In addition papers have appeared dealing with studies of specific problems by liver biopsy. Examples include studies on acute and chronic hepatitis (Roholm and Iversen, 1939; Krarup and Roholm, 1941; Dible et al., 1943; Sherlock, 1938), on hepatic changes in chronic alcoholism (Raby, 1944), on the correlation of liver function tests with biopsy histological appearances (Sherlock, 1946) and on the state of the liver in thyrotoxicosis (Piper and Poulsen, 1947). Gillman and Gillman (1945) evolved a modified technique which they have used in extensive investigations of nutritional liver disease in African natives.

The information provided by such biopsy material has proved of considerable value both in the academic field and in practical diagnosis of the individual case. It has, for example, allowed the natural history of diffuse hepatitis and of fibrosis of the liver to be followed throughout its course whereas previously only the end results could be studied at post mortem examination. An important instance of the use of liver biopsy in diagnosis is in the not infrequent case in which the issue is undecided as between hepatic and obstructive jaundice. Biochemical tests of liver function are often uninformative if not frankly misleading (Sherlock, 1946) and, in the face of such uncertainty, laparotomy is often advised (Wessel, 1924; Nordmann, 1925; Klemperer, Killian and Heyd, 1926; Schrumpf, 1932). The characteristic histological changes in a biopsy specimen usually allow a certain differentiation to be made in such a case (Harris, 1948). The operative mortality associated with laparotomies upon patients suffering from hepatitis may thus be avoided.

Difficulty in clinical diagnosis is greatest in cases of early disease or in those with minimal symptoms. That clinical and biochemical evidence of hepatic dysfunction should be slow in development may readily be appreciated by consideration of the physiological reserve capacity and of the regenerative capabilities of the organ. The reserve capacity of the liver is demonstrated by the experiments of Bollman and Mann (1936) who carried out partial extirpation of the organ in dogs and found that hepatic function was not detectably decreased even after more than 80% of the liver had been removed. The regenerative powers of the organ were illustrated by the same authors who showed that restoration of the original mass occurred in 6 - 8 weeks after removal of three-quarters of the liver in dogs. Comparable events occur clinically. MacCallum (quoted by Boyd, 1944) described

a boy in whom a previous hepatic necrosis had apparently destroyed every cell in his liver apart from a single mass the size of a small orange of proliferated cells which was adequate to keep the boy alive and free from symptoms for six months until death occurred from an incidental infection, an instance of the reserve capacity of the organ. In severe cases of infective hepatitis (Dible et al., 1943) and in toxic hepatic necrosis (present series, case A/6) the early picture of necrosis of the majority of cells in each lobule has been shown by serial biopsies to be followed by restoration of the normal appearance in a period of a week or so.

It may be readily understood, therefore, that biochemical tests of liver function may fail to give information of value. Many such tests have been employed singly and in combination. Recent reviews of these tests (Higgins et al., 1944; Pollak, 1947) indicate that biochemical methods are of little value in arriving at a diagnosis in an obscure case of liver disease although they can serve as an index of the progress of the disease in an individual case. Sherlock (1946) carried out parallel liver biopsies and function tests in many disorders of the liver and found the biochemical evidence often uninformative and occasionally misleading. She agreed with Soffer (1947) that histologically proven examples of all types of hepatic pathology, including diffuse hepatitis, might be associated with normal values for the tests employed, but that abnormal values were uncommon in the proven absence of liver disease. Sherlock (1946) mentions, however, 34 cases in whom disease of the liver was suspected on clinical or biochemical grounds and in whom liver biopsy showed entirely normal appearances. Similarly Raby (1944) found that seven out of 22 gross chronic alcoholics had entirely normal livers as judged by biopsy specimens despite clinical and biochemical suggestions of cirrhosis or, at least, of marked fatty changes.

It will thus be seen that, both from the academic and from the diagnostic points of view, clinical and biochemical approaches have serious short-comings. Actual histological examination of a small core of liver removed by a biopsy cannula would appear to offer the possibilities of more accurate information in many cases. In the present work the author is attempting to define the place of aspiration biopsy in academic study and in clinical management of various forms of disease of the liver.

Complications and Risks of Liver Biopsy.

It has been shown in the preceding section that a prima facie case exists in favour of the performance of liver aspiration biopsy in the elucidation of certain cases of hepatic disease. That the operation has not been generally adopted is due almost entirely to the fact that cases have been recorded in which death of the patient has resulted as a direct consequence of the biopsy. The physician is naturally hesitant to employ a procedure which entails such a risk even if the required information cannot be obtained in other ways devoid of such risk. It has already been emphasised that clinical and biochemical findings are often inconclusive. The value od the information which can be obtained by liver biopsy will be discussed later, but it would appear to be of value to consider the circumstances of each recorded post-operative death in which full details have been given. From such material lessons might be derived which would lead to the adoption of precautionary measures which would enhance the safety of an otherwise relatively simple procedure.

Dieulafoy (1872) portrays the manner in which the physicians of the nineteenth century came to grief in performing liver puncture for the drainage of abscesses or cysts of the organ. He describes, in cases where the initial thrust of the cannula is unproductive of fluid, how the operator presses the cannula further and further into the organ and even massages the tumour. It was not uncommon for peritonitis and death to follow such an unduly prolonged exploration. Dieulafoy himself, with gentler touch, had no grave results although transient nausea with pain radiating to the right shoulder occurred in a few of his woman patients.

Turning to published work in the last three decades, it is necessary to consider seperately that appearing before the paper of Iversen and Roholm in 1939. Such a division is necessitated by the fundamental alteration in technique introduced by these authors and by their adequate appreciation of the risks of haemorrhage due to hypoprothrombinaemia secondary to liver disease. Most workers since 1939 have adopted, without major alteration, the technique of Iversen and Roholm, the essential difference from all previous methods being that the biopsy is carried out rapidly while the patient holds his breath. The operation had hitherto been performed deliberately and without regard to respiratory movement, the possibility of a tear in the capsule and in the substance of the liver thus being considerable. Furthermore, in attempts to reduce the risk of haemorrhage from the puncture in the liver, some of the earlier workers introduced coagulants through the biopsy cannula after aspiration of liver substance, Bingel (1923), for example, injecting dilute

solution of iron chloride. Such a procedure served certainly to increase the time during which the cannula remained in the liver, thus increasing the likelihood of a considerable tear in the organ, with but problematical effects upon clot formation.

On theoretical grounds Roholm, Krarup and Iversen (1942) considered the risks of liver biopsy to be seven in number. (1) Pain and other transitory disturbances immediately following the biopsy; (2) damage to adjacent organs; (3) implantation of tumour cells in the puncture canal; (4) air embolism; (5) infection; (6) choleperitoneum; and (7) haemorrhage. Local and referred pain was described by Dieulafoy (1872) and found by Roholm st al. (1942) to be sufficiently severe as to require opiation in 21 of 297 punctures. Sometimes this pain bore a relationship to respiration and appeared thus to have originated in the pleura whereas in the other cases the authors considered that the pain was an expression of peritoneal reaction to slight haemorrhage on the surface of the liver. A condition resembling shock was seen in four of these patients and was ascribed to a nervous reaction. Barron (1939) also reported pain at the site of puncture and in the right shoulder in some of his cases. In only one case among the present series did severe pain in the right shoulder related to respiration necessitate the adminstration of morphia although local discomfort at the site of puncture lasting a few hours was not uncommon. Such local discomfort was comparable with that experienced after paracentesis thoracis for pleural effusion. Barron also observed vomiting immediately following the biopsy and this occurred in one of the present series. A slight rise of temperature for 24 or 48 hours following the operation was noted in three of the present series and was also observed by Barron.

As regards damage to adjacent viscera, the risk is apparently very slight. Barron (1939) withdrew a small piece of colon mucosa in one case but there were no ill-effects.

Points (3), (4) and (5) do not appear to have caused trouble in practice. Choleperitoneum has not been reported as a serious complication although Roholm, Krarup and Iversen (1942) twice observed bile in the aspirating syringe, in neither instance with apparent ill-effect on the patient.

Most authors agree that the major danger is that of haemorrhage from the puncture. Various techniques have been devised to lessen this risk. Bingel (1923) gave Euphyllin (theophyllina cum aethyllenediamina) and hypertonic sodium chloride solution intravenously before the puncture and injected iron chloride solution through the cannula after aspiration of liver material. Gillman

Recorded Fatalities following Liver Biopsy.

Author	Year	Total Biopsies	Deaths
Bingel	1923	100	2
Olivet	1926	140	3
Huard et al.	1935	163	-
Barron	1939	49	1
		452	6
Mortality rate before 1939.....1.3%			
Tripoli	1941	14	-
Rbholm et al.	1942	297	2
Hatieganu et al.	1943	45	-
van Beck and Haex	1943	200	-
Raby	1944	27	2
Hoffbauer	1945	65	-
Gillman and Gillman	1945	504	1
Sherlock	1945	264	2
Present series	1948	86	1
		1502	8
Mortality rate since 1939.....0.53%			

and Gillman (1945) describe a plexus of large veins lying under the diaphragm over the right lobe of the liver. To obviate damage to such vessels they advocate puncture of the left lobe through the subcostal angle. The predominant danger has, however, lain in the bleeding tendency brought about by lowering of the plasma prothrombin as a result of liver disease. Roholm, Krarup and Iversen (1942) insist that the prothrombin time, the bleeding time and the coagulation time should be determined in addition to a platelet count before any biopsy is undertaken. Any form of haemorrhagic diathesis may thus be excluded but, unless otherwise indicated, most workers are content with knowledge of the prothrombin time before liver puncture.

In the Table there are set out all the recorded deaths following liver aspiration biopsy, a division being made between the reports before and after adoption of the modern technique in 1939. In some papers full details of the fatal cases are given and a summary of each of these is now given.

(1) Bingel (1923). Death from haemorrhage in a patient grossly emaciated by carcinoma of the stomach with multiple metastases.

(2) Bingel (1923). Death from haemorrhage in a patient with severe pernicious anaemia (red cell count 500,000 per c.mm.). Post mortem examination showed a large tear in the liver.

(3) Olivet (1926). A patient emaciated by carcinoma of the stomach with multiple metastases including deposits in the suprarenal glands. Death due to haemorrhage into the peritoneal cavity.

(4) Olivet (1926). A patient of poor general condition with severe pernicious anaemia (haemoglobin 15%). Post mortem examination showed death to be due to haemorrhage from a large tear in the liver.

(5) Barron (1939). A patient with carcinomatosis of the liver among widespread metastatic deposits.

(6) Roholm, Krarup and Iversen (1942). Death from haemorrhage in a patient with carcinoma of the pancreas. There was evidence of a haemorrhagic diathesis and the prothrombin time, first determined after the operation, was found to be greatly reduced.

(7) Roholm et al. (1942). Death from intraperitoneal bleeding after liver biopsy in a patient with carcinoma abdominalis. By error prophylactic vitamin K was not administered prior to the operation despite previous demonstration of prolongation of the bleeding time.

(8) Raby (1944). An elderly man with senile dementia. He was stated otherwise to be healthy and to have normal blood coagulation. Pain like gall-bladder colic occurred immediately after puncture and haematemesis followed after a few hours. Jaundice appeared on the second day. Death took place on the fourth day without further change. Post mortem examination showed negligible intra-abdominal haemorrhage and the absence of any tear in the liver. The puncture wound could be followed to an abnormally placed branch of the portal vein which was thrombosed. There was no mechanical obstruction of the biliary passages to explain the jaundice. The liver was normal histologically.

(9) Raby (1944). An elderly woman with chronic hyper-tensive heart disease and with recent jaundice of uncertain origin. Coagulation of the blood was normal. Puncture was performed without incident. Evidence of intra-abdominal haemorrhage was noticed later on the day of the biopsy. Vitamin K was administered parenterally and a blood transfusion was given. Despite these measures deterioration was progressive to death 30 hours after the puncture. Post mortem examination showed that the cannula had penetrated a superficial branch of the portal vein from which had apparently issued the fatal haemorrhage. Microscopical examination of the liver showed the presence of subacute hepatitis.

Sherlock (1945) reported two deaths in 126 biopsies, but no details are available except that one of the cases was moribund with acute hepatic necrosis at the time of biopsy. This worker changed to a cannula with a bore of only 1 mm. and carried out a further 138 successive biopsies without a death.

In the present series of cases there was one instance of death on the same day as the biopsy. The patient was an elderly woman with clinical and radiological evidence of a rapidly progressive bronchogenic carcinoma with carcinomatosis of the liver. The patient was judged to be moribund when puncture was performed. Unfortunately permission for post mortem examination was not obtained.

Attention need not be concentrated now upon cases (1) to (5) because of the essentially unsatisfactory technique employed. Even in these cases, however, it is apparent that each of the patients concerned was suffering either from advanced malignant cachexia or from profound anaemia. With adoption of the modern technique, cases (6) and (7) proved fatal because of failure to ensure a normal prothrombin time by prophylactic adminstration of vitamin K, the failure in case (7) being entirely accidental. In case (8) death was explained by portal thrombosis with 'peritoneal shock', jaundice being attributed to spasm of the biliary passages. In

case (9) there was no evidence of hypoprothrombinaemia but a fatal haemorrhage occurred from a branch of the portal vein which had been fortuitously pierced.

Scrutiny of each of these fatal cases has served to show that they were all in patients in poor general condition and that in every case except (8) and (9) some point of technique was imperfect; even in the exceptional case (8) it is to be wondered how much co-operation can be obtained from a patient recorded as suffering from senile dementia.

It must be emphasised as a conclusion of this survey of the risks of liver aspiration biopsy that no case has been published where death has occurred as a result of the operation in a subject of good general condition suffering from some disease with a good prognosis such as epidemic hepatitis. Every published case has been in a patient of poor general condition and usually with some inevitably fatal malady. It would appear justifiable to state, therefore, that liver aspiration biopsy is a reasonably safe procedure, always providing that the dangers of hypoprothrombinaemia are appreciated and minimised.

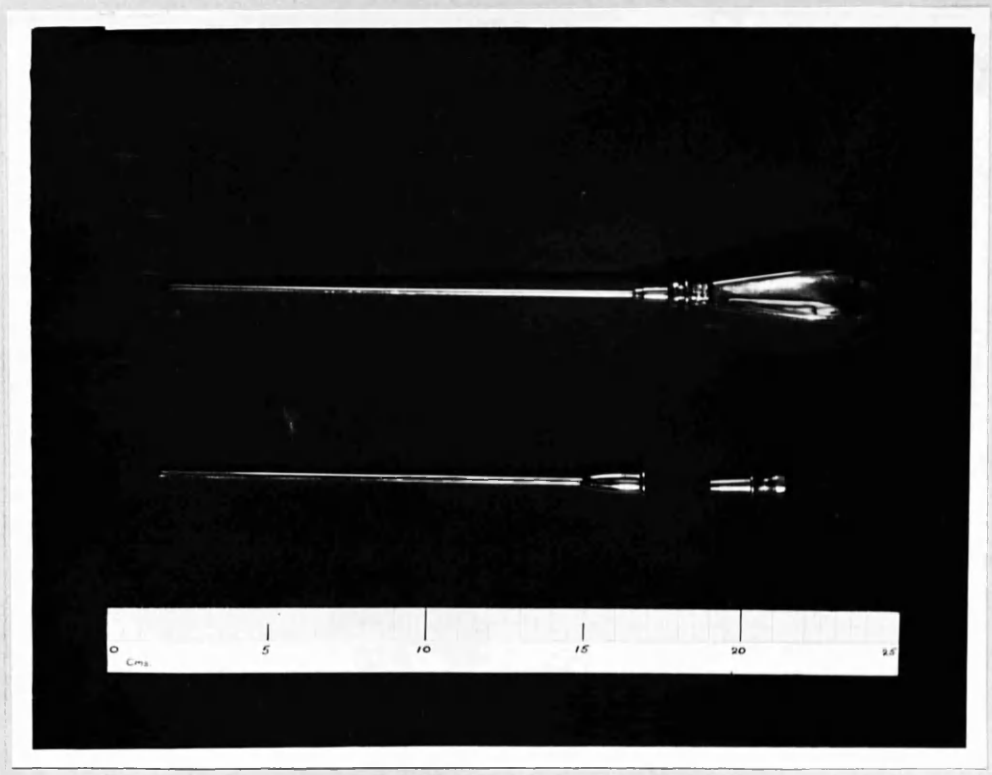
Technique.

The technique at present used by most workers is with but minor alterations that introduced by Iversen and Roholm (1939). In this method the biopsy is taken from the right lobe of the liver. In the modified method used by Gillman and Gillman (1945) the cannula is inserted in the angle between the xiphisternum and the right costal margin, thus penetrating the left lobe of the liver. These authors use a self-locking syringe to achieve the necessary negative pressure and claim a high proportion of successful punctures while avoiding blood sinuses which they describe as lying under the diaphragm in the area penetrated by the original approach. Puncture of the left lobe has the advantage that, in massive necrosis of the liver in particular, the changes are often very much more striking in the left lobe than in the right (Stewart, 1917; Himsworth, 1947). However it has been shown that the changes in the right lobe are usually representative of the pathology of the liver as a whole (Dible et al., 1943). Gillman and Gillman (1945) quote Iversen and Roholm (1939) as having 22.5% of fruitless biopsies but, as the percentage in the present series of cases was 9.3%, the necessity for using the somewhat complicated piece of apparatus devised by the South African workers is not appreciated.

The prothrombin level should be determined beforehand in all cases. The technique used by the present writer is that described by Innes and Davidson (1941). Should the index be low, a synthetic vitamin K analogue such as Kapilon is administered parenterally until the index is raised to a safe level. It is also advisable that the patient's blood should be grouped as a routine before biopsy is attempted and it may be said that liver puncture should not be carried out unless facilities are readily available for the transfusion of fresh blood.

In order to allay any anxiety on the part of the patient a suitable sedative should be administered before the operation. For the puncture the patient lies supine in bed with his right side on the edge of the bed; if there is undue hollowing of the centre of the bed, the patient's left flank may be supported by a pillow. The patient places his right hand up and behind his head. After preparation of his hands and of the skin of the right side of the lower chest and upper abdomen of the patient, the operator raises an intradermal wheal with 2% novocaine or other local anaesthetic solution in the 8th. or 9th. interspace in the mid-axillary line. Infiltration of the tissues is carried out until the needle touches the moving surface of the liver.

While waiting for the anaesthetic to take effect,



Liver biopsy trocar and cannula with adaptor for Record syringe.

Liver biopsy specimen with sections of 12 - 14 lobules ×6.

the patient is given simple instructions that a few deep breaths should be taken on command and followed by holding the breath in the position of expiration during the actual puncture of the liver. A trial is carried out of the patient's ability to carry out this simple, but important drill. Should there be lack of co-operation by the patient because of excitement or poor intelligence, the wisdom of proceeding with the operation should be debated.

The biopsy trocar and cannula has a length of 15 cms. and a bore of 2 mm. (fig.1). A small cut may be made in the anaesthetised skin and, the patient breathing quietly, the trocar and cannula are introduced. When definite respiratory movements are transmitted to the instrument from the surface of the liver the trocar is withdrawn. The patient takes a few deep breaths and then stops breathing in the expiratory position. The cannula is now pushed into the liver with a slight rotatory to-and-fro movement. After penetrating 2-3 cms., a dry-sterilised 10 or 20 ml. syringe is attached to the cannula by a special adaptor and gentle suction is exerted. The whole apparatus is then withdrawn, the negative pressure in the syringe being maintained, and the patient allowed to continue breathing. The small core of liver tissue is blown by the syringe on to a filter paper which absorbs any blood present and the specimen is transferred to a bottle containing fixative. To avoid handling the specimen, the filter paper around it may be cut out and transferred to the bottle of fixative with the liver adherent. The puncture wound is sealed and covered by an aseptic dressing. The patient lies quietly in bed for the remainder of the day and the pulse-rate is charted hourly. Should there be a rise in the pulse-rate or any other sign of internal haemorrhage, arrangements for transfusion of fresh blood should immediately be made.

Success in the operation depends largely upon two factors. Firstly the physician should be able to carry out the puncture smoothly and rapidly. Secondly the correct amount of negative pressure should be exerted by the syringe so that liver material is carried out in the cannula but not pulled up into the syringe and thus damaged. A guide as to this point is that the requisite suction is obtained when the piston of the syringe is withdrawn about half-way up the barrel. The apparatus described by Gillman and Gillman (1945) obviates the necessity for skill in this part of the procedure by exerting greater suction but having a grooved trocar which remains within the cannula and thus stops the core of liver from being aspirated into the syringe. American workers (Kumpe et al.,)1947) have introduced a split cannula which allows the worm of liver to be grasped and thus more readily withdrawn, again circumventing the difficulty of maintaining the correct degree of suction

by the aspirating syringe in the original method.

The biopsy specimen (fig. 2) is usually a small worm-like piece of tissue of about 2 mm. diameter and measuring 1-3 cm. in length. Sometimes, and especially with fibrotic livers, the specimen tends to be fragmented. The tissue is subjected to routine histological procedures and appropriate techniques may be adopted in different cases. Should two or more methods of staining demand different fixatives the specimen, if sufficiently long, is divided before fixation. For routine purposes and appreciation of the general histological picture, fixation in the present series has been by neutral formol-saline and staining by haematoxylin and eosin. Where desired, Mallory's stain, fat stains, Best's carmine stain for glycogen, methyl violet for amyloid infiltration and the Prussian Blue reaction for iron have been employed.

In seven instances attempted biopsy failed to yield any liver tissue at all. In a further four cases, one of primary hepatoma and three of hepatic fibrosis, the material obtained was greatly fragmented. Even in these latter instances, however, a correct histological diagnosis could be established in all but one of the four cases. In all, therefore, aspiration biopsy failed entirely to provide material adequate for histological study on eight occasions in the 86 biopsies of the present series, 9·3 per cent.

Discussion of Results.

For convenience the conditions of the liver which have been studied by liver aspiration biopsy will be divided into six categories according to the diagnosis finally established in each case.

(1) Hepatitis, including Acute Hepatic Necrosis and Hepatic Fibrosis or Cirrhosis.

(2) The Syndrome of Splenic Anaemia.

(3) Obstructive Jaundice and Biliary Cirrhosis.

(4) Malignant Disease of the Liver.

(5) Anaemias.

(6) Miscellaneous Conditions.

(1) Hepatitis, including Acute Hepatic Necrosis and Hepatic Fibrosis or Cirrhosis.

Liver biopsy has played an important part in advancing knowledge of these disorders. The ability to examine the histology of the liver in a living patient allowed of final proof that acute epidemic jaundice is a disease of the liver parenchyma (Roholm and Iversen, 1939; Dible, McMichael and Sherlock, 1943). The theory that jaundice in this disease was due to catarrhal obstruction of the ampulla of Vater (Virchow, 1865) was first seriously challenged by Eppinger (1922) who described parenchymal inflammatory changes in the livers of four soldiers who died of war wounds while suffering from epidemic jaundice. Similar evidence was obtained by surgical biopsies at laparotomies upon patients suffering from acute hepatitis who underwent operation because of mistaken diagnosis of obstructive jaundice (Wessel, 1924; Nordmann, 1925; Klemperer, Killian and Heyd, 1926; Schrumpf, 1932). Despite these reports, Virchow's views continued to be taught and there were many, including the late Sir Arthur Hurst, who held that there were two diseases, acute hepatitis and catarrhal jaundice, separable on clinical grounds. Roholm and Iversen (1939), however, finally disproved the catarrhal obstructive theory by demonstrating diffuse parenchymal changes by liver aspiration biopsy in each of a large series of cases of epidemic jaundice. Dible et al. (1943) confirmed these findings and demonstrated also that all grades of severity of the histological picture existed up to necrosis of every cell in the liver lobule, an appearance indistinguishable from acute massive necrosis or 'acute yellow atrophy'.

That diffuse fibrosis of the liver could follow acute hepatitis was shown by Krarup and Roholm (1943) who followed cases of severe, prolonged or relapsing hepatitis by serial biopsies. They were able to demonstrate intermediate stages between the residual periportal infiltration usually found after the acute phase and fully developed 'cirrhosis' of the organ. Dible et al. (1943) reported similar findings and suggested that cellular infiltration of the portal tracts persisting after all evidence of parenchymal damage had disappeared was an indication that fibrosis of the liver would develop. That such a state may be reversible, however, is suggested by the experimental work of Cameron and Karunaratne (1936) on carbon tetrachloride poisoning in dogs. This poison produces changes in the liver identical with those of acute hepatitis and the authors found that, after a single dose, acute centrilobular necrosis developed. During resolution of the lobular damage periportal infiltration developed and might persist for a period following clinical recovery. Such residual infiltration,

it was found, tended usually to disappear. Neefe (1946), on the other hand, carried out liver biopsy in certain volunteers with artificially induced hepatitis several months after the acute phase. The particular cases were chosen because of persistence of abnormality in serial function tests and histologically there was found to be undue cellularity of the portal tracts which the author considered as evidence of chronic hepatic disease. No control biopsy was taken, however, from any of the cases showing normal values in the function tests.

Sherlock (1948) followed cases of chronic hepatitis over long periods and suggests that, in some cases, diffuse fibrosis of the liver may be a non-progressive condition compatible with good health. In other cases of her series a subacute or chronic hepatitis accompanied the fibrosis and the condition progressed to parenchymal failure or to portal hypertension with ascites and haemorrhages from oesophageal varices. From experimental studies Himsworth (1947) concluded that fibrosis of the liver, once established, is an inevitably progressive condition leading eventually to portal hypertension or to functional failure of the organ. The work of Gillman and Gillman (1945) has been of importance in showing that severe deficiency in the diet of many African natives leads first to diffuse fatty changes in the liver and ultimately to the appearance of diffuse fibrosis of the organ. That a similar chain of events may occur in the malnutrition of some chronic alcoholics is indicated by Raby (1944).

It is apparent from the preceding account that liver aspiration biopsy has played a major part in the formation of our present conception of acute and chronic hepatitis. Modern work in this field is reviewed by Himsworth (1947) and it would appear probable from this monograph that biopsy of the liver will play an increasing part in future academic investigations.

Turning now to the practical value of aspiration biopsy in the individual case of hepatitis, acute or chronic, it is apparent that the diagnosis in any such case may be confirmed by biopsy unless, as may occur in certain examples of acute massive necrosis, the pathological changes are confined to the left lobe of the organ. In acute epidemic hepatitis, however, the prognosis is so good that the risk, albeit small, associated with the performance of biopsy renders the procedure unjustifiable as a routine measure. There are three main sets of circumstances when liver biopsy is indicated in a probable case of acute hepatitis. Firstly, undue severity of the symptoms and signs may suggest the presence of massive parenchymal necrosis of the viscus. In such a case the biopsy may allow histological confirmation of the latter diagnosis, prognostic

Histological differentiation between Acute Hepatitis and Cholangio-hepatitis.

		Liver Lobules			Bile Retention	Cellular infiltration of portal tracts
		Zonal necrosis	Infiltration by round cells etc.	Haemorrhage		
Acute Hepatitis	Early	Always present Centrilobular in distribution	Present	Often Present	Absent or slight	Present unless very early in disease
	Late	Absent due to restitution of lobule	Usually present	Usually absent	Usually absent	Present
Obstructive Jaundice (Cholangio-hepatitis)		Usually absent; if present periportal in distribution	Absent	Absent	Present	Present

information of considerable importance thus being obtained. Secondly, in cases of hepatitis presenting a prolonged course or displaying relapses biopsy may give invaluable information concerning the presence or absence of established fibrosis. Such evidence is again of great value in prognosis since the presence of anything but a minimal amount of fibrous tissue in the liver apparently constitutes an irreversible and often progressive condition leading ultimately to hepatic insufficiency (Himsworth, 1947). That some cases of hepatic fibrosis following hepatitis may remain quiescent is indicated by Sherlock (1948) and further experience is required before confidence can be gained in the interpretation and especially in the prognosis of any single case. Thirdly, cases are often encountered in which the diagnosis is uncertain as between acute hepatitis and an obstructive jaundice. Most commonly the difficulty arises with patients over the age of 40 years. Laparotomy has been widely used in such cases in order that the issue might be clarified and a major operation in a patient suffering from acute hepatitis entails an appreciable mortality rate which, although lessened in recent years by general application of the knowledge concerning hypoprothrombinaemia and of the hepatotoxic qualities of certain anaesthetic agents, remains much in excess of the risk of liver aspiration biopsy. In acute hepatitis and in mechanically obstructive jaundice there is in each case a characteristic histological picture in the liver which usually provides evidence for a confident diagnosis, evidence of a much more reliable nature than that yielded by biochemical tests of liver function (Sherlock, 1946). Detailed consideration of the histological differences between the two conditions is given by Harris (1948) and is summarised in the Table.

Aspiration biopsy of the liver was carried for diagnostic purposes in most of the cases in the present series. The diagnosis of acute hepatitis was made histologically in eight cases, three of which satisfied the clinical criteria of epidemic hepatitis. Two cases of acute hepatitis had been diagnosed clinically as obstructive jaundice and of two cases of hepatitis following intravenous injections one had been considered obstructive in nature. Histological changes similar to those occurring in infective hepatitis were found in a case of carbon tetrachloride intoxication. In two cases diagnosed clinically as of acute hepatitis, the biopsy appearances were of acute massive necrosis of the liver; one of these cases died and the diagnosis was confirmed post mortem while the other patient survived, serial biopsies demonstrating the development of subsequent fibrosis of the organ. In seven of the preceding cases the serum colloidal gold test was carried out and normal results were obtained in three cases. In one case of infective hepatitis and in the instance of carbon tetrachloride

Cases of . TABLE 1. Hepatitis.

Case	Initial Clinical Diagnosis	Plasma Alkaline Phosphatase (Bodansky)	Serum Colloidal Gold	Liver Biopsy Appearances	Ultimate Diagnosis
A/1	Acute hepatitis	2.4	000000	Massive necrosis	Massive necrosis of the liver
A/2	Acute hepatitis	2.6	544000	Centrilobular necrosis	Acute hepatitis
A/3	Acute hepatitis			Massive necrosis with hyperplasia	Massive necrosis with nodular hyperplasia
A/4	Thyrotoxicosis; Acute hepatitis			Centrilobular necrosis	Thyrotoxicosis; Acute hepatitis
A/5	'Syringe' hepatitis	3.2	543000	Centrilobular and midzonal necrosis	'Syringe' hepatitis
A/6	Carbon tetrachloride poisoning			Centrilobular necrosis; haemorrhages	Carbon tetrachloride poisoning
A/7	'Portal cirrhosis'	4.4	000000	Diffuse fibrosis	Diffuse hepatic fibrosis
A/8	Obstructive jaundice	8.9	000000	Regenerative changes in centrilobular zones; cellular infiltration of lobules with haemorrhages	'Syringe' hepatitis (in resolution)

Cases of

T A B L E 1. (Continued)

Hepatitis.

Case	Initial Clinical Diagnosis	Plasma Alkaline Phosphatase (Bodansky)	Serum Colloidal Gold	Liver Biopsy Appearances	Ultimate Diagnosis
A/9	Acute hepatitis	3.8	000000	Centrilobular necrosis	Acute hepatitis
A/10	Obstructive jaundice	4.8	300000	Centrilobular necrosis	Acute hepatitis
A/11	'Portal cirrhosis'	7.2	432000	Hepatic fibrosis	Diffuse hepatic fibrosis
A/12	Cholelithiasis	11.1	320000	Degenerative changes in cells of inner 2/3 of lobules	Acute hepatitis

poisoning serial biopsies were performed and allowed the progress of the hepatic damage in each case to be followed to complete resolution.

Apart from the cases of hepatic fibrosis to be described in the section dealing with splenic anaemia, three cases of 'cirrhosis' were encountered. In one case the diagnosis was obvious and the progress indicated increasing hepatic insufficiency, the serum colloidal gold test showing gross abnormality. In the other two cases, however, diagnostic difficulty was encountered as between secondary malignant disease of the liver and hepatic fibrosis; on one of the cases the biopsy confirmed the presence of diffuse fibrosis but in the other instance (case D/7) an initial biopsy showed only diffuse fibrosis whereas the progress of the case indicated malignant disease and a subsequent biopsy revealed invasion of the fibrotic organ by carcinomatous metastases,

Aspiration biopsy has thus proved of considerable diagnostic value in seven of the 13 cases discussed above and in at least two instances the biopsy findings obviated laparotomy. In addition the development of frank 'cirrhosis' was observed in case A/1 with consequent alteration in the prognosis. The unreliability of the serum colloidal gold reaction as a test of parenchymal damage is indicated by the normal results in three out of seven cases with histologically-proven parenchymal disease, most striking being the normal result in one of the cases of acute massive necrosis of the liver.

(2) The Syndrome of Splenic Anaemia.

Since Gretsel (1866) introduced the term 'splenic anaemia' there has been confusion as to the precise limitations and aetiology of the syndrome. Banti (1898) defined the condition as one of splenomegaly not associated with leukaemia, lymphadenoma, haemolytic anaemia, malaria, syphilis or other recognised disease. He described an initial stage of anaemia with leucopenia, splenomegaly and a liability to haemorrhages, an intermediate phase of hepatomegaly, urobilinuria and pigmentation of the skin, and a final stage of liver failure with ascites. Banti considered that the spleen was the primary seat of disease and that cirrhosis of the liver and thrombosis of the portal and splenic veins were the sequelae. McMichael (1934) pointed out that the changes in the spleen were consistent with chronic congestion of the organ and that the typical picture of 'fibro-adenie' followed the experimental production of hepatic cirrhosis in rabbits by the administration of manganese. In addition, Rousselot (1939) presented evidence of portal hypertension by direct measurement at laparotomy in patients with the clinical syndrome of Banti's disease. Himsworth (1947) considers that simple congestion of the spleen is not sufficient to explain the occurrence of the syndrome following primary liver disease and that toxic factors derived from protracted or recurring hepatic parenchymal degeneration are necessary before the syndrome of splenic anaemia will thus develop.

The present position (Davidson, 1948; Mackey, 1948) would appear to be that the syndrome of splenic anaemia or chronic congestive splenomegaly is probably secondary in all cases to portal hypertension or to thrombosis of the splenic vein; the portal hypertension may be caused by hepatic cirrhosis or by obstruction of the portal vein by thrombosis or by some lesion such as enlarged glands causing pressure on the vein with or without secondary thrombosis. Thompson (1940) states that in about 70% of cases the obstructive factor is found to be hepatic cirrhosis and that, if cirrhosis were not found at laparotomy or biopsy, it would not develop subsequently. Thrombosis of the splenic vein is a rare cause of the syndrome and splenectomy in such cases is effective in relieving the anaemia. In those instances in which the primary lesion is hepatic fibrosis, it is probable that surgical measures have no place in treatment and, since diagnostic laparotomy has a considerable mortality rate in such cases, it is apparent that exclusion of fibrotic changes by aspiration biopsy would be of great value in making a decision to perform an exploratory operation. There are no clinical or biochemical means of reaching a certain conclusion in the many instances in which the presence or absence of cirrhosis is in doubt and it is in such cases that liver aspiration biopsy has an

Cases of **TABLE 2.** Splenic Anaemia.

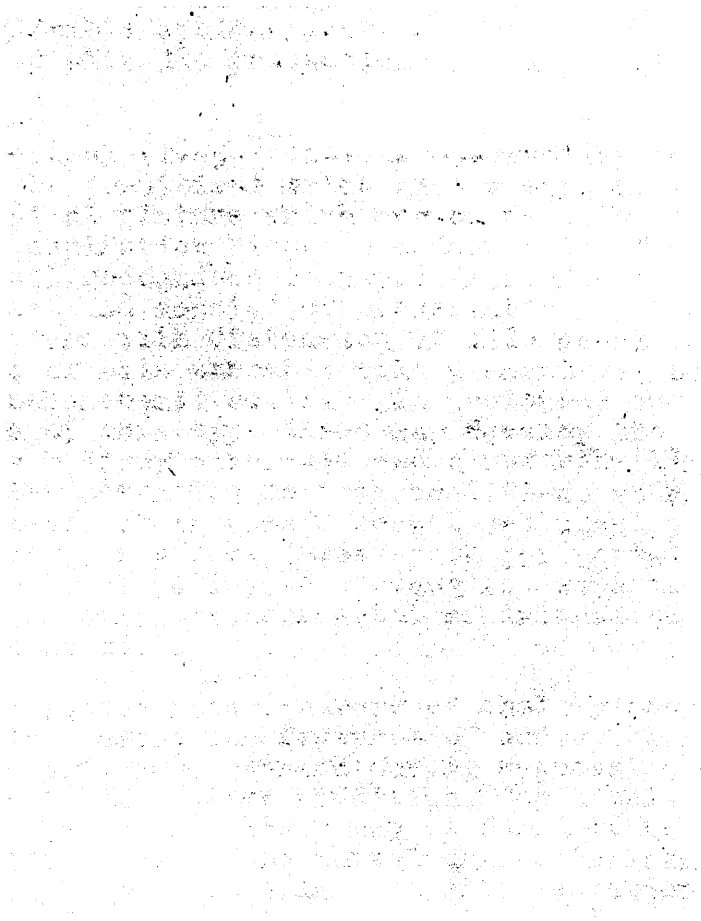
Case	Liver biopsy appearances	Plasma Alkaline Phosphatase (Bodansky)	Serum Colloidal Gold	Other remarks
B/1	Diffuse hepatic fibrosis			Originally diagnosed as Haemolytic Anaemia
B/2	Normal	3.0	000000	Liver found at laparotomy to be 'hob-nailed'
B/3	Diffuse hepatic fibrosis			
B/4	Diffuse hepatic fobrosis			
B/5	Normal	4.4	000000	Oesophageal varices present
B/6	Normal	2.6	300000	? Thrombosis of portal vein
B/7	Diffuse fibrosis; round-cell infiltration			
B/8	Diffuse fibrosis; round-cell infiltration	10.0	332100	Died of uraemia and chronic nephritis
B/9	Fibrosis not involving lobule.	3.3	200000	

important part to play in the pre-operative investigation of cases of splenic anaemia. Apart from splenectomy in the rare cases of thrombosis of the splenic vein, surgery now offers a hope for those free from hepatic cirrhosis. In cases of portal hypertension due to portal thrombosis Whipple (1945) advocates anastomosis of the splenic vein to the left renal vein after removal of the spleen and of the left kidney, junction between the veins being effected by special vitallium tubes.

Davidson (1948) accepts this attitude towards the syndrome of splenic anaemia and, after initial clinical and haematological studies to confirm the diagnosis and to exclude other forms of splenomegaly, he employs liver biopsy as a routine procedure. Should fibrosis of the organ be disclosed, he considers that operation is contraindicated and he treats the patient with iron in large dosage. Should biopsy show a liver of normal appearances, laparotomy is advised and, depending on the findings at operation, either Whipple's operation or splenectomy alone is considered. The decision to perform laparotomy is also based upon a balance of the risks involved in Whipple's operation and the dangers, as far as they can be assessed in the individual case, of fatal haemorrhage from oesophageal varices.

In the present series of cases subjected to liver biopsy there were nine cases fulfilling the diagnostic criteria of splenic anaemia. In six of these cases the biopsy material showed diffuse fibrosis of the liver to be present, but in one of the six the fibrosis did not involve every lobule and the view was taken, in accordance with the dicta of Himsworth (1947), that the appearances represented the effects of a previous massive necrosis of the liver. In case B/2 the biopsy material was free from fibrosis whereas the liver was found at laparotomy to be 'hob-nailed', the probability again being that that hepatic fibrosis was the result of the previous massive necrosis with residual unaffected areas of parenchyma; such a case indicates that the biopsy results may prove misleading in instances where fibrosis of the liver does not extend throughout the whole organ. In case B/6 the syndrome of splenic anaemia followed parturition and recovery was spontaneous; biopsy sections showing no evidence of fibrosis, the suggestion is made that the underlying lesion was thrombosis of the portal vein, the thrombus ultimately undergoing recanalisation. In case B/1 the diagnosis was initially in doubt and the disclosure by biopsy of the presence of subacute hepatitis with hyperplasia and fibrosis was the main factor in settling the issue. Case B/2 is an example of splenic anaemia as a sequel to massive hepatic necrosis with recovery and case B/7 had suffered a prolonged attack of infective hepatitis with relapses prior to the onset of splenomegaly. There was no history of jaundice in

four of the cases showing definite fibrosis on biopsy and the nature of the preceding processes must remain speculative in such instances.



(3) Obstructive Jaundice and Biliary Cirrhosis.

Cases of obstructive jaundice have been subjected to liver aspiration biopsy essentially because of diagnostic uncertainty. Prior to the introduction of the modern technique of biopsy it was not uncommon for laparotomy to be undertaken for diagnostic purposes in cases of jaundice of undetermined origin (Wessel, 1924; Nordmann, 1925; Klemperer, Killian and Heyd, 1926; Schrumpf, 1932). The operation in cases of hepatic jaundice carried a not inconsiderable mortality rate which, although reduced in recent years by the appreciation and application of the knowledge concerning hypoprothrombinaemia and the hepatotoxic qualities of certain anaesthetic agents, remains much in excess of the negligible accident-rate of aspiration biopsy when performed with due precautions and in relatively fit patients.

Sherlock (1945) mentions obstructive jaundice as one of the conditions which give a typical and diffuse histological picture which may be readily diagnosed from an aspiration biopsy specimen. The features are those well recognised from post-mortem examination of such cases and consist of preservation of the lobular architecture with distension of bile canaliculi and the presence of bile thrombi; bile pigment may be recognised within parenchymal cells. In prolonged or relapsing jaundice of this type there may develop the changes known as biliary cirrhosis and Himsworth (1947) pays particular attention to this condition, attributing the presence of increased portal cellularity sometimes associated, in severe cases, with periportal necrosis of parenchymal cells, to cholangitis superimposed upon partial or complete, permanent or intermittent closure of the bile ducts.

Clinically this syndrome of cholangiohepatitis may mimic closely the features of acute hepatitis and, should biopsy be performed during regression of jaundice in the latter condition, the lobular architecture of the liver may be found to be restored and infiltration of the portal tracts is invariably present. Important points of differentation are the presence of separation of the columns of liver cells in the obstructive form and of cellular infiltration of the lobules in acute hepatitis; further, bile retention is usually slight or absent in hepatitis whereas it is invariably a feature of obstructive jaundice providing that corrosive sublimate has not been used as a fixative because the subsequent processing with iodide tends apparently to remove the pigment from the sections. This question is dealt with by Harris (1948).

Cases of

TABLE 3.

Obstructive Jaundice.

Case	Clinical diagnosis	Plasma Alkaline Phosphatase (Bodansky)	Serum Colloidal Gold	Biopsy findings	Ultimate diagnosis
C/1	Acute hepatitis			Cholangio-hepatitis	Carinoma of pancreas; metastases in liver
C/2	Obstructive jaundice			Consistent with obstructive lesion	Carcinoma of gall-bladder
C/3	Obstructive jaundice	2.2		Consistent with obstructive lesion	Carcinoma of bile ducts
C/4	'Cirrhosis'			Biliary fibrosis	Carcinoma of pancreas
C/5	Obstructive jaundice			Consistent with obstructive lesion	Tuberculosis of pancreas
C/6	'Cirrhosis'			Biliary fibrosis	Nature of lesion not disclosed even by laparotomy
C/7	Carcinoma of pancreas			Consistent with obstructive lesion	Carcinoma of pancreas
C/8	Cholangio-hepatitis	7.9	200000	Fibrosis of uncertain distribution	Unsettled; laparotomy refused
C/9	Carcinoma of pancreas	6.4	320000	Consistent with obstructive lesion	Carcinoma of pancreas
C/10	Carcinoma of pancreas	23.0	332000	Consistent with obstructive lesion	Carcinoma of bile-ducts; metastases in liver

In the present series of cases there were ten ultimately determined as jaundice of obstructive type. In six cases the diagnosis clinically was confident and biopsy was carried out as a confirmatory measure, the diagnosis being proven subsequently in each case at laparotomy or by post mortem examination. In three of these obstructive cases estimation of the plasma alkaline phosphatase was carried out and in only one instance was there a significant rise; in each of two of the cases, however, the serum colloidal gold reaction showed definite abnormality. In one case the initial clinical features led to a diagnosis of acute hepatitis but the histological appearances of a biopsy specimen indicated that the lesion was obstructive in nature and the subsequent course of the illness (case C/1) was that of recurring jaundice due to cholangio-hepatitis, post mortem examination ultimately showing the presence of a carcinoma of the pancreatic head which did not cause complete obstruction of the bile duct. In two cases the clinical diagnosis was of 'portal cirrhosis' or diffuse fibrosis of the liver; the biopsy appearances were those of 'biliary cirrhosis' or chronic cholangio-hepatitis and in one of these cases carcinoma of the pancreas was disclosed at laparotomy. The other case is of considerable interest because two abdominal explorations had failed to discover an obstructive lesion and cholecyst-enterostomy did not result in amelioration of the jaundice; the biopsy clearly indicating bile obstruction, the suggestion was advanced that the obstructive lesion must be intra-hepatic but, as the patient did not come to post mortem examination, no proof of this suggestion is available. Similar cases are discussed by Dible, McMichael and Sherlock (1947). In the remaining case the clinical features included recurrent jaundice and were consistent with cholangio-hepatitis. The possibility of subacute hepatitis with fibrosis could not, however, be excluded and the biochemical tests of liver function were of no assistance in arriving at a decision. Aspiration biopsy of the liver succeeded in removing only fragments of tissue, the latter showing the presence of established fibrosis but, unfortunately, the distribution of the fibrosis could not be determined. As the patient refused laparotomy confirmation of the diagnosis was not obtained.

(4) Malignant Disease of the Liver.

Malignant metastases in the liver may be revealed by liver aspiration biopsy, but, owing to the scattering of neoplastic nodules in the liver, it is readily appreciated that a single biopsy specimen may contain no malignant cells. Sherlock (1945) concludes that, while a positive result gives unequivocal proof of diagnosis, a negative result is of no value in exclusion; Davis (1948), however, points out that, in the presence of enlargement of the liver and especially in cases where other clinical findings are consistent with the presence of malignancy, a liver biopsy specimen showing no abnormal histological features may be regarded as presumptive evidence of cancer since it tends to exclude other diffuse causes of hepatomegaly, chronic hepatitis in particular.

Eighteen cases of the present series were shown to have malignant disease of the liver. Two of the cases presented as obstructive jaundice (cases C/1 and C/10) and in these instances the biopsy sections failed to show evidence of neoplastic invasion of the organ although the changes observed indicated the obstructive nature of the jaundice; both cases were shown post mortem to have but scanty metastases in the liver. In twelve cases with secondary carcinomatosis of the liver, the primary lesion was demonstrated at operation, at post mortem examination or by unequivocal radiological examinations, and in seven of these cases liver biopsy showed no abnormality despite the presence of hepatomegaly. In two cases the presence of malignant disease of the liver was demonstrated by biopsy when hepatomegaly of uncertain cause was the presenting finding; the primary lesion was not discovered in these cases and in one of them (case D/7) the initial clinical diagnosis of 'cirrhosis' was supported by a biopsy which showed diffuse fibrosis of the liver; a subsequent biopsy, performed because of the later appearance of signs suggestive of malignancy, revealed anaplastic cell masses in the fibrotic organ. In one case (case D/2) gross hepatomegaly in a young adult male presented a problem in diagnosis which was resolved by the biopsy discovery of invasion of the liver by anaplastic carcinoma. In case D/12 the initial opinion was of 'cirrhosis' but the biopsy revealed the presence of metastases of an adeno-carcinoma later shown to originate from the stomach. Cases D/9 and D/13 were examples of melanomatosis of the liver and the diagnosis had been made before biopsy was undertaken in the former case; in the latter patient, however, the biopsy gave the first evidence of the presence of melanoma as the woman was admitted in coma due to a cerebral vascular accident and the enlargement of the liver was an incidental finding. In case D/8 hepatomegaly of uncertain origin was shown by biopsy to be due to the presence of

Malignant Disease — TABLE 4. — of the Liver.

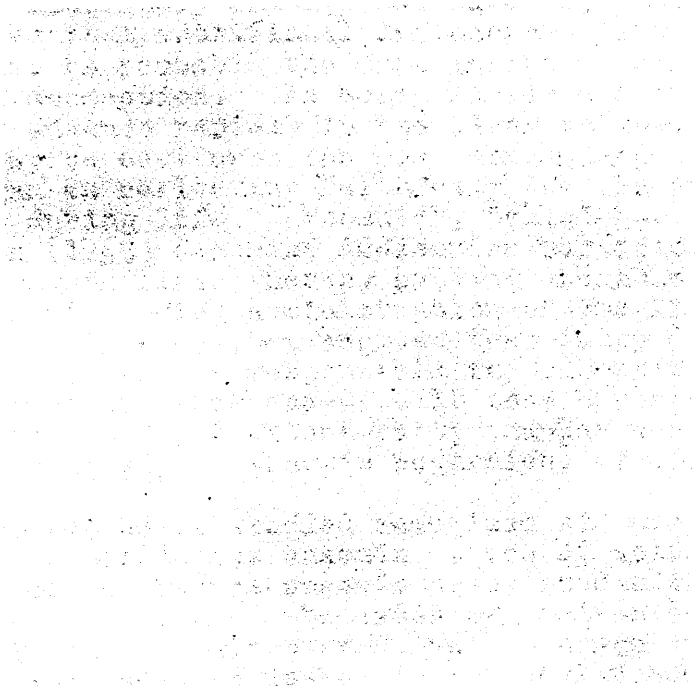
Case	Initial diagnosis	Liver biopsy appearances	Ultimate diagnosis
D/1	Secondary carcinoma of liver	Invasion by adeno-carcinoma	Secondary carcinoma of liver; primary undetermined
D/2	Hepatomegaly of uncertain cause	Invasion by anaplastic carcinoma	Bronchogenic carcinoma with metastases
D/3	Secondary carcinima of liver	Normal	Carcinoma of colon with metastases in liver
D/4	Carcinomatosis of lungs	Normal	Carcinoma of pancreas with metastases in liver
D/5	Carcinoma of stomach	Normal	Carcinoma of oesophagus with metastases in liver
D/6	Carcinoma of colon	Normal	Carcinoma of rectum with metastases in liver
D/7	'Cirrhosis'	Diffuse fibrosis; anaplastic carcinoma	Hepatic fibrosis; secondary carcinoma
D/8	Secondary carcinoma of liver	Hepatoma	Nodular hyperplasia of liver with primary hepatoma
D/9	Melanomatosis	Invasion by melanoma cells	Melanomatosis
D/10	Bronchogenic carcinoma	Invasion by anaplastic carcinoma	Carcinoma of bronchus with metastases in liver
D/11	Carcinoma of colon	Normal	Carcinoma of colon with metastases in liver

Malignant Disease — TABLE 4. (Continued) — of the Liver.

Case	Initial diagnosis	Liver biopsy appearances	Ultimate diagnosis
D/12	'Cirrhosis'	Invasion by adeno-carcinoma	Primary carcinoma of stomach
D/13	Cerebral thrombosis; hepatomegaly	Invasion by melanoma cells	Cerebral thrombosis; melanoma of choroid with hepatic metastases
D/14	Bronchogenic carcinoma	Invasion by anaplastic carcinoma	Carcinoma of bronchus with metastases in liver
D/15	Carcinomatosis	Invasion by anaplastic carcinoma	Carcinoma of bronchus with metastases in liver
D/16	Hepatomegaly? due to secondary carcinoma	Normal	Unsettled; Probable primary lesion in gastro-intestinal tract with metastases in liver and brain

a primary hepatoma, the diagnosis eventually being confirmed at post mortem examination.

Aspiration biopsy thus achieved ten positive results in eighteen cases of malignant disease of the liver. Two of the remainder were examples of obstructive jaundice while the rest, six in number, were instances of hepatomegaly associated with normal histological appearances of biopsy specimens, this combination being presumptive evidence in favour of malignancy.



(5) Anaemias.

Apart from the use of aspiration biopsy in the syndrome of splenic anaemia (vide supra), the technique was adopted by Sherlock (1945) in the investigation of obscure blood disorders and she mentions cases of otherwise unsuspected histiocytic medullary reticulosis and of Gaucher's disease which were thus diagnosed. Sherlock also describes a case suspected as one of haemolytic anaemia in which there was no evidence of increased red cell fragility; the finding of haemosiderosis in a liver biopsy specimen was apparently taken as supporting the diagnosis.

In the present series ten cases of severe anaemia were subjected to liver biopsy as part of an investigation into the effect of anaemia upon the liver. Current teaching (Beattie and Dickson, 1943) holds that old age, starvation, cachectic conditions and severe anaemias cause generalised fatty degeneration of the liver. The clinical reports of Gillman and Gillman (1945) upon South African natives and the experimental work on laboratory animals described by Himsworth (1947) indicates that nutritional deficiency, particularly of proteins, is probably the most important single factor in this connection. As degenerative and autolytic changes advance rapidly in the liver following death, doubt may be cast upon the post mortem appearances in the organ as reflecting faithfully the changes actually present during life. Moosnick, Schleicher and Peterson (1945) describe Addisonian pernicious anaemia refractory to liver therapy proving amenable to such treatment following administration of the lipotropic factor choline and they suggest that fatty degeneration of the liver may be responsible for suboptimal responses to treatment in such cases. It thus appeared important to discover to what extent fatty changes were induced in the liver by severe anaemia regardless of other factors.

The ten cases studied comprised six examples of Addisonian pernicious anaemia, three of aplastic anaemia and one of an obscure anaemia associated with tabes dorsalis. In two of the cases of Addisonian anaemia no stainable fat was discovered, but in three cases fatty changes were evident in the centrilobular and midzonal regions. In the sixth case the liver on admission was enlarged; following the administration of choline the organ resumed its normal size and a subsequent biopsy showed fatty changes to be absent. It is tempting to assume that hepatomegaly had been due to deposits of fat which had been cleared by the lipotropic agent. In case E/6 three injections of liver extract were given initially and the red cell count rose from under 1 million per c.mm. to about 3 millions per c.mm. Biopsy during the phase of red cell increase showed diffuse fatty

Cases of **TABLE 5.** Anaemia.

Case	Diagnosis	Haemoglobin (% of 14 G.)	Red cell count (millions/c.mm.)	Liver biopsy appearances
E/1	Addisonian pernicious anaemia	25	0.93	Moderate fatty changes
E/2	Blackwater fever (originally diagnosed as acute hepatitis)	50	2.29	Abundant haemosiderin and malarial pigment
E/3	Addisonian pernicious anaemia			Fatty changes absent
E/4	Addisonian pernicious anaemia			Fatty changes absent
E/5	Addisonian pernicious anaemia; secondary carcinoma of vertebrae	27	0.80	Fatty changes and deposits of haemosiderin in centrilobular and mid-zonal areas
E/6	Addisonian pernicious anaemia	40	1.30	Well marked fatty changes
E/7	Aplastic anaemia	28	1.32	Fatty changes absent.
E/8	Aplastic anaemia	33	1.59	Mild fatty changes in inner third of lobules
E/9	Aplastic anaemia	19	0.93	Moderate fatty changes in centrilobular zone.
E/10	Addisonian pernicious anaemia	43	1.57	No fatty changes
E/11	Tabes dorsalis	24	0.83	Fatty changes in centrilobular zone

changes in the liver. No further liver extract was given and the red cell count began to fall. Choline was then given parenterally and a rise in the red cell count followed. A second biopsy was performed 17 days after the commencement of choline therapy at a time when the red cell count was still below 4 millions per c.mm. and sections of this specimen failed to show any evidence of fatty changes. That the disappearance of fat in this case was not necessarily attributable to the action of choline is shown by the results found in case E/1 in which similar fatty changes were found before liver therapy was commenced. A second biopsy was carried out when, following an optimal reticulocyte crisis, the red cell count reached 3.6 millions per c.mm. and sections of this material showed that stainable fat was no longer present. The question of the haemopoietic activity of choline is discussed by Davis and Brown (1947).

The results in the three cases of aplastic anaemia were variable. In one case fat was apparently absent from the biopsy specimen whereas fatty changes were present in both the other cases, to a slight degree in one and to a moderate extent in the second; this variation did not seem to depend on the degree of the anaemia. In the case of anaemia associated with neurosyphilis fatty changes were present, were moderate in degree and were confined to the centrilobular zone.

In each of the cases of Addisonian anaemia and of aplastic anaemia studied and in the case associated with chronic syphilis, deposition of haemosiderin in the liver biopsy sections was observed. Sherlock (1945) apparently accepted the finding of haemosiderosis as evidence supporting a diagnosis of haemolytic anaemia but the present result indicates that dyshaemopoiesis must be considered as an alternative in such instances. In the single case of haemolytic anaemia encountered (case E/2) the patient was admitted as suffering from acute hepatitis. There was, however, a recent history of malaria, the urine contained haemoglobin and Plasmodium falciparum was detected in smears of peripheral blood. Liver biopsy showed the presence of abundant haemosiderin and of malarial pigment.

(6) Miscellaneous Conditions.

Liver biopsy may prove of great value in the recognition of several miscellaneous conditions which give rise to identifiable changes in the organ. Sherlock (1945) has diagnosed Gaucher's disease by this means and the same author has found biopsy valuable in the study of cases possibly suffering from amyloid disease particularly in view of the fallibility of the Congo Red test, Stemmerman and Auerbach (1944) finding 25% false negative and 5% false positive results in a large series. In case F/2 of the present series appropriate staining of a biopsy specimen allowed exclusion of amyloidosis in the initial investigation of a patient in whom the clinical features suggested that diagnosis; amyloidosis subsequently developed and was discovered at a post mortem examination at which the primary lesion causing ascites was found to be a gumma of the caudate lobe of the liver. In case F/6 the clinical features again suggested amyloid disease secondary to a chronic pulmonary infection; the biopsy was free from amyloid change and post morten examination later confirmed the absence of amyloidosis.

Sherlock states that liver biopsy is preferable to splenic puncture in the diagnosis of kala-azar inasmuch as sections of liver tissue are more likely to give diagnostic information than are smears of splenic pulp. She states that, even though no Leishman-Donovan bodies are found, there is a characteristic hepatic pathology by which the disease can still be recognised. Scadding and Sherlock (1948) describe the finding of typical lesions in liver biopsy studies of three consecutive cases showing other features suggestive of a diagnosis of sarcoidosis while similar lesions were found in the liver of a fourth case showing no other evidence of that syndrome.

Case F/1 of the present series was characterised by pigmentation of the skin, diabetes mellitus and heptomegaly, a syndrome strongly suggestive of haemochromatosis. Biopsy of the skin showed only slight pigmentary changes, but aspiration biopsy of the liver revealed gross diffuse fibrosis of the organ with abundant deposits of haemosiderin. Confirmation of the diagnosis was thus obtained.

In case F/5 the combination of splenomegaly and obliteration of the medullary cavities of the bones as shown radiologically indicated that the enlargement of the spleen was probably due to extra-medullary haemopoiesis; biopsy of the liver in this example of myelo-sclerosis was carried out for academic purposes and sections of the specimen showed recognisable

Miscellaneous TABLE 6. disorders.

Case	Diagnosis	Liver biopsy findings
F/1	Haemochromatosis	Diffuse fibrosis of liver with marked haemosiderosis
F/2	Gumma of liver	Normal
F/3	Lupus erythematosus disseminatus	Mild fatty changes in centrilobular zone
F/4	Haematemesis of uncertain cause	Normal except for mild fatty changes
F/5	Myelosclerosis	Haemopoietic foci in liver
F/6	? Moniliasis of lungs; nephritis	Normal
F/7	Haematemesis of uncertain cause	Normal
F/8	Subleukaemic myeloid leukaemia	Normal except for mild fatty changes

haemopoietic foci in the organ.

Sherlock (1945) performed liver biopsy on a few cases of leukaemia and found infiltration of the viscus in each case. Patient F/8 in the present series was shown by sternal marrow studies to have chronic subleukaemic myeloid leukaemia and liver biopsy was carried out for research purposes; examination of the sections failed to reveal any evidence of infiltration of the liver.

Liver biopsy was performed on case F/3 for diagnostic reasons when the precise nature of the malady, ultimately recognised as disseminate lupus erythematosus, was obscure. No abnormality other than mild fatty changes were seen and the biopsy added nothing to the understanding of the case apart from aiding exclusion of amyloidosis as a possible diagnosis.

Aspiration biopsy is also of value in the exclusion of liver disease. Sherlock (1945) mentions a series of cases suspected on clinical or biochemical grounds of having disease of the liver in whom liver biopsy revealed normal histological appearances. Piper and Poulsen (1947) report a series of biopsies in patients with thyrotoxicosis in whom liver function tests had given abnormal results; no changes of significance were noted in the biopsy specimens studied. Relevant to this discussion is the fact that in no way did the course of acute hepatitis in case A/4 appear unduly severe although, as the observations of Himsworth (1947) would indicate, the liver might be found over a large series of such cases to be more vulnerable to hepatitis due to excessive utilisation of protective amino acids as a consequence of the increased metabolism. Raby (1944) studied gross chronic alcoholics and found that seven of 22 cases had no demonstrable liver disease, the remainder having either fatty or fibrotic changes.

Two instances were encountered in the present series in which no explanation clinically or radiologically could be advanced for recurrent haematemeses. A haemorrhagic diathesis having been excluded, the diagnosis was felt to lie between peptic ulceration and oesophageal varices secondary to hepatic fibrosis. The absence of fibrosis in the biopsy specimens in each case served to exclude 'cirrhosis' as the primary lesion and peptic ulceration was provisionally accepted as the diagnosis.

Summary and Conclusions.

Liver puncture in the nineteenth century was used essentially for aspiration of cysts and abscesses of the organ. In the earlier part of the twentieth century investigators attempted to obtain material for histological study by making smears of blood aspirated from the liver by fine needles. Such smears were sometimes found to contain isolated liver cells but a coherent picture of the structure of the organ as a whole could not be formed from such material and no real advance in knowledge accrued from these studies.

Realisation of our incomplete understanding of early and intermediate phases of certain liver disorders prompted the evolution in 1939 of a method of aspiration biopsy whereby a solid core of liver tissue adequate for histological study could be obtained. The specimen is removed from the right lobe and it has been shown to be representative of the organ as a whole except in a few particular instances. Appropriate routine and special methods of histological preparation can be applied to the material in different cases. The technique may be expected to fail to provide a satisfactory specimen in about 10 per cent. of puncture, the likelihood of failure being greatest in cases of fibrosis of the liver.

The procedure is not without risk. Study of the recorded fatalities has shown, however, that the patients concerned were invariably in a poor general condition because of progressive disease, most commonly advanced malignant disease. Haemorrhage due to hypoprothrombinaemia has usually been the immediate cause of death. Estimation of the prothrombin index should thus be a routine precautionary measure. As a further precaution, blood grouping should be carried out before the biopsy and facilities for immediate transfusion of fresh blood should be available against the eventuality of haemorrhage after the operation.

Studies by liver aspiration biopsy have added greatly to our knowledge of hepatitis. The parenchymatous nature of the lesion in acute epidemic jaundice has thus been established. All grades of severity of acute hepatitis have been described up to a picture of acute massive necrosis of the organ. It has also been shown that fibrosis of the liver may follow acute hepatitis, especially in those cases in which the acute phase is prolonged or in which relapse of jaundice occurs. In the individual case of acute hepatitis, biopsy of the liver, although allowing proof of diagnosis, cannot be recommended as a routine measure because of the benign prognosis. Should the case appear unduly severe or prove unduly protracted in its course, massive necrosis

or developing fibrosis may be demonstrated by biopsy with consequent effect upon prognosis.

In obstructive jaundice, acute or chronic, there is a characteristic histological pattern which can readily be recognised in a biopsy specimen. Aspiration biopsy is thus of considerable value in allowing differentiation in the not uncommon case of jaundice where the diagnosis is uncertain as between hepatitis and an obstructive lesion. In such instances, biopsy is much more reliable than biochemical tests of liver function.

The presence or absence of fibrosis of the liver may be demonstrated by liver aspiration biopsy in cases of the syndrome of splenic anaemia. Such information is of great importance in determining the therapeutic approach to the individual case.

In secondary malignant disease of the liver, aspiration biopsy allows proof of the diagnosis in about 50 per cent. of cases. Presumptive evidence of malignancy may be taken from the finding of a normal biopsy specimen from an enlarged liver. In primary hepatoma biopsy has allowed histological confirmation of the diagnosis.

Aspiration biopsy studies of the liver in various anaemias are being carried out.

In various conditions including haemochromatosis, the lipoidoses, amyloidosis, kala-azar and sarcoidosis, liver biopsy may allow recognition of the characteristic changes in the organ and thus provide a means of accurate diagnosis.

Aspiration biopsy has proved of value in certain cases by demonstrating the absence of liver disease when clinical or biochemical evidence suggests the contrary.

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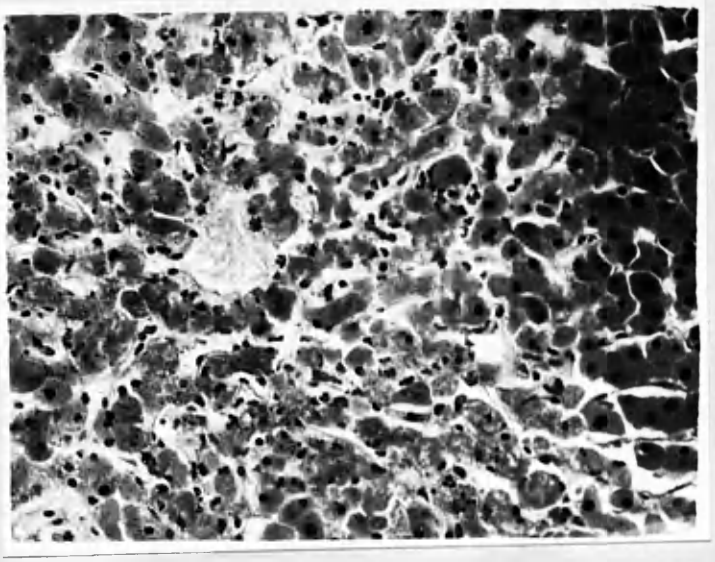
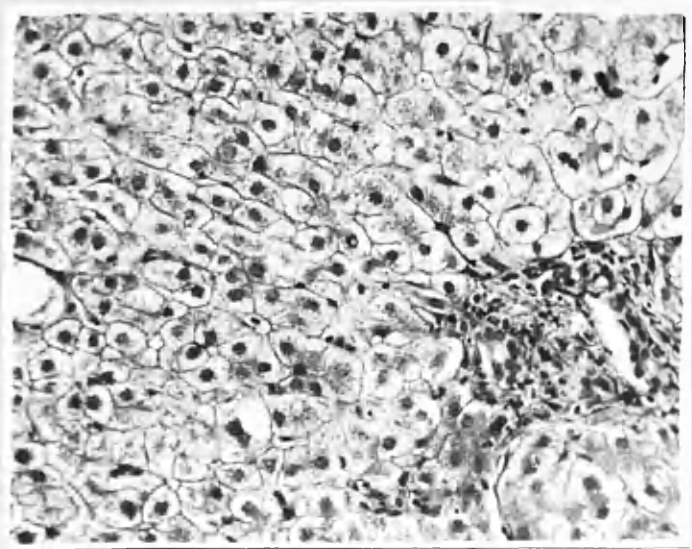
fig.1.



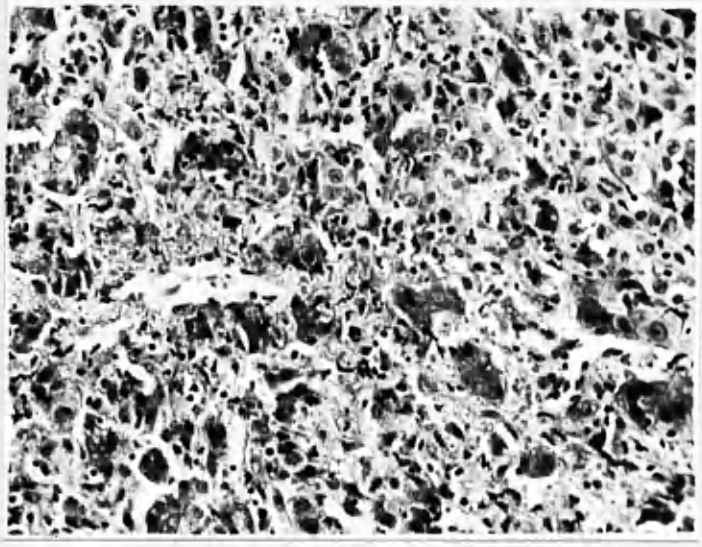
Acute hepatitis. Region around central vein showing parenchymal degeneration and cellular infiltration. ×200.

fig.2.



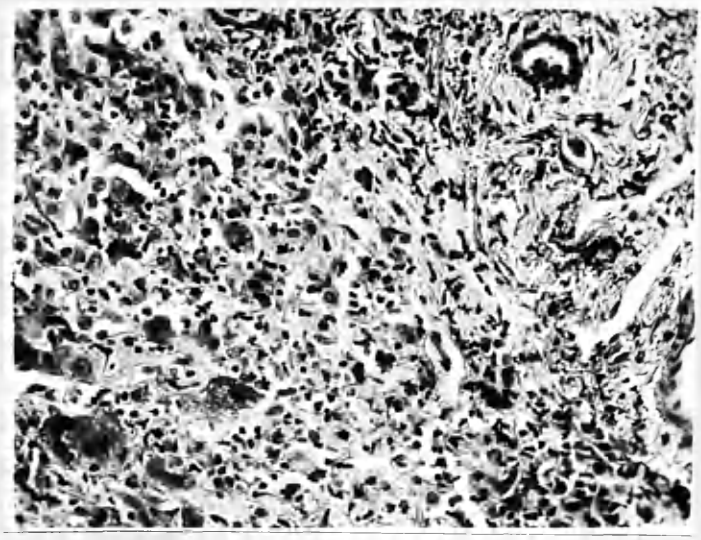
Same case as fig.1. Three weeks later showing restoration of lobular architecture and residual portal infiltration.

fig.3.



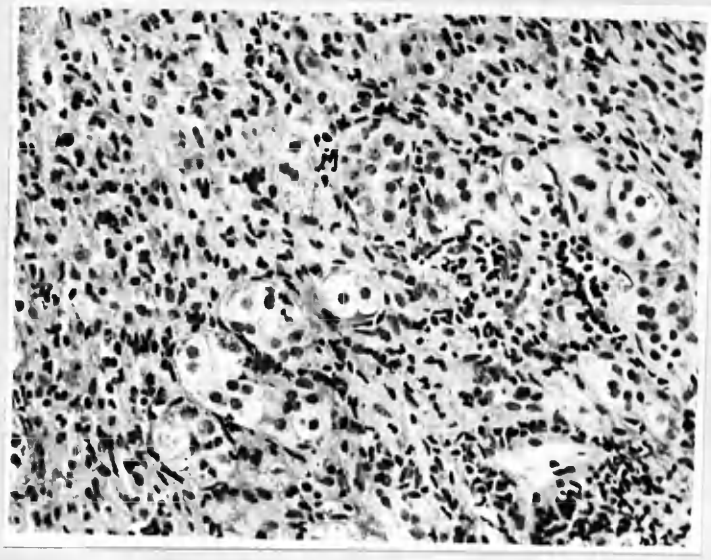
Severe case of acute hepatitis showing degeneration and necrosis of liver cells in the centrilobular zone. Round-cell infiltration is abundant.

fig.4.



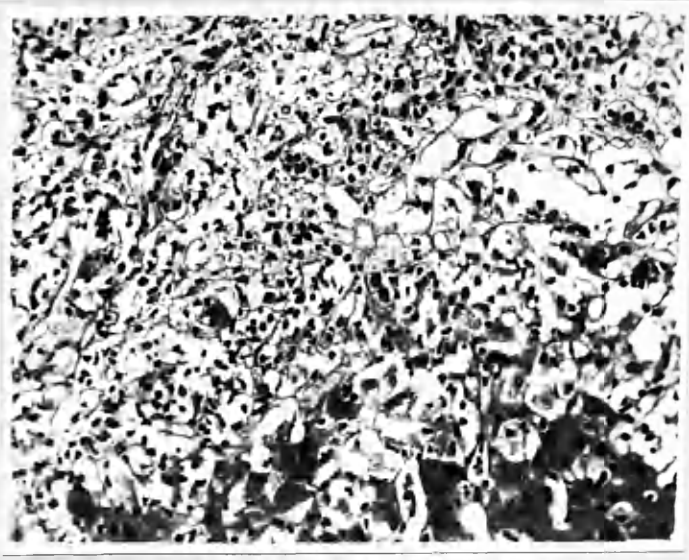
Same lobule as in fig.3. showing that the lesions are also evident around the portal tract, indicating the severity of the case.

fig.5.



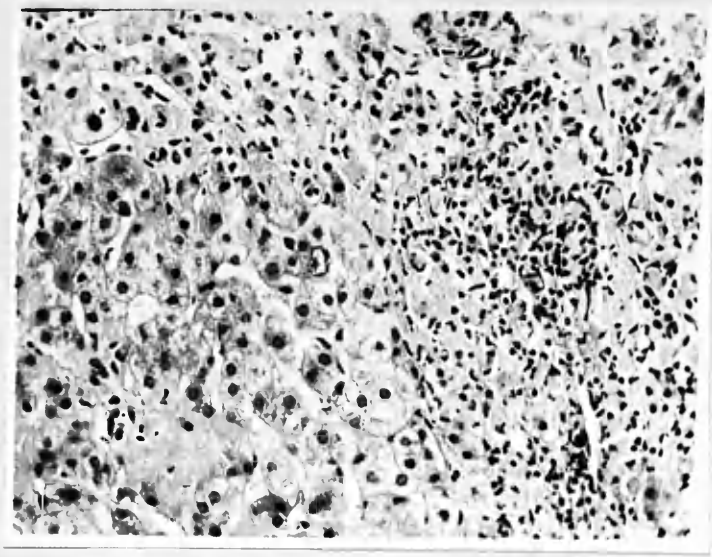
Same case as figs.3 & 4 after clinical recovery. Established fibrosis is present and hyperplastic bile duct cells are evident.

fig.6.



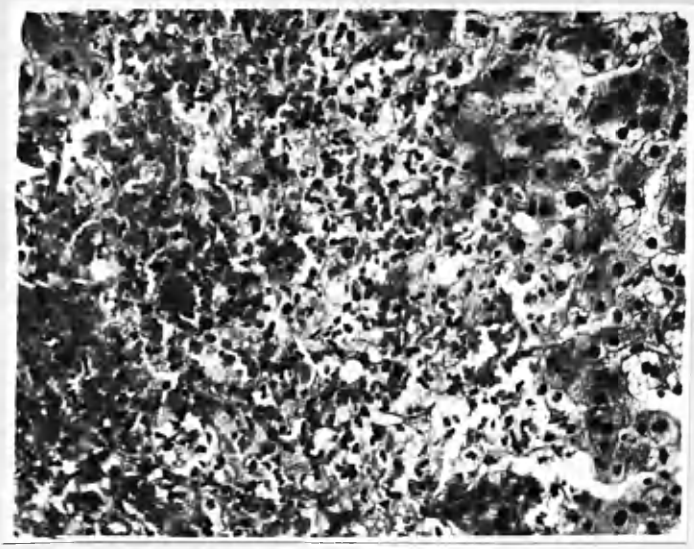
Acute hepatic necrosis showing the extent and severity of the parenchymal damage.

fig.7.



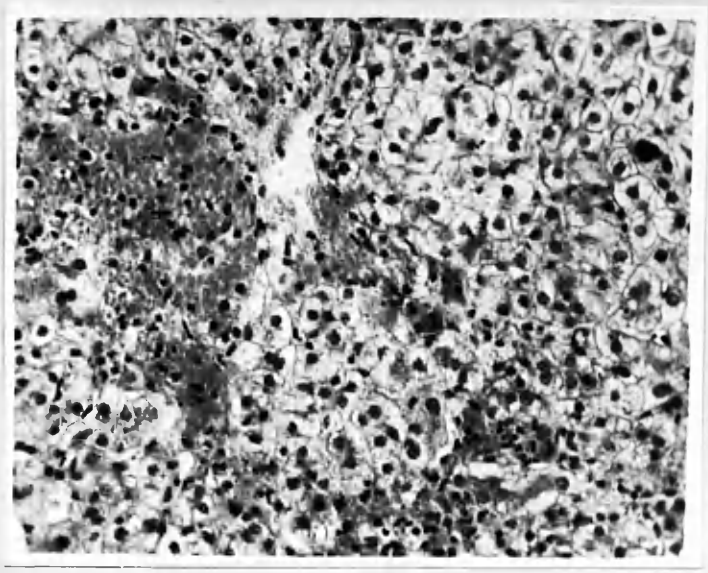
Chronic hepatitis or "cirrhosis". A cellular connective tissue separates and invades the hepatic lobule.

fig.8.



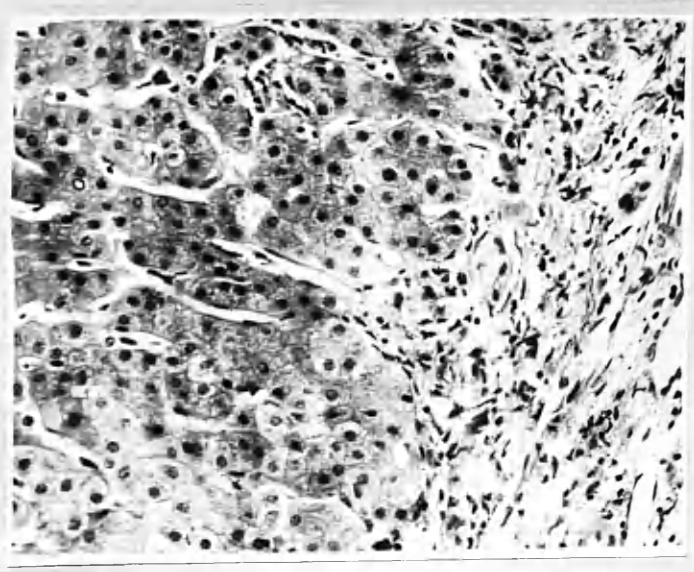
Acute carbon tetrachloride poisoning showing centrilobular necrosis with cellular infiltration and considerable haemorrhage.

fig.9.



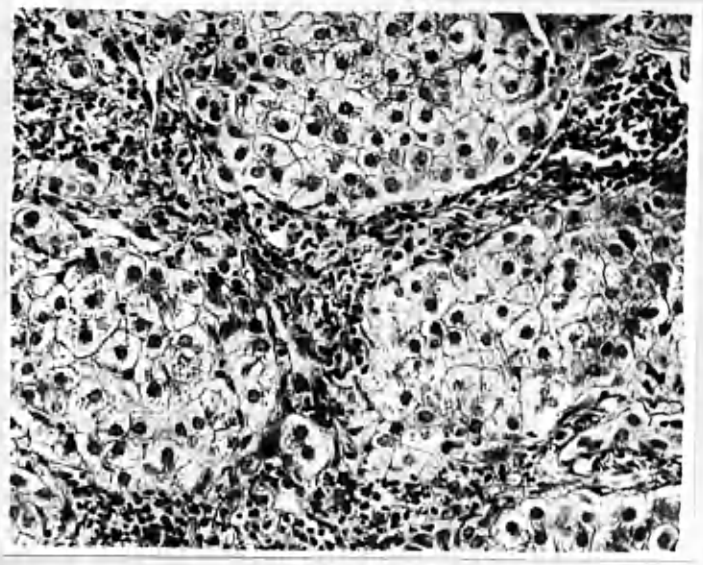
Same case as fig.8. a fortnight later. Restoration of the lobular architecture is evident but there is residual haemorrhage and cellular infiltration.

fig.10.



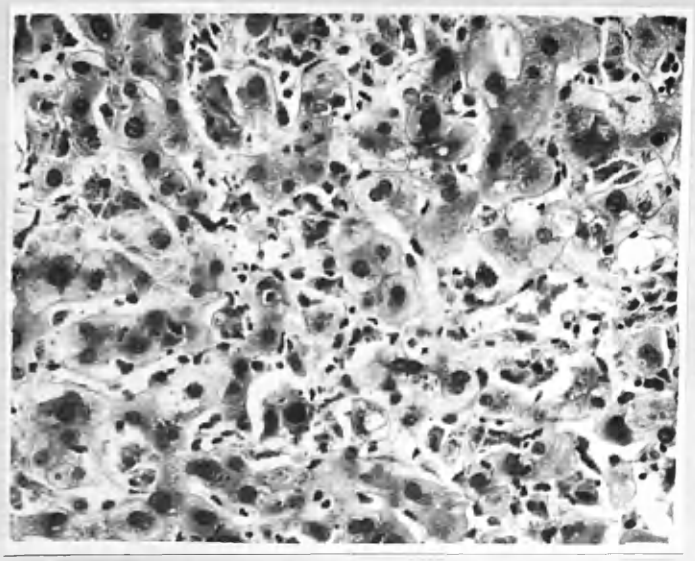
Fibrosis of the liver found in a case of splenic anaemia.

fig.11.



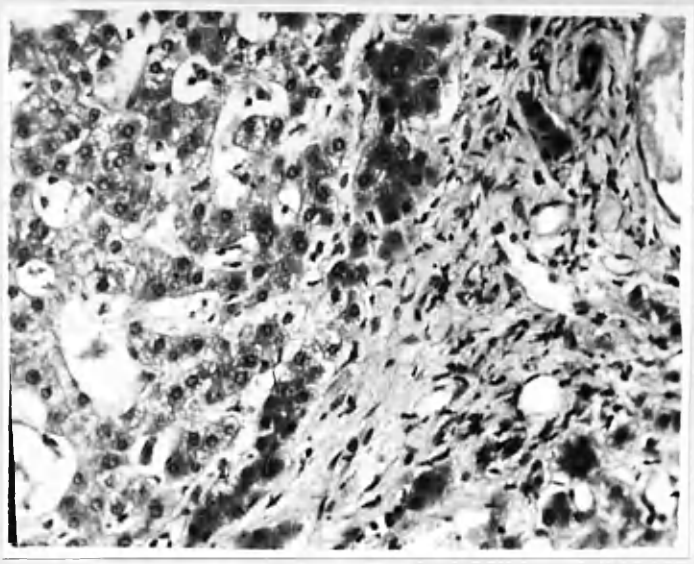
Subacute hepatitis in a more rapidly progressive case of splenic anaemia.

fig.12.



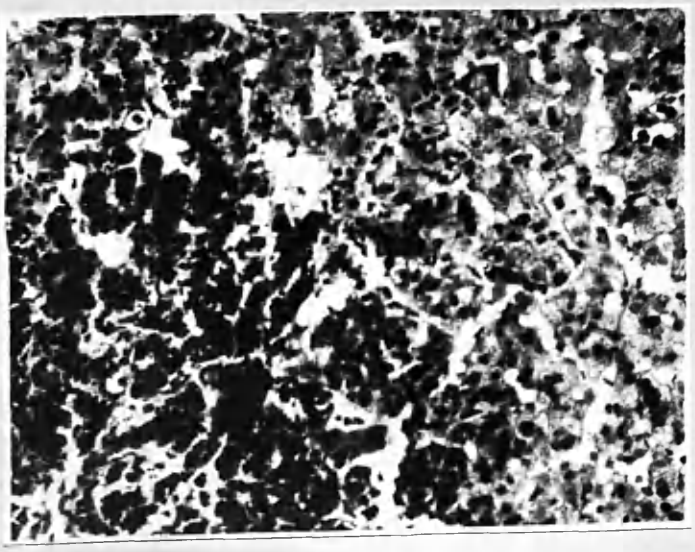
Obstructive jaundice showing dilatation of the sinusoids. Black areas indicate retained bile pigment.

fig.13.



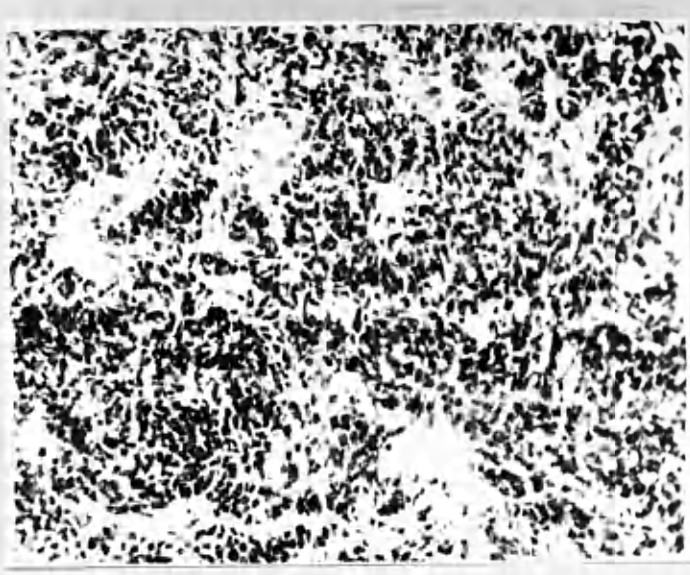
Biliary cirrhosis in a case of prolonged obstructive jaundice.

fig.14.



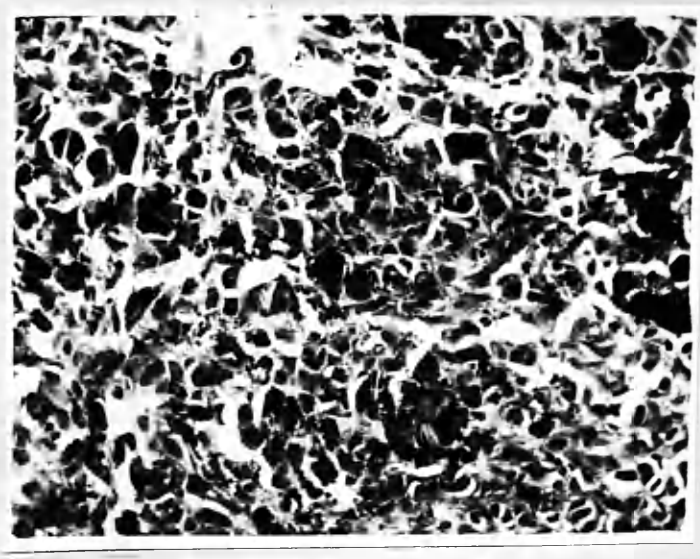
A nodule of secondary carcinoma in the liver.

fig.15.



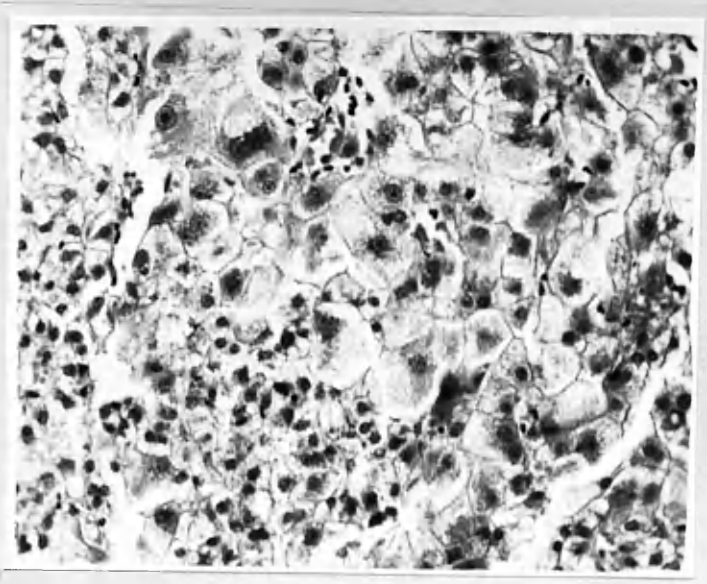
Diffuse carcinomatosis of the liver.

fig.16.



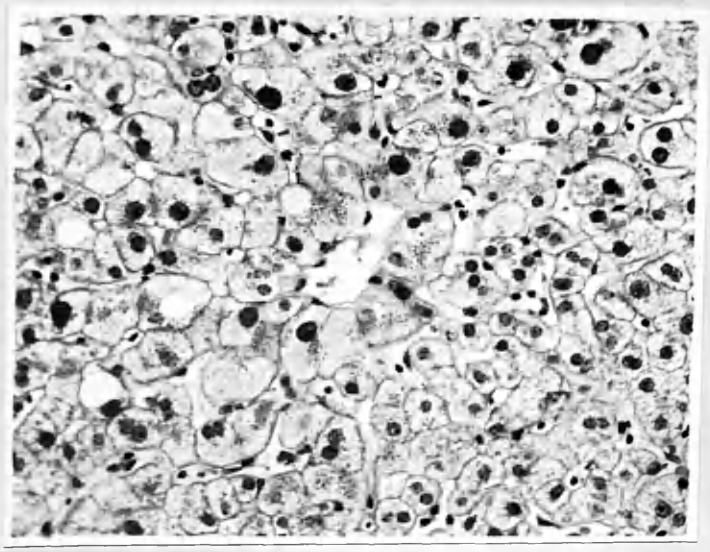
Melanomatosis of the liver.

fig.17.



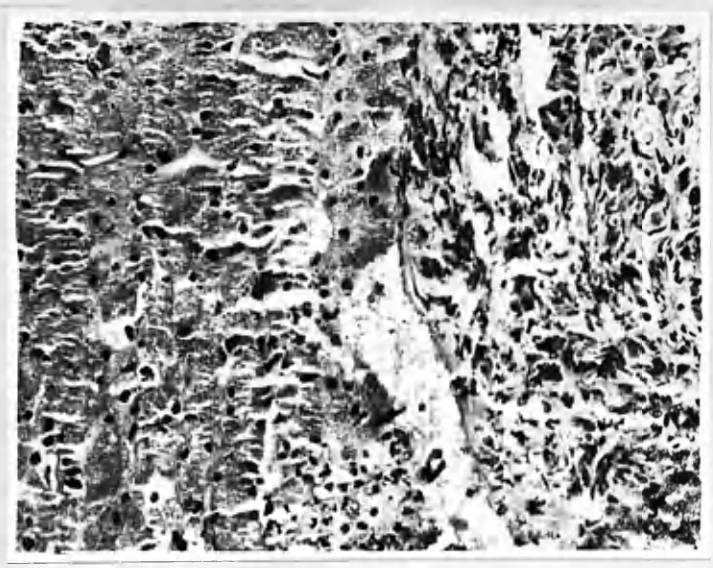
Primary hepatoma arising in a case of subacute hepatitis.

fig.18.



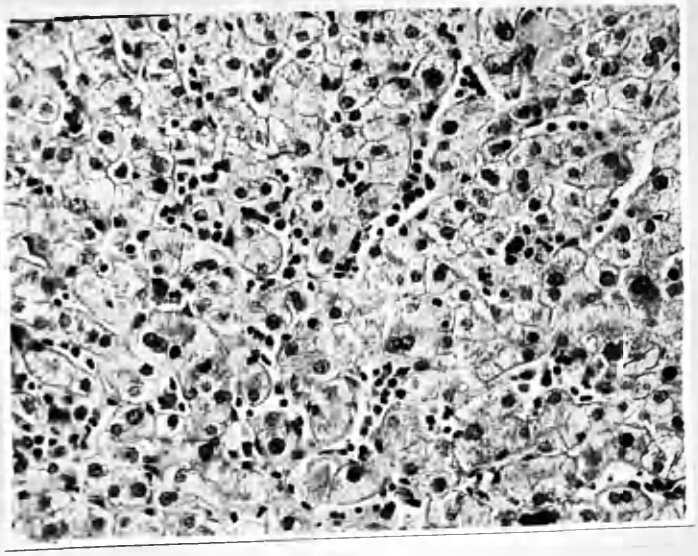
Fatty changes in a case of Addisonian pernicious anaemia before treatment.

fig.19.



Coarse fibrosis and diffuse haemosiderosis in a case of bronzed diabetes.

fig.20.



Foci of extra-medullary haemopoiesis in the liver in a case of myelosclerosis.

Case Reports with Commentaries.

Group A	... ...	Hepatitis (including acute hepatic necrosis and cirrhosis).
Group B	... ...	Splenic anaemia.
Group C	... ...	Obstructive jaundice and biliary cirrhosis.
Group D	... ...	Malignant disease of the liver.
Group E	... ...	The liver in anaemia.
Group F	... ...	Miscellaneous cases.

Case A/1.

J.L., male aged 26 years, ex-Royal Navy. Complaints of dyspepsia and anorexia for 3 weeks; increasing jaundice with pruritus for 2 weeks. Alcholism ++. Examination showed absence of fever, moderately deep icterus; scratch marks were present and there was bradycardia. Spleen not enlarged, area of liver dullness normal. The urine contained bilirubin ++. Serum bilirubin 20 mgm., plasma alkaline phosphatase 2.4 Bodansky units; serum colloidal gold curve 000000. Leptospiral agglutination negative. Liver biopsy showed retention of the lobular appearance but with necrosis of the majority of liver cells in each lobule, only a small rim of apparently unaffected cells remaining around each portal tract, the latter being infiltrated by round cells and polymorphonuclear leucocytes. Treatment was by bed rest with a diet low in fat but with high protein and carbohydrate contents.

Jaundice continued to deepen for a further fortnight when some mental confusion became apparent. Slight improvement then occurred and, at the end of a month, a second liver biopsy showed that the parenchymal cells had not been restored to normal, their appearance being but little altered from the previous specimen; the portal tracts, however, showed a more marked infiltration with round cells and fibrous tissue were now discernible. Bile pigment retention in the centre of the lobules was present. Steady improvement in the clinical condition followed, but diminution in the area of liver dullness was coincidently noted. After 2 months of jaundice, the urine became free from bilirubin. A third liver biopsy was carried out before discharge from hospital and only a small scrap of liver tissue was obtained; sections of this material showed cellular connective tissue with islets of hyperplastic liver cells. The patient has been followed for 1½ years since discharge and he continues well apart from an occasional sense of discomfort in the right hypochondrium not related to meals.

Comment: Biopsy was carried out initially in this case to allow histological confirmation of the clinical diagnosis of acute infective hepatitis. The extensive nature of the parenchymal necrosis was surprising in view of the normal function tests, but that the liver damage was serious was shown by the prolonged course of the illness. Second and third biopsies showed a change from lobular collapse with commencing portal fibrosis to gross fibrosis, the fibrous tissue containing hyperplastic liver cell nests. The picture was that of acute hepatitis proceeding to a massive hepatic necrosis, preceding alcoholism probably playing a part in the severity of the liver damage. In this case, liver biopsy served to confirm the clinical diagnosis and to give material on which the prognosis, both immediate and ultimate, could be based.

Case A/2.

Mrs. J. H., housewife aged 35 years. Complaints of nausea for 3½ weeks and of fluctuating jaundice for 3 weeks. Stools had been pale and the urine dark. There had been transient pruritus. Examination showed an obese woman with moderate icterus. Neither liver nor spleen enlarged. Bilirubinuria ++. White cell count 5,000/cu.mm. Plasma alkaline phosphatase 2.6 Bodansky units; serum colloidal gold curve 544000. Liver biopsy showed centri-lobular necrosis with round cell infiltration of the portal tracts; regeneration was evident in the form of hyperplastic liver cells.

The patient was treated with bed rest and a low fat diet. Icterus gradually diminished and bile pigment disappeared from the urine after a week in hospital. A fortnight later, just before discharge, a second liver biopsy was performed and sections showed that restoration of the lobular architecture had occurred, the only residual abnormality being undue cellularity of the portal tracts without fibrosis.

Comment. Aspiration biopsy was carried out in this case to allow confirmation of the diagnosis of infective hepatitis. The course of the illness proved free from incident and a second biopsy 7 weeks after the onset of the disease showed complete restoration of the histological picture but with residual portal infiltration almost certainly without significance for the patient's future

Case A/3.

Mrs. E. C., housewife aged 23 years. Complaints of anorexia, nausea and vomiting for 6 days and jaundice for 3 days. Two days before admission the patient had become febrile and the onset of delirium on the day of admission had necessitated removal to hospital. No exposure to hepato-toxic drugs, no intravenous procedures and an apparently adequate diet. Examination showed her to be well-nourished with deep jaundice and enlargement of the liver to 2 inches below the costal margin. Adenopathy and purpura absent. On the day following admission, the liver edge had receded to the costal margin and delirium deepened to coma on the third day. The urine contained bilirubin +++ and protein +. White cell count 10,000/cu.mm. Aspiration biopsy on the third day showed chaotic changes with complete absence of recognisable lobules; almost all the liver cells were necrotic and there was a diffuse infiltration by round cells and polymorphonuclear leucocytes. There were a few foci of hyperplastic liver cells and the histological interpretation was that of acute necrosis of the liver probably with

Case A/3 (Continued)

some degree of nodular hyperplasia.

Despite active therapy with intravenous administration of glucose and amino acids, the course was progressive to death on the 4th day and, at post mortem examination, the liver was seen to be small and necrotic with areas of hyperplasia.

Comment. The initial clinical diagnosis in this case was that of infective hepatitis, but the recession of the enlargement of the liver combined with the onset of marked mental changes suggested that the lesion had proceeded to a massive form of hepatic necrosis, a suggestion that was confirmed by the appearances of a biopsy section. Despite vigorous treatment, death occurred and the post mortem appearances were those of "acute yellow atrophy" with nodular hyperplasia. In the absence of previous hepato-toxic factors, the case appears to be one of those rare fatal instances of infective hepatitis.

Case A/4.

W.P., a joiner aged 48 years. Complaints of dyspnoea on exertion for a year, anorexia and vomiting for 3 weeks, jaundice for 2 weeks. Examination showed moderate icterus; there was also tachycardia, diffuse goitre, tremor of hands and upper lid retraction, indicative of thyrotoxicosis. The urine contained bilirubin $_{++}$. Liver biopsy showed centrilobular necrosis with evidence of parenchymal regeneration and with marked round cell infiltration of the portal tracts.

Recovery from the infective hepatitis was uneventful and the thyrotoxicosis was then investigated, the basal metabolic rate being + 48%. The condition responded to the administration of methyl thiouracil.

Comment. In view of the frequency with which liver function tests suggest insufficiency in cases of thyrotoxicosis, this case is interesting inasmuch as neither the clinical nor the histological manifestations of acute hepatitis were unduly severe despite the presence of a definite degree of hyperthyroidism. The biopsy in this case was carried out partly to confirm the diagnosis of hepatitis and partly from an academic interest in the appearances of the liver in hepatitis complicating thyrotoxicosis.

Case A/5. W.R., a labourer aged 30 years. Complaints of anorexia, nausea and vomiting for 6 days; of jaundice

Case A/5. (Continued)

for 1 day. Recent intravenous injections of arsenicals had been given as treatment for syphilis. Examination showed a well-nourished man with moderate icterus. The liver was enlarged to 1 inch below the costal margin. There was a low grade pyrexia (never above 100°F.) with a white cell count of 8,200/cu.mm. The urine contained bilirubin + and excess urobilinogen +. Plasma bilirubin 8.0 mgm. Plasma alkaline phosphatase 3.2 Bodansky units. Serum colloidal gold reaction 543000. Leptospiral agglutination, Wassermann and Kahn reactions all negative. A diagnosis of "syringe" hepatitis was made and the patient treated by bed rest and a high protein-low fat diet with additional dried milk, yeast, bemax and glucose drinks.

The jaundice steadily deepened and there was no sign of improvement until after the elapse of 3 weeks from admission. Biopsy of the liver on the 10th day of jaundice showed centrilobular necrosis with spread of the cellular damage into the midzonal regions; there was also some round cell infiltration of the portal tracts.

A relapse occurred during the 5th week in hospital with increased jaundice, plasma alkaline phosphatase 3.1 Bodansky units and serum colloidal gold curve 543000. Aspiration biopsy was repeated at the end of the week and the histological picture was essentially unchanged except that the parenchymal cell destruction and damage was somewhat more extensive; regeneration of liver cells was now apparent and there was retention of bile pigment. The cellular infiltration of the portal tracts was increased.

Clinical improvement then followed and all evidence of disease had disappeared by the end of the 9th week.

Comment. The clinical severity of this case of syringe-transmitted hepatitis was paralleled by the extent of the cellular necrosis in the liver lobules as shown by aspiration biopsy. The biopsy was undertaken to confirm the diagnosis of hepatitis and, because of the unusually deep and progressive nature of the jaundice, the sections served also positively to exclude a mechanically-obstructive jaundice. Whether or not this patient will eventually develop hepatic fibrosis cannot be answered; it is unfortunate that a third biopsy had not been carried out immediately before discharge from the wards.

Case A/6.

J.H., male aged 24 years. Admitted intoxicated

Case A/6. (Continued)

with the history of having swallowed an unknown quantity of carbon tetrachloride. No physical abnormality apparent. The urine was normal. Plasma bilirubin 2.0 mgm. Blood urea 95 mgm. Oliguria for 3 days led to intravenous infusions with added glucose; on the third day, spontaneous diuresis occurred, the urine containing protein + with blood, bilirubin and granular casts. The liver edge was just palpable below the ribs and, for 48 hours, there was a slight yellow tinge to the sclerae. On the 5th day, liver aspiration biopsy was performed and sections showed centrilobular necrosis with considerable haemorrhage in the area. Suitable staining demonstrated intense fatty changes in the midzone, examination by polarized light showing, however, that only a minimal amount of doubly-refracting lipoid material was present. The presence of occasional mitotic figures indicated that regeneration of liver cells had already commenced. There was a cellular infiltration of the portal tracts.

After the first few days, treatment was by a high protein, high carbohydrate and low fat diet. The progress was with untoward incident except that the blood urea did not regain normal levels until a fortnight had passed. A second liver aspiration on the 23rd day failed to recover liver tissue but a third biopsy on the 33rd day showed complete restoration of the liver lobule with scanty residual haemorrhages in the centrilobular zones. Reticulm and fibrous tissue stains showed that there was some increased fibroblastic activity around the portal tracts, but this was minimal in amount. Fat was now scanty and without zonal distribution. The patient was last seen 7 months later and he was then in good health. The liver was not palpable nor yet was the area of liver dullness decreased.

Comment. Liver biopsy in this case of carbon tetrachloride poisoning served to show the extent of the hepatic damage and also to confirm the remarkable recuperation of the liver srchitecture. The minimal fibrosis demonstrated at the final biopsy is probably without significance as far as the ultimate possibility of the development of hepatic fibrosis is concerned.

Case A/7.

Mrs. C. M., a housewife of 44 years. The history extended over the previous 9 months in which there had been increasing lassitude with loss of weight, night sweats and slowly increasing brownish pigmentation of her skin, the pigmentation having been subject to transient waxing and waning. There had been occasional attacks of nausea with vomiting. Latterly dyspnoea on

Case A/7. (Continued)

exertion had developed. She was admitted because of a small haematemesis. No history of jaundice or exposure to hepato-toxic agents. Examination showed a good nutritional state with dull brown pigmentation especially well marked on the face. The liver was firm, regular and extending to the level of the umbilicus. The spleen was not enlarged and there were no other physical abnormalities. The urine was negative to routine testing.

There was anaemia (red cell count 2,680,000/cu.mm. and haemoglobin 56% Sahli) influenced, presumably, by the preceding haemorrhage. Plasma alkaline phosphatase 4.4 Bodansky units; serum colloidal gold reaction 000000. Icterus index 2. Plasma prothrombin index 59%. Radiological examination failed to demonstrate manifest oesophageal varices and there was no evidence of peptic ulceration. After parenteral vitamin K therapy, aspiration biopsy of the liver gave sections showing well-marked diffuse hepatic fibrosis with multilobular and monolobular distribution; with connective tissue stains, strands of fibrous tissue were seen to penetrate the lobules between the columns of liver cells.

Treated by bed rest and a diet with minimal fat and with supplementary choline and vitamins, recovery from the blood loss ensued. The patient was discharged a month later with a red cell count of 3,970,000/cu.mm. and haemoglobin level of 78%.

Comment. This case bears contrast with case D/11. In both instances there was gross hepatomegaly with diffuse pigmentation of the skin in middle-aged women. Liver biopsy in the present case showed the presence of diffuse fibrosis and established the diagnosis of "portal cirrhosis". In case D/11, the biopsy sample appeared normal and the discovery radiologically of a colonic neoplasm allowed a presumptive diagnosis of hepatomegaly due to secondary malignant deposits.

Case A/8.

F. F., a furnace stoker aged 46 years. In the previous four weeks he had experienced anorexia and nausea with the slow and progressive onset of jaundice. The stools had been pale from the onset until 5 days before admission. He had contracted venereal disease 20 years previously and had had a recent course of intravenous injections, the last treatment being given 2 months before the onset of the present malady. Examination showed a well-nourished man with deep jaundice and clubbing of fingers; the liver was enlarged 2 finger-

Case A/8. (Continued)

breadths and the tip of the spleen was just palable. An x-ray film of the chest showed changes consistent with a pneumoconiosis. The urine contained bile pigment. Icterus index 48; plasma bilirubin 9.1 mgm.%; serum colloidal gold reaction 000000 and plasma alkaline phosphatase 8.9 Bodansky Units. Wassermann and Kahn reactions negative.

Biopsy of the liver was carried 6 days after admission and sections showed normal lobular architecture with poor staining of the liver cells. There was no separation of the columns of liver cells but a cellular infiltration was apparent throughout the lobules with small haemorrhages irregularly distributed; round cell infiltration of the portal tracts was well-marked. The appearances were interpreted as those of hepatitis in resolution.

The case was treated on conventional lines and bile pigment disappeared from the urine after 19 days in hospital. After a further 8 days a second biopsy showed normal staining of the parenchymal cells without cellular infiltration of or haemorrhages in the lobules; the infiltration of the portal tracts was even more marked then in the previous specimen but there was no demonstrable fibrous tissue. The picture was accepted as of a further stage in resolution without fibrosis. The patient was discharged 3 days later and reported 2 months after with a barely palpable liver, an impalpable spleen and normal urine.

Comment. In this case there was doubt clinically as to the non-obstructive nature of the jaundice, particularly as the information about the recent anti-specific treatment had been witheld for a period by the patient. The biochemical reactions could not settle the issue and the first biopsy gave sections which showed no liver cell necrosis; however, the histological verdict was of resolving hepatitis rather than cholangio-hepatitis or biliary cirrhosis because of the round-cell infiltration of the lobules, the haemorrhages and the absence of separation of the columns of liver cells and of retained bile pigment. The subsequent course of the disease confirmed this interpretation. The diagnosis adopted was that of "syringe" hepatitis.

Case A/9.

W. T., a male of 26 years. Complaints of nausea, vomiting and jaundice for a fortnight, sickness lasting a week. He had had no recent injections, was not exposed to industrial hepato-toxic agents nor to

Case A/9. (Continued)

rat-infested environments. He was afebrile with moderate jaundice and the liver was readily palpable. Pulse 60/minute. Blood pressure 105/65 mm. Hg. The urine contained bilirubin + and urobilinogen + . White cell count 4,400/cu.mm. Plasma bilirubin 10 mgm.; plasma alkaline phosphatase 3.8 Bodansky units; serum colloidal gold reaction 000000. Negative serological reactions to Leptospirae icterohaemorrhagica and canicola.

Aspiration biopsy 4 days after admission showed a picture of centrilobular necrosis with some haemorrhage and with round-celled infiltration of the portal tracts. On conservative regimen progress was uneventful and the icterus had disappeared after a further fortnight.

Comment. In a classical case of infective hepatitis, aspiration biopsy served to confirm the diagnosis and allowed study of the liver histology in the acute phase of the disease.

Case A/10.

A. L., a commercial traveller of 50 years, was admitted with darkening of the urine for three weeks and jaundice for ten days. Apart from some loss of appetite during the previous weeks there were no other symptoms.

Examination showed a well-nourished man with moderate jaundice, scratch marks on the skin and a liver just palpable below the costal margin. The blood pressure was 100/65 mm. Physical examination otherwise revealed no abnormality. The urine contained bilirubin and the icterus index was 60. Plasma alkaline phosphatase 4.8 Bodansky units; serum colloidal gold reaction 300000.

Liver biopsy was performed and sections showed centri-lobular necrosis of liver cells with infiltration of the lobules and of the portal tracts with scavenger cells; there was also diffuse fatty change in the unaffected cells of the lobules.

After a further 10 days in hospital the urine became free from bilirubin and recovery was uneventful.

Comment. In this case progressive jaundice over ten days in a man of 50 years not associated with definite gastric upset was suggestive of an obstructive lesion, probably due to a neoplasm, but aspiration biopsy studies indicated the presence of a diffuse hepatitis. The

Case A/10. (Continued)

Comment. (Continued)

latter diagnosis was vindicated by the biochemical tests of liver function and, more definitely, by the subsequent course of the disease.

Case A/11.

W.B., an unemployed labourer of 49 years, was first admitted in October, 1947 because of haematemesis. He gave a history of dyspepsia over the previous two months, aching pain in the epigastrium not being related to meals and never wakening him from sleep. Apart from effects of the haemorrhage, there were no abnormalities on physical examination and the patient was treated by sedation and blood transfusion. Recovery from the blood loss was achieved. Subsequent barium meal examination showed no evidence of peptic ulceration. He was discharged six weeks after admission.

Readmission was necessitated in February, 1948 because of ascites which had been present for a fortnight. There had been much epigastric distress and progressive loss of weight since discharge from the wards. The urine contained an excess of urobilinogen. Plasma alkaline phosphatase 7.2 Bodansky units; serum colloidal gold reaction 432000; icterus index 33; prothrombin index 62%. Liver aspiration biopsy was performed after paracentesis of the abdomen; the organ was felt to be hard and only small scraps of tissue were recovered. Sections of the material obtained showed, however, the presence of definite fibrosis.

Despite appropriate treatment the condition progressed to death seven weeks after admission. No post mortem examination was permitted.

Comment. This case was accepted as being of hepatic fibrosis or 'cirrhosis' presenting originally as haematemesis from oesophageal varices and ultimately as ascites and hepatic failure. The biochemical function tests supported hepatic parenchymal insufficiency and aspiration biopsy, carried out for diagnostic purposes, demonstrated established fibrosis but failed to allow recognition of the precise form of the 'cirrhosis' owing to the fragmented nature of the material.

Case A/12.

Miss S. W., a policewoman aged 38 years, had been under observation as a case of disseminated sclerosis of four years' duration when jaundice appeared. A course of intravenous arsenicals had been given, the last

Case A/12. (Continued)

injection being made on 26.1.48. On 16.3.48 anorexia, nausea and vomiting commenced; jaundice was first noticed on 19.3.48 and was associated with severe colicky pain in the right hypochondrium. She was admitted on 21.3.48 and examination showed, apart from neurological abnormalities, deep jaundice and enlargement of the liver to 1½ inches below the costal margin, the organ being soft and tender. The urine contained bilirubin. Biochemical investigation showed plasma alkaline phosphatase 11.1 Bodansky units, serum colloidal gold reaction 320000, icterus index 170 and prothrombin index 70%.

Jaundice continued to deepen and vomiting persisted despite the absence of further pain. The icterus index increased to over 200 and the prothrombin index fell progressively to 61% despite parenteral administration of vitamin K. Improvement commenced at the beginning of April and, with a prothrombin index of 79%, liver biopsy was carried out. Sections showed changes in the cells of the inner two-thirds of the lobules which were consistent with recovery from cellular necrosis; haemorrhages were present in the centrilobular regions which contained also some retained bile pigment. Cellular infiltration was present in the lobules to a slight degree and, somewhat more markedly, also in the portal tracts; such infiltration was not, however, prominent.

The progress was now of slow recovery, bile disappearing from the urine on 14.4.48. All dyspeptic symptoms regressed and the patient was discharged on 10.5.48 with the liver just palpable below the costal margin. The serum colloidal gold reactions still showed definite abnormality (432000) at the time of discharge. Radiological examinations excluded the presence of gall-stones.

Comment. The presence of severe colicky pain in the right hypochondrium at first suggested cholelithiasis as the cause of jaundice in this case. Biochemical examinations were, however, consistent with parenchymal insufficiency and aspiration biopsy provided confirmatory diagnostic evidence of regressing diffuse hepatitis. The severity of the disease together with the recent course of intravenous medication suggested the diagnosis of syringe-transmitted hepatitis despite the fact that all syringes were sterilised by boiling in the unit before use.

Case B/1.

Mrs A. O'D., a housewife aged 37 years. Complaints of lassitude and dysponea on exertion increasing over 6 months; right hypochondriac pain on stooping for 4 months; development of numerous ulcers on the legs and thighs during 3 months; orthostatic oedema of ankles for 2 months; loss of weight. Four years previously she had collapsed while at work in a dye factory (nature of chemicals used unknown) and had been retained in a hospital for 3-4 months, the final diagnosis (checked by hospital records) being "bronchitis and debility". Family history negative. She appeared ill and had a dirty brown pigmentation of the skin tinged with jaundice; oedema of ankles; numerous ulcers of legs and thighs; purpuric rash on forearm; spleen and liver both enlarged. Urine contained excess urobilinogen but no bilirubin. There was anaemia (haemoglobin 43% Sahli; red cell count 2,500,000/cu.mm.; mean corpuscular volume 88 cu.μ) with leucopenia (white cell count 2,800/cu.mm.). Reticulocytes 2.5%. Fragility of red cells in hypotonic saline with normal limits (thrice repeated). Sternal marrow actively normoblastic. Under observation, reticulocytosis persistent 1.4 - 5.5%. Owing to uncertainty of diagnosis, liver biopsy carried out after two months in hospital, the clinical picture being largely unchanged. Sections showed a grossly abnormal appearance with considerable fibrosis mainly centred upon and linking portal tracts, the central veins often being completely free from infiltration. No bile retention, no hyperplasia of bile ducts, no necrosis of parenchymal cells. Numerous hyperplastic nodules of liver cells usually completely surrounded by fibrous tissue.

Liver extracts, parenteral and oral, and iron were given without specific response, but the patient's general condition slowly improved and she was discharged after a stay of three months in hospital. Haemoglobin 65% Sahli. A month later she reported feeling well and with haemoglobin value of 80%.

Comment. The anaemia with persistent reticulocytosis and splenomegaly initially led to a diagnosis of haemolytic anaemia in this case. Hepatomegaly, however, was admitted to cast doubt upon this interpretation and aspiration biopsy was carried out in order that the histology of the liver might be studied. The sections showed features consistent with diffuse hepatic fibrosis and nodular hyperlasia; the condition was apparently of a subacute massive necrosis. In this case, then, biopsy allowed the recognition of primary liver pathology and established the presence of the syndrome of splenic anaemia.

Case B/2.

Agnes McN., a dress-maker aged 17 years. Three years before admission she began to suffer morning nausea with occasional vomiting. Brief but recurrent bouts of left hypochondriac pain commenced 4 months later and jaundice was then noticed. The icterus progressed and she was admitted to a hospital 6 months after the onset of her symptoms; the clinical notes record jaundice, hepatomegaly, splenomegaly, normochromic anaemia and a normal white cell picture. While in hospital her condition further progressed with diminution in the size of the liver and the appearance of ascites. Ultimately slow improvement set in and she was discharged after over 3 months with remission of jaundice and absence of ascites. She remained relatively well for a further 11 months despite a persistent ache in the left side. Definite lassitude then developed with the return of frequent attacks of nausea; on one occasion she vomited some dark clotted blood. She was therefore admitted to hospital and physical examination showed sallowness without frank icterus, splenomegaly and diminution in the area of liver dullness; ascites was not demonstrable. The urine from time to time contained an excess of urobilinogen. Blood values were red cells 4,280,000/cu.mm., haemoglobin 78% Sahli, reticulocytes less than 1%, white cells 2,200/cu.mm. (neutrophils 78%, eosinophils 2%. lymphocytes 19%, mono-cytes 1%) and sedimentation rate 4 mm. Platelet counts 50-100,000/cu.mm. Sternal marrow fatty and hypocellular with normoblastic erythropoiesis and a relative increase in early erythroblasts; there was a degree of myeloid maturation arrest and megakaryocytes were increased in number despite a paucity of platelets. A barium swallow examination failed to demonstrate oesophageal varicosities radiologically.

Biochemical investigations included plasma albumen 3.2 g., globulin 1.6 g., cholesterol 256 mgm., all per 100 ml. Plasma alkaline phosphatase 3.0 Bodansky units and serum colloidal gold reaction 000000. Prothrombin index 55%.

Iron, proteolysed liver, pyridoxin and folic acid were alike in failing to affect the blood picture. As a possible cause of toxic depression of the bone marrow, a gross unilateral chronic mastoiditis was dealt with radically under penicillin "cover". Transient post-operative cerebral manifestations were ascribed to possible intra-cerebral haemorrhagic lesions associated with the thrombocytopenia; recovery was otherwise uneventful. No alteration in the white cell picture followed operation.

Liver biopsy was carried out twice, no tissue being

Case No.B/2. (Continued)

recovered on the first occasion which was followed by transient nausea. A satisfactory specimen from the second puncture showed preservation of the lobular architecture with slight increase of cellularity of the portal tracts; there was no obvious fibrosis. The general condition remained static but repeated bouts of perisplenitis were distressing. Splenectomy was ultimately decided upon and, at operation, the liver was found to be decreased in size and definitely "hob-nailed". The spleen was successfully removed but the patient died the following day. Post mortem examination was not permitted and a biopsy of the liver was not taken at laparotomy; sections of the excised spleen showed changes consistent with the diagnosis of splenic anaemia.

Comment. Normochromic anaemia with leucopenia and splenomegaly indicated a clinical diagnosis of splenic anaemia. The history of the case and the absence of gross changes in a biopsy sample from the right lobe of the liver indicated that the primary lesion had probably been in the nature of a massive form of hepatic necrosis. This case illustrates well the development of splenic anaemia following manifest liver disease. Aspiration biopsy proved difficult owing, no doubt, to the small size of the liver and to the fibrosis; sections of the biopsy material showed relatively normal lobules and this fact, in conjunction with the "hob-nailed" appearance of the liver established at laparotomy, suggested that the primary liver disease had been in the nature of a massive hepatic necrosis.

Case B/3.

Mrs A. R., housewife aged 46 years. She gave a history of three haematemesis over the previous three years and was referred to a Blood Clinic because of anaemia. Splenomegaly was noted and the patient admitted for investigation. The general condition was good, the liver and the spleen were both enlarged and there was occult blood in the faeces. A barium swallow examination showed the presence of oesophageal varices. The blood values were red cells 3,820,000/ cu.mm. with haemoglobin 10.1 g., mean corpuscular volume 98 cu.μ and mean corpuscular haemoglobin concentration 27%. Aspiration biopsy of the liver was performed and sections showed diffuse hepatic fibrosis.

Comment. In this case of splenic anaemia enlargement of the liver pointed to the presence of primary hepatic disease. Aspiration biopsy confirmed this diagnosis by establishing the presence of "portal cirrhosis".

Case B/4.

Mrs A. H., a housewife aged 50 years. Complaint of dyspnoea on exertion for 2 years. Examination showed pallor and enlargement of both the spleen and the liver. There was hypertension and moderate hypochromic anaemia. The white cells were normal. Liver aspiration biopsy showed mild diffuse fibrotic changes.

Comment. As in the previous case, liver biopsy demonstrated conclusively the presence of fibrosis of the liver in this example of the syndrome of splenic anaemia.

Case B/5.

G. K., male aged 30 years. Admitted as a case of haematemesis and melaena, he gave a history of increasing lassitude for 3 years; there had been no dyspepsia. Examination showed palpable enlargement of the spleen. The urine was normal. There was moderate normochromic anaemia (red cells 3,800,000/cu.mm.; haemoglobin 78%) with leucocytes 6,000/cu.mm. Plasma alkaline phosphatase 4.4 Bodansky units; serum colloidal gold reaction 000000. Radiological studies showed the presence of oesophageal varices and the absence of evidence of peptic ulceration. Liver aspiration biopsy gave material in which there was no demonstrable abnormality.

In view of the patient's age, the satisfactory general condition, the apparent grossness of the varices in the oesophagus and the normal appearance of the liver biopsy, laparotomy was advised with either Whipple's operation or splenectomy in view; operation, however, was refused. Administration of iron resulted in remission of the anaemia.

Comment. In this case of splenic anaemia, there was no evidence of liver disease clinically, biochemically or in a biopsy specimen. In view of the severe haemorrhage and the apparently gross oesophageal varices surgical measures were advised, but the patient declined operation.

Case B/6.

Mrs J. D., a housewife aged 38 years. Eleven days before admission she gave birth to her 8th baby; pregnancy had been accompanied in the later months by swelling of the ankles and undue protuberance of the abdomen. After an otherwise uneventful labour the abdomen remained distended and 20 pints of clear ascitic fluid were removed by paracentesis. As no

Case B/6. (Continued)

gynaecological cause for the ascites could be found, the patient was transferred to the medical wards for investigation. She had been treated by her own practitioner for anaemia during the previous year, but otherwise her health had hitherto been enviable.

Examination in the medical unit showed a well-nourished woman with marked pallor and sallow complexion. The finger nails were flattened but true koilonychia was absent. The spleen was enlarged 3 finger-breadths below the costal margin and the lower border of the liver could just be felt on deep inspiration. Clinical signs of ascites were equivocal. The urine from time to time contained an excess of urobilinogen. There was hypochromic anaemia (red cells 2,890,000/cu.mm., haemoglobin 40% Sahli) with a leucocyte count of 4,800/cu.mm. Plasma alkaline phosphatase 2.6 Bodansky units; serum colloidal gold reaction 300000. Barium swallow examination showed the presence of oesophageal varices radiologically. Liver aspiration biopsy was carried out on two occasions, ascitic fluid being tapped at the first puncture. Sections of the two specimens showed perfectly normal histological appearances of the organ, there being no trace of cirrhotic change.

After initial transfusion of 2 pints whole blood, iron therapy was commenced in adequate dosage and the blood levels 5 weeks after admission were red cells 4,240,000/cu.mm. and haemoglobin 73% Sahli. The presumed clinical diagnosis of portal thrombosis led the advisal of laparotomy with Whipple's operation in view; operation was, however, declined and the patient discharged. Five months later she was apparently well and no longer anaemic.

Comment. In this case definite splenomegaly with established oesophageal varicosities and hypochromic anaemia indicated a diagnosis of splenic anaemia. There was no indication of primary liver disease clinically or on biopsy of the organ and the primary lesion was presumed to be thrombosis of the portal vein. The subsequent satisfactory progress of the patient with freedom for several months from ascites led to the suggestion that recanalisation of the portal vein thrombosis had occurred. The biopsy in this case of splenic anaemia aided exclusion of hepatic fibrosis as the primary lesion with consequent alteration in the remote prognosis.

Case B/7.

J. E., ex-Royal Navy, aged 42 years. Admitted with slight icterus, ascites, splenomegaly and apparent

Case B/7.(Continued.)

diminution in the size of the liver. He was a chronic alcoholic who had had malaria several times and had been treated with arsenicals for syphilis. About a year prior to admission, while in Sicily at a period when infective hepatitis was epidemic, he suffered an illness with jaundice and ascites which lasted for 3 months. Two months later jaundice and ascites re-appeared, hepatomegaly and splenomegaly being noted; this illness lasted 2½ months and he was then boarded from the Service.

After a further 5 months the disease recurred and the patient admitted for investigation. Apart from the physical findings noted above, there was an excess of urobilinogen in the urine and lowering of the plasma proteins. Wassermann reaction negative. Radiology demonstrated oesophageal varices. Aspiration biopsy of the liver recovered a small piece of tissue which was unduly cellular and contained established fibrous tissue. A more definite histological diagnosis was felt desirable but a second biopsy was not carried out owing to the development of a confusional psychosis which necessitated his removal to a mental observation ward from which his relatives obtained his discharge a month later, the mental condition somewhat improved.

Comment. There were several circumstances in this patient's history with potentials for liver damage. Hypochromic anaemia was associated with splenomegaly and clinical evidence of hepatic cirrhosis on the last hospital admission; a diagnosis of splenic anaemia was made and aspiration biopsy served to confirm diffuse fibrosis of the liver.

Case B/8.

Mrs. C. B., housewife aged 34 years. In December 1943 the patient was admitted to a hospital because of vomiting, diarrhoea and low back pain; the liver and spleen were found to be enlarged and there was a hypochromic anaemia. Administration of iron resulted in improvement and health was maintained until July 1946 when relapse was associated with menorrhagia and oedema of the ankles. Again in hospital, hypochromic anaemia and evidence of chronic nephritis (fixed specific gravity urine, proteinuria, haematuria and cylindruria) were found; blood transfusion and iron therapy effected amelioration of her condition. Further menorrhagia in April 1947 precipitated relapse and she was admitted to wards under the writer's observation in May 1947. Pallor, enlargement of both spleen and liver, enlargement of the heart and a blood

Case B/8. (Continued)

pressure of 120/90 mm. were noted. The urine contained protein, pus cells and coliform organisms and was of a low relatively fixed specific gravity. There was severe amaemia (red cell count 1,280,000/cu.mm. with haemoglobin 17% Sahli) but no leucopenia. Immediately after admission a flare-up of the urinary tract infection led to sulphadiazine therapy with adequate response. Administration of iron resulted in improvement of the blood state (7 weeks after admission, red cells 3,150,000 and Hb. 60%); masked hypertension was then disclosed, the readings rising to 200/125 mm. Plasma alkaline phosphatase 10 Bodansky units and serum colloidal gold reaction 332100. Radiologically there was no evidence of oesophageal varices. Liver biopsy was now performed and showed well-marked diffuse hepatic fibrosis.

Testosterone was used to combat menorrhagia and iron therapy was continued. The general condition continued to be reasonably satisfactory until January 1948 when manifestations of uraemia became apparent and the patient died in February 1948 with convulsive seizures. At post mortem examination small granular kidneys, an enlarged and diffusely cirrhotic liver and an enlarged and firm spleen were found.

Comment. On clinical and pathological grounds this unfortunate woman was deemed to have suffered two diseases, splenic anaemia and chronic nephritis, the latter ultimately proving fatal. Aspiration biopsy served in this case to establish the presence of diffuse fibrosis of the liver, a finding suggested by clinical enlargement of the organ and by the biochemical reactions.

Case B/9.

S. T., a baker aged 39 years, was admitted with a history of recurrent haematemeses over a period of three years. A year before admission splenectomy had been undertaken at another hospital, a moderately enlarged spleen being removed of which the pathological features were stated to be consistent with Banti's syndrome. He had never had jaundice nor had dyspepsia been experienced.

On admission he was anaemic (red cells 3,370,000/c.mm., haemoglobin 61%) but response to iron therapy was satisfactory (after 5 weeks, red cell count 5,000,000/c.mm., haemoglobin 94%) despite the presence of occult blood in the faeces for 3 weeks after admission. Biochemical investigations included plasma alkaline phosphatase 3.3 Bodansky units, serum colloidal gold reaction 200000, plasma proteins 5.48 G. (A/G =

Case B/9. (Continued)

3.28/2.20). Liver biopsy was performed and sections showed the presence of definite fibrosis which did not, however, involve every lobule. The appearances were suggestive of fibrosis following a previous massive necrosis of the liver. Radiological examinations and oesophagoscopy failed to demonstrate oesophageal varicosities and showed no evidence of peptic ulceration.

Comment. In this case of splenic anaemia, repeated haematemeses were taken to indicate the presence of oesophageal varices although such could not be demonstrated by radiology or by endoscopy. As anaemia had persisted following splenectomy, thrombosis of the splenic vein was excluded as a cause. Liver biopsy served to demonstrate fibrosis of the liver of the type following massive necrosis of the organ. Because of the constant danger of a fatal haemorrhage, it is proposed that porto-caval anastomosis be undertaken.

Case C/1.

J. F., a coal-miner aged 57 years. Admitted with history of constant epigastric discomfort for a fortnight and jaundice increasing over 10 days. The stools had been putty-coloured since the onset. Pruritus had been troublesome. His mine workings were damp but no rats had been seen in them. There was no history of recent injections. Examination showed a well-nourished man with moderate jaundice and numerous scratch-marks on the skin. No other abnormality on physical examination. The urine contained bile. Plasma bilirubin 7.0 mgm.%.

Liver aspiration biopsy showed widespread cellular exudate, mostly lymphocytic, around the portal tracts; the liver cells in the centre of the lobules showed degenerative changes but no actual necrosis was seen. In places the bile canaliculi were distended with pigment. A pathologist considered the features to be consistent with a diagnosis of acute hepatitis.

Treatment was by bed rest and a diet of high protein, high carbohydrate and low fat content. No change in the clinical condition occurred, however, until after a month when a mass was felt in the right hypochondrium. Full radiological examination of the alimentary canal was carried out as the question of malignancy arose. Barium enema study showed no abnormality but a barium meal showed that the stomach, normal in itself, was displaced upwards and that the duodenal loop was widened; these features led the radiologist to suggest the possibility of tumour of the head of the pancreas. In consultation with a surgeon, laparotomy was decided upon but, after a few days, colour returned to the stools and the jaundice lessened in intensity. Again in agreement with the surgeon, operation was cancelled. Clinical improvement continued and the urine became free from bile pigment after a further few days. Apparently well, the patient was soon discharged from hospital. Before discharge, a second liver biopsy showed regeneration of liver cells at the periphery of the lobules with round cell infiltration of the portal tracts in which there was scanty new formation of fibrous tissue.

Six weeks later the patient was readmitted with return of jaundice and pruritus. There was no sign of wasting but the liver was now readily palpable with a firm edge 1 inch below the costal margin. Liver biopsy showed considerable round-celled infiltration of the portal tracts with slight, but definite, increase of fibrous tissue. The liver cells were widely separated and retention of bile pigment was apparent. A pathologist described the appearances as those of early

Case C/1. (Continued)

cirrhosis with bile retention. On a regime similar to that adopted during his first admission, after 3 weeks jaundice again lessened and after a further 3 weeks he was discharged with slight residual jaundice but otherwise well; the enlargement of the liver was unaltered.

The patient was kept under observation for a further 8 months without apparent alteration in his condition when readmission was necessitated by the development of ascites with consequent oedema of the ankles; loss of weight was now obvious. After 9 pints of ascitic fluid were removed by paracentesis, the liver could be felt ½ inch below the costal margin; liver biopsy was attempted but no material was recovered. The clinical diagnosis was of hepatic cirrhosis and surgical intervention was considered with the possibility of Whipple's operation in mind; however, deterioration in the general condition was rapid and death 3 weeks later.

At post mortem, a small carcinoma of the head of the pancreas was found nearly to surround, but apparently not obstructing, the ampullary orifice; there were metastases in various parts of the body including the liver which was fibrotic.

Comment. In this, one of the earliest cases studied in the present series, the true interpretation of the evidence presented was long-delayed. Review of the biopsy sections made it clear that the hepatic pathology was not of diffuse hepatitis; the portal infiltration with ultimate fibrosis, the separation of the columns of liver cells and the retention of bile pigment, together with the absence at all times of parenchymal cell necrosis, point conclusively to what Himsworth (1947) describes as cholangio-hepatitis. The condition of the liver post mortem was that of biliary cirrhosis and not of a diffuse fibrosis, no fibrous tissue being found in the region of the central veins. Clinical evaluation of the case proved as erroneous as did interpretation of the biopsy histology. As for the radiological evidence, it is difficult to credit that a tumour of the pancreatic head measuring only 2.5 x 2 cms. at autopsy could have caused widening of the duodenal loop more than a year previously.

Case C/2.

R. H., civil servant aged 53 years. Insidiously increasing jaundice over 6 weeks with loss of weight. The liver was firm and uniformly enlarged to 1½ inches below the costal margin. In order finally to exclude chronic hepatitis, liver biopsy was carried out and

Case C/2. (Continued)

sections showed wide separation of the columns of liver cells with distension of the bile canaliculi by retained pigment; there was no necrosis of liver cells and no fibrosis, although slight infiltration of the portal tracts by round cells was evident. As this picture was consistent with cholangio-hepatitis and an obstructive form of jaundice, laparotomy was carried out and carcinoma of the gall-bladder was found extending along the cystic duct to involve the common bile duct.

Comment. In this uncomplicated case of obstructive jaundice, biopsy served to confirm the diagnosis.

Case C/3.

R. H., an elderly male. While under out-patient observation because of degenerative cardio-vascular disease with slow fibrillation and evidence of failure, jaundice suddenly developed and proved variable in intensity. Loss of weight was progressive from the start and the abdomen became swollen. Examination showed cachexia, marked jaundice, ascites and oedema of the legs. The liver extended down to the level of the umbilicus and had a firm, apparently irregular edge. There was also enlargement of the heart to the left, a slow fibrillating and collapsing pulse (blood pressure 150/60 mm.) and distension of neck veins.

The urine contained bilirubin. There was anaemia, the red cell count being 2,600,000/cu.mm., haemoglobin 6.5 g., mean corpuscular volume 104 cu. μ and mean corpuscular haemoglobin concentration 25%. Plasma prothrombin 70% and alkaline phosphatase 2.2 Bodansky units. Aspiration biopsy of the liver showed degenerative changes in some of the parenchymal cells particularly in the centrilobular zone with separation of the columns of liver cells; there was some increase in the fibrous tissue, the distribution of which was monolobular and based on the portal tracts.

Treatment was palliative and progress inoxerable to death. At post mortem examination, carcinoma of the left hepatic duct was found extending to involve the right duct.

Comment. Aspiration biopsy showed changes consistent with the clinical diagnosis of obstructive jaundice and, in addition, the tendency to centrilobular degenerative changes found in congestive cardiac failure were present. Despite the anaemia, the cachexia and the congestive failure, there were no fatty changes obvious in the liver.

Case C/4.

Miss A. B., aged 68 years. This woman had had persistent jaundice for 6 months before admission to hospital. The icterus was accompanied by a refractory hypochromic anaemia and by enlargement of the liver to 2 inches below the costal margin. Radiological study of the alimentary canal failed to provide evidence of a primary neoplasm. The case was considered to be one of obstructive jaundice due probably to a carcinoma and a surgeon consulted with a view to laparotomy; the surgeon, however, preferred a diagnosis of hepatic cirrhosis and declined to operate. Aspiration biopsy was then performed and sections showed dissociation of the columns of liver cells with retention of bile pigment; there was some increase of fibrous tissue around the portal tracts with proliferation of bile ducts. In view of this fresh evidence of the obstructive nature of the case, the surgeon reconsidered his decision and at laparotomy carcinoma of the head of the pancreas was disclosed.

Comment. In this case of prolonged jaundice in an elderly woman, clinical opinion was not decided as between hepatic cirrhosis and obstructive jaundice. The definite evidence provided by liver biopsy led to operative confirmation of the diagnosis of bile duct obstruction by a pancreatic carcinoma.

Case C/5.

J. M., a male cashier aged 52 years. A fortnight before admission he had experienced dull right hypochondriac pain associated with nausea; these symptoms lasted only a few days but, a week before admission, jaundice had appeared and steadily increased in severity. Examination showed moderately deep icterus and a palpably enlarged gall-bladder. Incidentally there were symptoms and signs attributable to primary hypertension. A clinical diagnosis of obstructive jaundice was made and aspiration biopsy performed to assist confirmation; sections showed separation of the columns of liver cells and distension of bile canaliculi with retained bile pigment, features consistent with the clinical diagnosis. At operation the gall-bladder was found to be much enlarged and to be filled by gall-stones; the head of the pancreas was hard and taken to be carcinomatous. Post operative death occurred and, at post mortem, the lesion in the pancreas was established as calcified tuberculosis with a marked surrounding inflammatory reaction.

Comment. In this case which eventually proved to be due to chronic tuberculosis of the pancreas, an unusual lesion, liver biopsy served to confirm the obstructive nature of the jaundice present.

Case C/6.

Mrs M. McM., aged 68 years. This woman gave a history of jaundice persistent over 18 months during which period two operations had been performed; at the first the gall-bladder and adjacent viscera were stated to appear healthy and at the second these findings were confirmed and a cholecyst-gastrostomy performed without subsequent effect on the icterus. Examination showed a thin, not cachectic, woman with deep jaundice and a barely palpable liver. In view of the negative surgical findings, a diagnosis of chronic primary liver disease was suggested. Liver aspiration showed, however, distension of the intralobular bile canaliculi by retained pigment with preservation of the lobular architecture and round cell infiltration with some fibrosis in the portal tracts, findings consistent with an obstructive jaundice.

Comment. The obstructive nature of this case was proved by liver biopsy evidence. Two laparotomies failed to reveal the cause of the obstruction and the question remains undetermined. The biopsy also showed commencing biliary cirrhosis, a not unexpected finding in view of the duration of the jaundice.

Case C/7.

R. M., male aged 78 years. Progressive jaundice with loss of weight for 8 weeks. Examination showed marked jaundice, emaciation and enlargement of the gall-bladder. Liver biopsy was performed to allow confirmation of the clinical diagnosis of obstructive jaundice probably of neoplastic origin. The biopsy showed bile retention, preservation of lobular architecture and slight round cell infiltration of the portal tract, features in accord with an obstructive jaundice. Laparotomy was performed and carcinoma of the head of the pancreas with distension of a healthy gall-bladder disclosed.

Comment. Both clinically and histologically this case was a classical example of obstructive jaundice due to pancreatic carcinoma; the biopsy served to confirm the diagnosis of an obstructive lesion.

Case C/8.

Mrs J. N., a housewife of 72 years, was admitted for investigation with a history of two attacks of jaundice in the previous seven months. The second attack had commenced about three months before admission and the icterus was fading when admitted. There had also been some malaise and slight loss of weight with weakness; these symptoms had become more marked in the

Case C/8. (Continued)

previous three weeks when aching pain in the right hypochondrium had appeared and had persisted for two weeks associated with vomiting which occurred after meals. The appetite has been poor since the onset. There had never been colicky pain.

Examination showed an apparently well nourished woman with fading jaundice; the liver was enlarged, a firm irregular edge being palpable about an inch below the costal margin. The stools were normally coloured and the urine contained no bile. The plasma alkaline phosphatase was 7.9 Bodansky units and the serum colloidal gold curve 200000. The prothrombin index was 66%. Plasma proteins 10.7 G. (A/G = 5.7/5.0). A cholecystogram showed no apparent calculi and a 'non-functioning' gall bladder.

Liver aspiration biopsy was carried out and the organ felt to be hard; scraps of tissue were recovered, sections showing the presence of obvious fibrosis. The precise nature of the lesion could not, however, be identified. Surgical opinion was sought and laparotomy advised. The patient declined operation and was discharged.

Comment. The clinical features in this case suggested either recurrent diffuse hepatitis with fibrosis or an incompletely obstructive lesion due either to cholelithiasis or to carcinoma of the pancreas or elsewhere with superimposed cholangio-hepatitis and biliary 'cirrhosis'. A diagnosis of gallstones was favoured by the radiological findings. Liver biopsy unfortunately failed to give a specimen of sufficient size for accurate histological assessment, but the presence of established fibrosis was confirmed.

Case C/9.

F. B., a clerk of 58 years, was admitted with a history of attacks of severe upper abdominal pain in the previous three months and of jaundice for two weeks. Anorexia and loss of weight had accompanied these symptoms. Flatulent dyspepsia had been present for a few years.

Examination showed emaciation, deep jaundice and enlargement of the liver to an inch below the costal margin, the edge being regular and firm. Bilirubin was present in the urine. The plasma alkaline phosphatase was 6.4 Bodansky units and the serum colloidal gold curve 320000. Serial readings of the icterus index showed a progressive rise from 170 to 240 over the following fortnight. A barium meal examination showed no

Case C/9. (Continued)

abnormality and no opaque calculi were to be seen in the gall-bladder. Liver aspiration biopsy was carried out and sections showed increased portal cellularity with retention of bile pigment; no parenchymal disease was seen.

The jaundice was regarded as obstructive in type and, owing to the history of severe pain, cholelithiasis could not be excluded as a cause. Laparotomy was therefore undertaken. At operation, inoperable carcinoma of the head of the pancreas was found with glands in the portal fissure.

Comment. In this case of obstructive jaundice, clinical diagnosis was confident but the biochemical reactions were misleading in that they suggested parenchymal disease. Liver biopsy showed histological evidence in favour of obstruction and subsequent laparotomy disclosed carcinoma of the pancreas.

Case C/10.

A. F., aged 76 years, gave a history of upper abdominal pain for 8 weeks and of progressive jaundice for 5 weeks. Flatulent dyspepsia and loss of weight had accompanied these symptoms. Examination showed an emaciated old man with deep jaundice. The liver edge was palpable an inch below the costal margin. The urine contained bilirubin. Biochemical investigations included plasma alkaline phosphatase 23 Bodansky units, serum colloidal gold reaction 332000 and an icterus index progressively rising from 198 to 270. Radiological examination showed no evidence of cholelithiasis. Sections of a liver biopsy specimen showed increased cellurarity of the portal tracts, retention of bile pigment and some separation of the liver cell colums.

The progress was steadily downhill and death occurred three weeks after admission. Post mortem examination disclosed a primary carcinoma involving the cystic duct and the common bile duct; scanty metastases were present in the liver.

Comment. The clinical opinion of obstructive jaundice due to a neoplasm was beyond reasonable doubt in this case; liver biopsy served to confirm the obstructive nature of the jaundice but failed to demonstrate secondary deposits in the organ.

Case D/1.

E. H., a spinster of 50 years. Unable to give a clear history, examination showed emaciation and enlargement of the liver to the level of the umbilicus. A clinical diagnosis of secondary malignant disease of the liver was made and liver biopsy performed; sections showed masses of highly anaplastic adeno-carcinoma cells in otherwise normal liver tissue. The patient would not co-operate in further investigations, particularly in radiological examination of the intestinal tract, and was discharged.

Comment. Aspiration biopsy of the liver gave proof of the clinical diagnosis of secondary malignancy in this case of gross hepatomegaly.

Case D/2.

P. B., a German P.O.W aged 32. Lumbo-sacral, sciatic and right hypochondriac pain led to the discovery of hepatomegaly, the latter under observation proving astonishingly rapid in its progress. Radiological examination of the skeleton, the lungs and the gastro-intestinal tract was negative and liver biopsy requested to clarify the diagnosis. Sections showed invasion of the liver by highly cellular and undifferentiated carcinoma. The clinical progress was of rapid deterioration to death and, at post mortem, a small primary bronchial carcinoma with multiple metastases was found.

Comment. Liver biopsy served in this case to prove that rapid enlargement of the liver in a young adult was due to invasion of the organ by highly malignant deposits from a primary bronchogenic carcinoma.

Case D/3.

D. W., a labourer aged 46 years. Complained of dyspnoea on exertion increasing over 10 years and of loss of weight during the 3 months preceding admission. Examination showed good nutritional status with pallor and flattening of the nails. The chest was barrel-shaped, moving poorly, and rhonchi were present in both lung fields. The liver edge was palpable 2 inches below the costal margin and was irregular to the touch. Blood examination showed a hypochromic microcytic anaemia and occult blood was constantly present in the stools. A barium enema examination showed a filling defect in the hepatic flexure suggestive of an adeno-carcinoma. Liver biopsy showed normal histological appearances of the tissue removed. Laparotomy confirmed the presence of colonic carcinoma and there was direct spread of the neoplasm into the liver. An ileo-transverse colostomy

Case D/3. (Continued)

resulted in a general improvement warranting discharge from the wards.

Comment. Apart from downward displacement of the organ by the chronic lung condition, actual enlargement of the liver by secondary malignant deposits was confirmed at laparotomy; liver biopsy, however, gave essentially normal histological appearances.

Case D/4.

A. C., a male aged 53 years, admitted to hospital with complaints of pain in the back and in the right hip which had persisted for over 7 weeks. There had been loss of weight. No significant abnormality was found on examination apart from evidence of recent loss of weight and early clubbing of the fingers and toes. Radiological examination of his skeleton at this time showed no abnormality but changes were seen in the lungs consistent with carcinomatosis. About a fortnight later, further x-rays of the skeleton were taken and showed foci indicating secondary malignant deposits in the lumbar vertebrae. The liver was now slightly enlarged and aspiration biopsy was performed. Sections of this material showed normal appearances apart from mild fatty changes; there was no evidence of malignant infiltration. Death occurred a month later and, at post mortem, primary carcinoma of the pancreas was found with numerous secondary deposits in the liver as well as throughout the abdominal cavity and in the lungs.

Comment. In this case, the presence of normal histological appearances in a biopsy specimen from an enlarged liver was further evidence in favour of malignant deposits as the cause of the hepatomegaly because the majority of the other causes of enlargement of this organ give changes diffusely throughout and which can usually be recognised in a biopsy specimen.

Case D/5.

H. J., an elderly male of 72 years. The patient had vomited up almost everything he had attempted to eat or drink in the 6 weeks prior to admission; the appetite had been lost and he was in an emaciated condition. There were enlarged glands in the left supra-clavicular region. The gastric juice contained altered blood and radiological examination of the lungs showed the changes of carcinomatosis. There was smooth and regular enlargement of the liver of moderate degree and aspiration biopsy was performed. Sections showed no foci of secondary tumour and no other significant pathological change. No radiological examination of

Case D/5. (Continued)

the stomach was attempted owing to the patient's weak condition. About a fortnight later death occurred. At post mortem examination there was found primary carcinoma of the lower end of the oesophagus spreading into the stomach and with metastatic deposits in the liver.

Comment. Like the preceding case, the absence of significant pathological changes in a liver biopsy specimen was taken as evidence in favour of malignant deposits as the cause of the hepatomegaly.

Case D/6.

J. S., aged 74 years, admitted for investigation of diarrhoea which had fluctuated in severity for 5 months and which was associated with loss of weight. Mucus and blood had been present in the stools. Examination showed emaciation, moderate and nodular hepatomegaly, and a hard mass in the rectum just within reach of the examining finger. Endoscopy showed the mass almost to encircle the lumen and to have a friable and ulcerated appearance. Rectal carcinoma with liver metastases was diagnosed. Biopsy of the liver gave a specimen containing no malignant deposits and showing no other significant pathological changes.

Comment. This case is a further example of normal histological findings in a liver biopsy specimen taken from an enlarged organ, such findings being presumptive evidence in favour of secondary malignant deposits rather than of any other cause for the hepatomegaly.

Case D/7.

Mrs. M. B., a housewife of foreign extraction aged 75 years. She had experienced persistent upper abdominal pain for 4 months before admission; the pain had been associated with anorexia and nausea, but no weight loss had occurred. Examination showed regular enlargement of the liver to 3 inches below the costal margin. There was mild hypochromic anaemia and histamine-fast achlorhydria. Occult blood was not present in the stools. Aspiration biopsy showed the presence of established periportal cirrhosis with fibrous infiltration of the lobules. No neoplastic changes were seen. Despite this evidence, the clinical suspicion was of gastro-intestinal malignancy and radiological examinations attempted; owing to inablilty to speak English, the patient could not co-operate and the results were unsatisfactory. The appearances of the oesophagus suggested the presence of varices; the stomach could not be properly visualised.

Case D/7. (Continued)

A second biopsy of the liver was carried out 10 days after the first and again the appearances were of a diffuse fibrosis without evidence of secondary malignancy. A few days later jaundice developed and, after a further fortnight, the liver became further enlarged with palpable nodules. A third biopsy was now carried, puncture being deliberately made into one of the nodules. The specimen showed invasion of the cirrhotic organ by carcinoma cells of an anaplastic type whose origin could not be determined. The patient was discharged at her own request and later died at home. Autopsy was not performed.

Comment. The initial biopsies in this case were misleading owing to the fact that there were apparently two pathologies, hepatic cirrhosis and secondary carcinomatosis. A third biopsy into a recently-developed nodule in the still enlarging organ showed, however, actual neoplastic cells invading the cirrhotic liver. Proof of the clinical diagnosis was thus obtained.

Case D/8.

P. D., an engineer of 57 years, was admitted because dull pain in the right hypochondrim had persisted for seven weeks and had been associated with increasing dyspnoea and loss of weight. Examination showed an emaciated man with obvious breathlessness and diffuse dirty brown pigmentation of the skin. The liver was hard, regular and extended to the level of the umbilicus. The urine was found intermittently to contain an excess of urobilinogen. Full radiological examination of the gastro-intestinal tract showed no abnormality. Biochemical liver function tests within normal limits.

Liver puncture was carried out and fragments of tissue obtained. Despite the fragmentation it was clear that the normal lobular architecture was lost. In one area the cells varied greatly in size, many being binucleate, and they were arranged in irregular columns and clumps. A few mitotic figures were seen, but atypical nuclei with vacuoles were numerous. Another fragment of tissue was composed almost entirely of formed fibrous elements with small deeply staining cells included, the latter showing in places an acinar arrangement indicative of new bile duct formation. There were unduly numerous blood vessels and, in one vein, there were liver cells lying free in the lumen. The appearances were interpreted as those of a primary hepatoma superimposed upon hepatic fibrosis with nodular hyperplasia.

The patient's condition steadily deteriorated with progressive emaciation and the development of ascites

Case D/8. (Continued)

which required repeated paracenteses. Death occurred three months after admission and post mortem examination showed a grossly enlarged liver (4,000 g.) composed almost entirely of firm yellow nodules with, in one area, a softish red necrotic area, well demarcated. A gland at the hilum showed neoplastic involvement.

Comment. Diagnosis in this case was almost impossible on clinical grounds and no aid could be obtained from biochemistry. The probable diagnosis appeared to be of carcinomatosis of the liver secondary to some occult lesion in, for example, the lungs or the gut. The absence of biochemical evidence of hepatic insufficiency despite the gross morbid anatomical changes was striking. Post mortem examination confirmed the biopsy diagnosis of hepatoma superimposed upon a nodular hyperplasia.

Case D/9.

E. H., a male aged 40 years admitted to hospital with gross emaciation, enlargement of the liver to below the umbilicus, ascites and jaundice. He gave a history of enucleation of one eye two years previously because of a "tumour". The urine was found to contain protein and bilirubin; the reactions for melanin were positive.

Aspiration biopsy of the liver was performed and sections showed melanomatosis of the organ. The patient died a few days later; permission for post mortem examination was refused.

Comment. Diagnosis of melanomatosis was made in this case on the previous history of enucleation of an eye and on the presence of melanuria. Liver biopsy, however, allowed histological proof of particular value in the absence of post mortem examination.

Case D/10.

R. J., a male aged 40 years experienced transient left-sided chest pain in March, 1947; this was followed by a cough productive of sputum sometimes streaked with blood. An x-ray of the lungs showed no abnormality in June. In early August, anaesthesia of the left side of the face developed together with distension of the upper part of the abdomen associated with continuous epigastric pain. Weight loss was now evident. Hoarseness of the voice appeared shortly before admission in mid-August.

Examination showed cachexia, hard glands above either clavicle and irregular enlargement of the liver to below the umbilicus. There was shift of the heart to the left with flattening of the left side of the chest

Case D/10. (Continued)

which moved less freely than the right. Percussion was impaired at the left base where transmitted vocal sounds were greatly diminished and the respiratory murmur inaudible. There was a recurrent laryngeal nerve palsy on the left side. Radiological examination showed collapse of the left lower lobe and, by means of tomography, obstruction to the main bronchus of the affected lobe with glandular enlargement in front of the carina. No secondary deposits were seen in films of the skeleton. Liver biopsy gave a specimen which sections showed to consist almost entirely of small, highly anaplastic carcinomatous cells. Death occurred at the end of August, 1947. Permission for autopsy was not obtained.

Comment. On clinical and radiological grounds, the diagnosis of primary bronchogenic carcinoma could hardly be doubted, but liver biopsy gave final proof of secondary carcinomatosis of the liver, especially valuable in the absence of post mortem examination.

Case D/11.

Miss M. P., aged 50 years, was admitted complaining of nausea before meals of six month's duration. During this time her bowels, previously regular, had tended to be constipated with occasional bouts of diarrhoea. There had been no loss of weight. Examination showed diffuse dusky brown pigmentation and enlargement of the liver to below the umbilicus, the organ being slightly nodular. Liver biopsy was carried out and showed entirely normal histological appearances. In view of this and of the bowel irregularity, a barformed and showed a filling defect in the pelvic colon indicative of a carcinoma.

Comment. With gross hepatomegaly, liver biopsy sections that appeared normal suggested that the enlargement of the organ was due to secondary deposits of cancer. Irregularity of bowel rhythm led to the discovery of a primary colonic neoplasm.

Case D/12.

J. P., a man of 57 years who had previously enjoyed robust health, was admitted to a surgical ward with a diagnosis of cirrhosis of the liver. He gave a history of epigastric discomfort with post prandial flatulence for about two months. The appetite was retained and there had been no loss in weight.

Examination showed a ruddy well-nourished man with irregular enlargement of the liver to 1½ inches below the costal margin. At the request of the surgeon biopsy of the liver was carried out and sections showed the

Case D/12. (Continued)

the organ to be invaded by masses of adeno-carcinoma the structure of which suggested a gastro-intestinal primary lesion. Subsequent radiological examinations demonstrated the presence of carcinoma of the stomach.

Comment. In this case of hepatomegaly in an elderly man liver aspiration biopsy, carried out for diagnostic purposes, showed the organ to be the seat of metastases from a primary adeno-carcinoma subsequently discovered in the stomach.

Case D/13.

Mrs E. L., a housekeeper of 55 years, was admitted in coma. From relatives the history was obtained of steady deterioration in her health in the previous year accompanied by loss of weight. Swelling of the abdomen and legs had been present for three weeks. She had been a heavy consumer of alcohol for many years.

Examination showed flaccid left hemiplegia, proptosis of the left eye, gross enlargement of the liver with ascites, and pitting oedema of the legs. The peripheral arteries were readily palpable and the blood pressure was 160/80 mm. The urine gave reactions consistent with the presence of melanin. The plasma proteins were normal and the serum colloidal gold curve 000000. Liver biopsy was carried out and sections showed the presence of well-established diffuse fibrosis with marked fatty changes in the parenchymal cells; congestion of the sinusoids was present towards the central veins. In addition, areas of melanoma cells were present, singly and in groups, throughout the specimen; there appeared to be reactive fibrosis around the neoplastic elements.

Without significant changes, death occurred 10 days after admission. Post mortem examination showed thrombosis in atheromatous cerebral arteries; there was a malignant melanoma of the left choroid with metastases in the liver, heart, lungs and peritoneum.

Comment. Apart from the intracranial vascular catastrophe which probably occasioned death in this case, liver biopsy was utilised to investigate the gross hepatomegaly present. The presence of melanomatosis was thus disclosed and the chemical reactions of the urine then provided further evidence.

Case D/14.

A. K., aged 65 years, was admitted with a history of pain in the lumbar region, thighs and left shoulder for five weeks associated with retrosternal pain and cough productive of blood-stained sputum, dysuria and

Case D/14. (Continued)

loss of weight. Examination showed evidence of consolidation of the upper lobe of the left lung and of emaciation. The liver was not enlarged and there were no palpable lymph glands.

Radiological examinations showed an irregular narrowing of the left main bronchus with collapse of the left upper lobe. The serum colloidal gold curve showed slight abnormality (200000) but the plasma prothrombin index was normal (106%). Liver aspiration biopsy demonstrated invasion of the organ by highly anaplastic cells whose oval appearance suggested origin from a bronchogenic carcinoma.

Comment. The diagnosis of bronchogenic carcinoma in this case was established by radiological evidence. On clinical grounds involvement of the liver by metastases was suspected despite absence of enlargement of the organ; biopsy served to confirm this suspicion and, further, to add histological confirmation of the presence of malignancy.

Case D/15.

R. H., a master springsmith of 46 years, was admitted with a history of left hypochondriac pain, constriction of the chest and pains in the shoulder girdle and lumbar region for five months. He had lost weight.

Examination showed emaciation, oedema of the legs and thighs, enlargement of the liver to 2 inches below the costal margin and evidence of ascites. Radiological examinations showed a mass in the hilum of the left lung and changes in the spinal column indicative of malignant metastases. Aspiration biopsy of the liver was performed and sections showed invasion of the organ by masses of anaplastic cells. Temporary symptomatic benefit with notable relief from pain followed a course of nitrogen mustard. The patient was enabled to leave the ward only to return after a week because of the onset of paraplegia. A further course of nitrogen mustard resulted in definite lessening of the paralysis but steady deterioration of the general condition was progressive to death shortly afterwards.

At post mortem examination the diagnosis of bronchogenic carcinoma was confirmed, the primary lesion being found in the left upper bronchus and secondary deposits in the liver and in various bones.

Comment. The radiological evidence of lesions in the lung and in various bones pointed strongly to the presence of a bronchial neoplasm with metastases, but aspiration biopsy of the liver provided histological proof of

Case D/15. (Continued)

Comment. (Continued)

carcinomatosis.

Case D/16.

P. McG., 63 years old, with a history much of which was culled from relatives. He had complained of epigastric discomfort for about a month and had vomited about once a day for a week or so before admission. Loss of flesh had been observed. Haematemesis had occurred four days previously and had been repeated on the day before admission; the stools had been black during these few days during which mild confusion had been noticed. There was no previous history of dyspepsia or other relevant ill-health.

Examination showed an emaciated man manifesting mild mental confusion. No abnormality was otherwise present at the time of admission but the liver enlarged whilst under observation and the lower edge eventually reached over an inch below the costal margin. The urine was normal. The faeces contained occult blood. Anaemia was present (red cells 3,800,000/c.mm., haemoglobin 75%) and there was no response to iron therapy. Owing to faintness, satisfactory barium meal examinations could not be carried through, but no abnormality was seen in the available films of the lungs and gastro-intestinal tract. Aspiration of gastric fasting juice showed the latter to contain no free HCl and no blood. The plasma prothrombin index was estimated at 92% and liver biopsy was carried out. The histological appearances of the sections were normal.

Increasing mental confusion associated with noisiness and aggressiveness compelled his removal to mental observation wards. In the few days before discharge scanty haemoptyses were observed.

Comment. From the loss of weight and the hepatomegaly, a probable diagnosis of secondary malignant disease of the liver was indicated. Persistence of occult blood in the faeces suggested a gastro-intestinal site for the primary lesion; the occurrence of haemoptysis required the consideration of a promary bronchogenic carcinoms. The presence of mental symptoms indicated the possibility of cerebral metastases. It was hoped that aspiration biopsy of the enlarged liver might confirm the presence of carcinomatosis of the organ but no abnormality was seen in sections of the biopsy material.

Case E/1.

Mrs M. McC., a housewife aged 47 years. Complaints of paraesthesiae of the extremities for 3 months; of fatigue and dyspnoea on exertion for 2 months; of increasing loss of appetite. Examination showed lemon-yellow pallor, a spleen just palpable, a smooth tongue, a soft apical systolic murmur and an intact nervous system. Red cell count 930,000/cu.mm., haemoglobin 25% Sahli (colour index of 1.3), mean corpuscular volume 118 cu.μ, mean corpuscular haemoglobin concentration 34%, leucocytes 2,000/cu,mm. Blood smear showed typical macrocytic picture with occasional nucleated red cells. Liver function tests normal. Histaminefast achlorhydria. Sternal marrow hypercellular, megalo-blastic. Liver biopsy showed fatty changes.

Response to a potent parenteral liver extract was optimal, a reticulocyte crisis reaching 36%. A second liver biopsy was carried out when the red cell count had reached 3,610,000/cu.mm. and in this specimen there was no stainable fat. The general architecture of the liver, apart from the fatty changes and the presence of scanty deposits of haemosiderin, was normal on both occasions.

Comment. Liver biopsy was undertaken in this case, which showed all the classical features of Addisonian pernicious anaemia, as part of a systematic investigation into hepatic function and pathology in severe anaemia. Biochemical tests showed no deviation from the normal, but biopsy revealed definite fatty changes which apparently cleared rapidly after the administration of liver extract and while the blood level was still only 3,600,000 erythrocytes per cu.mm.

Case E/2.

J. J., a West African mining engineer (white) was admitted to a surgical ward as a case of jaundice with the following history. Five days previously he had had an attack of shivering accompanied by headache and followed by profuse sweating which he attributed to malaria and for which he treated himself with quinine and mepacrine for 3 days. Two days before admission he suffered acute epigastric pain with vomiting and diarrhoea. He then noticed that his urine became very dark in colour. He stated that for the previous year he had taken 5 gr. quinine each night and 10 gr. bi-weekly as a prophylactic measure against malaria; two months before admission, on joining ship to return to this country, he took a course of 3 tablets of mepacrine (0.1 G.) daily for 10 days and then discontinued all suppressive measures. On arrival in this country he had a typical malarial attack which

Case E/2. (Continued)

he cured by 10 gr. quinine and 1 tablet mepacrine daily for 3 days.

Examination showed marked pallor with moderate icterus, slight hepatomegaly and a barely palpable spleen. The urine contained oxyhaemoglobin. Blood examination showed red cells 2,290,000/cu. mm. and haemoglobin 50% with white cells 4,000/cu. mm. Prolonged search of blood smears revealed scanty ring forms of Plasmodium falciparum; one 'crescent' was seen. The red cells showed anisocytosis with polychromatic pseudomacrocytes and ? microspherocytes. Reticulocytes numbered 5%. A red cell fragility test showed initial lysis at 0.48% NaCl and complete lysis at 0.34%; quantitive analysis showed a definitely increased fragility in the range 0.48 - 0.44% NaCl. The sternal marrow was active and normo-blastic with much parasitic debris.

Liver biopsy on admission showed congestion of the bile canaliculi with bile pigment, the latter also being present in many of the liver cells. Some of the Küpffer cells were seen to contain malarial pigment. Haemosiderin was slightly increased in amount.

The patient was treated by blood transfusion, mepacrine and a scale preparation of iron. Response was satisfactory and he was discharged with a haemoglobin of 62%. Followed as an out-patient his blood later regained normal levels. Prophylactic paludrin therapy was commenced on his return to Africa.

Comment. Liver biopsy was performed in this case of blackwater fever largely for academic reasons and showed the pigmentary disturbances to be anticipated after such a sudden intravascular haemolytic crisis.

Case E/3.

Mrs I. A., a housewife aged 34 years, was successfully treated by anahaemin injections five years previously as a case of 'pernicious anaemia'; relapse on two subsequent occasions was similarly relieved and injections of liver extract had been given regularly every 2-4 weeks during the two years before the present admission. Despite these injections symptoms of fatigue, dyspnoea, pallor with slight yellow tinge, and glossitis appeared and increased during the few months before admission. Two years previously thyroidectomy was performed because of symptoms of thyrotoxicosis.

Physical examination revealed no abnormality other than pallor with slight dirty lemon tinge, glossitis and

Case E/3. (Continued)

prominence of the eyes. Blood counts were red cells 1,480,000 per c.mm., haemoglobin 46%, colour index 1.55, reticulocytes less than 1% and white cells 5,400 per c.mm. A stained film showed marked anisocytosis with poikilocytes and well-filled macrocytes. The sternal marrow was highly cellular and erythropoiesis frankly megaloblastic. Free HCl was present in the gastric juice after injection of histamine. A single injection of a known potent batch of anahaemin provoked a reticulocyte response of 6% but there was no rise in the red cell or haemoglobin levels. Choline chloride was thereafter given orally and parenterally during 10 days without effect on the blood picture; a single injection of anahaemin was given on the seventh day of choline therapy on the basis that the latter might potentiate the liver, but no response occurred. A liver biopsy was carried out after these experiments and sections showed marked fatty changes throughout the hepatic lobules together with the presence of haemosiderin in both the littoral and the parenchymal cells. Folic acid was thereafter given in daily dosage of 20 mgm. orally and resulted in a maximum reticulocyte response of 58% and ultimate restoration of the blood levels to normality after a phase of iron deficiency had appeared and had been countered by administration of ferrous sulphate.

The aetiology of this anaemia being obscure, further investigations were carried out. Fat balance estimations on daily intakes of 50 G. and of 150 G. fat showed normal results as did repeated glucose tolerance curves. Radiography of the intestinal tract revealed no abnormality. The basal metabolic rate was estimated on several occasions and varied from -2 to +20. Relapse of the blood condition occurred on trial substitution of folic acid by anahaemin whilst the patient was taking an adequate dietary.

Comment. In this obscure case of megaloblastic anaemia, blame could not be placed on nutritional factors, on deficiency of 'intrinsic factor', on defective intestinal absorption or on refractoriness of the marrow. Liver biopsy showed a fatty liver in which the deposits of fat had not apparently resolved on the administration of choline chloride; there were also considerable amounts of haemosiderin in the organ. It is difficult to ascribe the fatty changes other than to the effects of anaemia.

Case E/4.

Mrs J. C., a housewife of 71 years, was admitted with weakness, dyspnoea on exertion, swelling of the

Case E/4. (Continued)

ankles, anorexia and pallor of three months' duration. She had previously enjoyed excellent health. Examination showed good nutritional status, marked pallor with a slight yellow tinge, pitting oedema of the legs, a systolic murmur audible over the whole of the praecordium and a blood pressure of 185/80 mm. There were no other abnormal physical signs. Blood examination showed red cells 1,560,000 per c.mm., haemoglobin 46%, colour index 1.5, reticulocytes less than 1%, and white cells 5,000 per c.mm. Marrow examination showed erythropoiesis to be megaloblastic. There was histamine-fast achlorhydria. An experimental period of choline administration, orally and intravenously, failed to affect the blood picture apart from a rise in the reticulocyte count to 2.5%. Liver puncture was performed before the period of choline therapy which lasted 11 days. The specimen no abnormality apart from some congestion of the sinusoids; there were no fatty changes and no obvious deposits of haemosiderin.

Administration of a potent liver extract provoked a reticulocyte response and ultimate restoration of the blood picture to normal.

Comment. In this example of Addisonian pernicious anaemia, liver biopsy showed the absence of observable fatty changes in the liver despite the presence of a considerable degree of anaemia. The failure of choline to provoke any haematological response may be corelated with the absence of deposits of fat in the liver and the case may be compared with case E/6.

Case E/5.

Mrs J. N., was admitted in 1946 at the age of 68 years. She complained of dyspnoea on exertion, looseness of the bowels, glossitis and anorexia developing during the previous year; in addition three attacks of 'lumbago' had occurred in the four months before admission. She gave a long history of ill-health dating from a gall-bladder operation in 1918 since when her diet, owing to an indefinite dyspepsia, had been self-limited to white meat and milk puddings, with an occasional vegetable and a few potatoes. In 1944 she was operated upon because of intestinal obstruction and her appetite then became very poor; a milk diet had been her means of sustenance since the operation.

Examination showed a very pale woman of poor nutrition with slight enlargement of the heart to the left. There was moderate tachycardia and occasional extra-systoles interrupted the regularity of the pulse;

Case E/5. (Continued)

a moderately loud apical systolic murmur was present. There were no other abnormal physical findings.

Examination of the blood showed red cells 800,000 per c.mm., haemoglobin 27% and white cells 4,400 per c.mm. Sternal marrow examination showed frankly megaloblastic erythropiesis. There was histamine-fast achlorhydria. Liver biopsy showed normal architecture of the organ with moderate amount of fat in the cells of the inner two-thirds of the lobules; haemosiderin granules were present in most of the littoral cells but were absent from the parenchymal cells.

Injections of a known potent concentrated liver extract produced a prolonged irregular low-grade reticulocyte response and a very sluggish rise in the red cell count (from 800,000 to 1,500,000 in 21 days). Concentrated liver extract was thereafter given orally with acceleration in the red cell increase to 4,210,000 per c.mm. after a further six weeks, the reticulocyte count subsiding to below unity after three weeks of the oral therapy without a definite 'secondary' peak being manifest.

Radiological examination of the skeleton showed changes in lumbar vertebrae consistent with the presence of metastatic carcinomatous deposits; repeated clinical and radiological examinations failed to reveal a primary lesion either in the gastro-intestinal tract, the lungs, the breasts or pelvic organs, or elsewhere; the benzidine test on the faeces was consistently positive, however, even when the patient was on a milk diet.

Comment. In this case of pernicious anaemia refractory to parenteral injection of a refined liver extract, oral administration of liver gave a satisfactory response. Liver biopsy showed that the organ was the seat of moderate fatty changes which were less marked than was anticipated in view of the prolonged dietary inadequacy and the profound degree of anaemia. Subsequent study showed the presence of carcinomatosis of the lumbar vertebrae but no primary lesion could be discovered; it is possible that malignancy was responsible, at least in part, for the refractoriness of the anaemia.

Case E/6.

Mrs M. S., a housewife aged 65 years. This woman first developed symptoms of anaemia (pallor with dysponoea on exertion) at the age of 59 years when a clinical diagnosis of pernicious anaemia and a course of

Case E/6. (Continued)

ten liver injections given with satisfactory clinical improvement. Therapy was not regularly maintained until two years later when monthly injections were commenced and continued until about 6 months before admission whereupon clinical relapse occurred. No response had followed several injections of liver in the 3 weeks before admission and she was admitted as a case of pernicious anaemia in relapse and refractory to parenteral liver therapy. The dietary had been adequate.

Examinstion showed an apparently well nourished woman with gross pallor and slight light yellow colouration of the skin. The liver could be felt just to extend below the right costal margin; there were no other abnormal physical signs. Examination of the blood showed red cells 1,300,000/cu.mm., haemoglobin 40% Sahli (100% = 14.0 G.), colour index 1.5, P.C.V. 16% M.C.V. 124 cu. μ, reticulocytes less than 1%, and white cells 4,600/cu. mm. A stained film showed well stained macrocytes with gross anisocytosis and poikilocytosis. Sternal puncture revealed a highly cellular marrow with frankly megaloblastic erythropoiesis. Chemical tests of liver function were within normal limits. There was histamine-fast achlorhydria.

A known potent 'refined' liver extract was given as a single dose on 12.11.46 and there was a reticulocyte response reaching on 18.11.46 a 16% peak. The blood values reached red cells 3,020,000/cu. mm. and haemoglobin 66% on 5.12.46. Liver aspiration biopsy was carried out on 2.12.46 and sections showed that well-marked fatty changes were present; there was no other histological abnormality.

The red cell count now ceased its steady rise as the effect of the single injections wore off and a definite downward trend was observed. Choline was administered experimentally beginning on 11.12.46 with 1 G. intravenously for 13 days followed by oral dosage of 15 G. daily. There was a rise in the red cell count reaching a maximum of 3,700,000/cu. mm. on 29.12.46 unaccompanied by a reticulocyte response. On 28.12.46 a second liver biopsy served to show that the organ was quite free from detectable fatty change or other abnormality. Following this, the red cell count again fell slowly despite the continued exhibition of choline which was therefore discontinued and on 11.1.47 further liver extract was given, the red cell count being now at 2,900,000/cu. mm. On 17.1.47 there was a reticulocyte peak of 7% and the blood values thereafter progressed to reach normal levels. Fat balance estimations were subsequently performed with normal results.

Comment. In this case of Addisonian pernicious anaemia liver biopsy was first performed after the red cell count had been raised from 1 to 3 millions; gross fatty changes were observed. A second biopsy after the count had risen from 3 to 3.7 millions during the administration of choline showed the absence of detectable fat in the organ. Fatty changes are stated, on post mortem evidence, to be common in severe anaemias and are usually attributed to diminution in the oxygen supply of the hepatic cells. The results recorded in this case suggest that choline deficiency plays an important role in the production of fatty changes and, further, that such fatty changes may impair the efficiency of the liver in utilising the haemopoietic principle.

Case E/7.

G. H., a retired labourer of 77 years, was admitted with a history of illness which started 8 months previously following a bout of alcoholism. Dyspnoea on exertion with readily induced fatigue was first noticed and later a productive cough developed. His diet had been markedly inadequate for several years and there had been a regular daily consumption of a moderate quantity of spirits. Three months before admission the urine had become noticeably darker in colour, this abnormality persisting for several weeks before a normal hue was regained. Two months before admission there appeared dark red spots on the arms and elsewhere on the body, these spots persisting. Three weeks before admission he had a severe epistaxis, a recurrence of which led to collapse and immediate admission to the wards.

Examination showed an elderly man of poor nutritional status with marked mucosal pallor. Purpuric spots were present diffusely over the body. Slight enlargement of lymph nodes in the axillae and grions was noted. Other than evidence of arterio-sclerosis and a blood pressure of 140/60 mm., no abnormal physical sign was present. The urine contained a slight excess of urobilinogen. Blood examination showed red cells 1,320,000/c.mm., haemoglobin 28% and white cells 2,800/c.mm. (polymorphs 24%, lymphocytes 72% and monocytes 4%). Sternal puncture showed the marrow to be fatty and grossly hypocellular, consistent with a diagnosis of aplastic anaemia. On the third day in hospital, broncho-pneumonia developed and led to death 4 days later despite blood transfusions and penicillin therapy. Liver biopsy was carried out before the onset of the acute pulmonary infection and sections showed congestion around the central veins with degeneration in the centrilobular cells; there was no evidence of fatty or fibrotic changes.

Post mortem examination confirmed vascular

Case E/7. (Continued)

sclerosis, marrow aplasia and terminal broncho-pneumonia. The liver was small (930 G.) and pale with cloudy swelling; some recent blood clot over the surface of the right lobe was associated with the biopsy puncture wound. The spleen was small and atrophic with fibrosis of the pulp. In the stomach there was a recent longitudinal ulcer extending 2.5 cm. from the cardiac orifice towards the oesophagus; maemorrhage from this ulcer had filled the stomach with blood.

Comment. In this case of aplastic anaemia evidence of fatty or fibrotic changes in the liver was anticipated owing to the severe degree of anaemia, the defective diet and the chronic alcoholism. Biopsy, which was carried out as part of a research into hepatic changes in anaemia, showed only some degenerative changes in the centrilobular cells. The liver was not fatty and showed no evidence of fibrosis.

Case E/8.

L/Cpl. P., a Polish soldier of 41 years, was admitted after a fortnight of illness which included irregular pyrexia, malaise, cough, pains in the chest, back and limbs, and recent haemoptysis and bleeding from the gums. Examination showed pallor, enlarged axillary and inguinal glands, and evidence of patchy consolidation in the right lung. The urine contained an excess of urobilinogen. Blood values were red cells 1,590,000/c. mm., haemoglobin 33% and white cells 2,100/c.mm. Sternal puncture with strong aspiration succeeded in removing flecks of marrow which proved to be fatty and extremely hypocellular. A diagnosis of aplastic anaemia was thus established. Despite transfusions, penicillin, proteolysed liver and pyridoxin, the course was steadily downhill to death three weeks after admission.

Liver biopsy was performed shortly before death and sections showed normal architecture with cloudy swelling and mild fatty changes in some of the liver cells. Haemosiderin was deposited in some of the centrilobular cells and slight round cell infiltration of the portal tracts was evident. Post mortem examination showed scattered petechial haemorrhages. The spleen was enlarged (120 G.) and gave a positive prussian blue reaction. The liver weighed 1,700 G. was soft, yellowish and gave a positive reaction for iron; a large red clot on the anterior surface of the right lobe was in relationship to a jagged puncture wound a few millimetres in length. The kidneys were pale and failed to give an iron reaction. Histologically the marrow was aplastic; in the liver degenerative changes were present around the central veins.

Case E/8. (Continued)

Comment. Ante mortem liver biopsy was carried out in this case as part of a research project. Two points emerge from a study of the material; firstly that the anticipated fatty changes in the organ were remarkably slight and, secondly, that the definite degenerative changes in the centrilobular zone noted in the post mortem specimen were absent in the biopsy tissue taken only a matter of hours before death.

Case E/9.

J. H., a male aged 71 years was admitted complaining of weakness with dyspnoea on exertion. Three years previously he had been diagnosed as suffering from 'pernicious anaemia' and had spent 18 months in another hospital where treatment was by repeated blood transfusions; since discharge from this hospital he had had regular liver injections.

Examination showed him to be pale but well-nourished; there was a faint icteric tinge and a few purpuric spots were present on the shoulders. Apart from signs of chronic bronchitis, physical examination was otherwise negative. Blood examination showed red cells 930,000/c.mm., haemoglobin 2.9 G./100 ml., M.C.V. 102 c.μ, M.C.H.C. 31%, reticulocytes 1.5% and white cells 2,400/c.mm. The marrow was normoblastic and not hypoplastic. No response occurred to any form of haematinic therapy and the patient was kept alive by repeated blood transfusions.

Liver aspiration biopsy was carried out and sections showed moderate fatty changes without appreciable fibrosis; deposition of iron pigment in the liver cells was prominent. Some months later the patient came to post mortem examination in a different hospital; a report states that the marrow was then aplastic and that the lungs were the seat of bronchiectatic changes.

Comment. In this case liver biopsy was carried out because of the suspicion that chronic liver disease underlay the failure to respond to any form of haematinic therapy. At the time of biopsy, aplastic anaemia was not considered as a justifiable diagnosis because of the slight reticulocytosis and of the apparent cellularity of the sternal marrow biopsy specimen.

Case E/10.

J. C., aged 68, a retired artisan, was admitted with a history of dyspnoea on exertion and anorexia for 5 months. His haemoglobin level had previously been found to be low and a clinical diagnosis of pernicious anaemia had been made. Seven injections of liver extract had been given

Case E/10. (Continued)

prior to admission without apparent effect.

Examination showed satisfactory nutrition with marked pallor and a light yellow tinge in the skin. The face was slightly puffy and there was pitting oedema of the ankles. The tongue was neither smooth nor red. The liver was soft and enlarged about 1 inch below the costal margin. The urine contained no abnormality. Blood examination showed red cells 1,570,000/c.mm., haemoglobin 43%, M.C.V. 133 c.μ, reticulocytes less than 1% and white cells 2,200/c.mm. Sternal puncture showed the marrow to be hypercellular with frankly megaloblastic erythropoiesis. A test meal showed histamine-fast achlorhydria. The Wassermann and Kahn reactions were definitely positive on three occasions.

After a control period of a few days without treatment, a known potent liver extract was given intramuscularly on 31.3.47 and on 1.4.47; a reticulocyte response occurred and reached a peak of 18% on 6.4.47. No further liver was given and the blood levels reached red cells 2,870,000/c.mm. and haemoglobin 59% on 15.4.47 when reticulocytes were again less than 1%. The counts remained steady until 20.4.47 when the figures were red cells 2.910,000 and haemoglobin 61%. Choline chloride was then given in dosage of 1 g. intravenously daily for 5 days. The blood values showed a concomitant rise to reach on 27.4.47 red cells 3,510,000 and haemoglobin 69%, the level thereafter falling again to 3,210,000 on 29.4.47 after which regular parenteral liver therapy was commenced and the blood values climbed to 4,660,000/c.mm. with haemoglobin 98% on 1.9.47.

Liver biopsy was performed on 15.5.47 prior to discharge from the wards and at a time when the liver was no longer palpably enlarged. Sections showed that the organ appeared entirely normal histologically.

Appropriate anti-specific treatment was initiated in view of the persistently positive serology.

Comment. In this case of Addisonian pernicious anaemia enlargement of the liver was probably due to fatty changes; it is to be regretted that biopsy was not carried out before as well as after the administration of choline but comparison with case E/6 suggests that fatty changes in the liver were cleared by the lipotropic action of choline, that the organ was thus improved functionally and that the consequent slight rise in the blood levels were attributable to this mechanism.

Case E/11.

Mrs. E. T., a housewife of 48 years, for two years had noted progressive lassitude and weakness associated with dyspnoea on exertion; oedema of the ankles had been present in the evenings for about a year. Relatives had commented upon increasing pallor. There had been uncertainty in the use of her hands with a coarse tremor for an indefinite period. Enquiry elicited a history of severe 'stabbing pains' in the region of the ankles and feet over the previous nine years. There were no other relevant points in the personal or family history.

Examination showed a woman of average nutrition with marked pallor, a slight dirty yellow tinge to the skin and a definitely palpable spleen tip. Neurologically there was emotional instability, Argyll Robertson pupils, absent knee and ankle jerks, dorsiflexor plantar response and loss of pain sensibility in the tendo Achilles.

Laboratory investigations showed Wassermann reactions negative in the blood but positive in the cerebro-spinal fluid; in the latter the colloidal gold curve was 555,432,100, but the protein and cell contents were normal. Blood examination showed red cells 830,000/c.mm., haemoglobin 24% (=2.6 G.), colour index 1.4, mean corpuscular volume 110cu.μ, mean corpuscular haemoglobin concentration 29%. White cells numbered 4,400/c.mm. and a differential count showed the presence of about 8% large atypical mononuclear cells with basophilic cytoplasm which were thought to be derived from the reticulo-endothelial system. The sternal marrow was somewhat hypercellular and contained large numbers of the mononuclear cells already mentioned. Radiological examination of the skeleton showed no abnormality.

Treatment consisted of full courses of penicillin as an anti-luetic measure and of blood transfusions with, at different times, liver extracts parenterally and orally, and folic acid to combat the anaemia. The anaemia failed to respond and, in view of the possibility of an atypical leukaemia, a course of urethane was given but without effect. Severe leucopenia, further lowering of the red cell count and the finding of a now hypoplastic marrow suggested that aplasia of the marrow had developed; the prognosis was thought to be hopeless and treatment discontinued. Three months after admission and a fortnight after the demonstration of marrow hypoplasia, however, spontaneous improvement in the general condition and in the blood values occurred. She was discharged with red cells 3,290,000/c.mm., haemoglobin 70% and white

Case E/11.(Continued)

cells 2,400/c.mm. The peripheral blood still contained a few atypical mononuclear cells but the sternal marrow at this time was apparently normal. Further anti-syphilitic treatment is proposed.

Liver biopsy was performed a fortnight after admission and sections showed fatty changes together with deposits of haemosiderin in the cells of the liver lobules, particularly around the central veins.

Comment. The refractory anaemia and the unusual haematological picture in this case were, most probably, to be ascribed to the presence of chronic syphilis. Liver biopsy was performed in the hope that it might shed light on the nature of the anaemia and to assist exclusion of, for example, leukaemia. The fatty changes and the deposits of haemosiderin found are to be associated with the severity of and the refractoriness of the anaemia.

Case F/1.

J. C., a printer's warehouseman aged 58 years, was admitted because of the loss of 2 stones in weight over the previous year and of increasing weakness for 5 weeks. It was elicited that, also during the previous 5 weeks, there had been polydipsia, gross polyuria and corresponding increased frequency of micturition. For 20 years he had suffered dyspepsia and, in 1942, frequent vomiting led to a laparotomy at which a fibrosed pylorus was found; gastro-enterostomy gave relief to all his symptoms but an incisional hernia unfortunately developed. The patient stated that his skin had always been dark and that he had noticed no change in it; his son, however, volunteered the opinion that his father's skin had, in fact, darkened during the few months prior to admission.

Examination showed moderate emaciation with a slatey-grey generalised pigmentation of the skin. Langour and weakness was obvious. There were no enlarged lymph glands. Systemic examination showed the incisional hernia and enlargement of the liver to 4 fingers'-breadth below the costal margin, the upper border of hepatic dullness being at the 4th. rib in the right midclavicular line. The spleen was not palpable but there was an increase in splenic dullness along the 9th. and 10th. ribs reaching as far as the left costal margin.

Relevant laboratory investigations revealed marked glycosuria, a glucose-tolerance curve of 187, 200, 277, 301 and 261 mgm. with reduction of Benedict's reagent by all specimens of urine. There was slight anaemia (red cells 4,520,000/c.mm. and haemoglobin 92% Sahli); the white cell count and the appearance of a stained film were normal. Sternal puncture revealed a somewhat hypoplastic marrow in the matrix of which haemosiderin granules were readily demonstrable; erythropoiesis was normoblastic.

Liver aspiration biopsy was carried out and sections showed that there was diffuse fibrosis of the organ with areas of hyperplasia; the liver cells were packed with haemo-siderin which was also lying free among the fibrous tissue. Biopsy of the pigmented skin was also carried out and the prussian blue reaction revealed a minimal quantity of iron-staining pigment in the superficial layers of the corium. Radiological examination of the lungs showed bilateral fibrotic tuberculous lesions.

Four months later he was readmitted with ascites, hypoglycaemic bouts and a swinging pyrexia apparently due to activation of the tuberculosis. Deterioration was hence-forward rapid and death occurred a month later with

Case F/1. (Continued)

uncontrollable diabetes, hypocalcaemia and coma. Post mortem examination showed an enlarged fibrotic liver and a small hard pancreas both of which gave a positive iron reaction. The lungs showed changes consistent with chronic fibro-caseous tuberculosis.

Comment. A clinical diagnosis of haemochromatosis was suggested in this case by the combination of emaciation, pigmentation of the skin, diabetes mellitus and enlargement of the liver. Aspiration biopsy of the liver demonstrated diffuse fibrosis of the organ and gross deposition of haemosiderin, the latter being very much more striking than the pigmentary changes in a biopsy specimen of skin. It would appear that liver biopsy is the method of choice for the confirmation of the diagnosis in this rare and obscure condition.

Case F/2.

T. G., a labourer of 47 years, was admitted on 2.8.46 because of gross swelling of his abdomen, scrotum and legs which had developed abruptly the previous day after a week's prodromal indefinite malaise. His health had previously been excellent. Examination showed a tense distended sbdomen with evidence of ascites, pitting oedema of the legs and sacral area, and oedema of the scrotum and penis. There were no other abnormal physical signs.

The urine contained protein+++ and a few red cells, casts being absent; the specific gravity varied normally whilst under observation. There was anaemia (red cells 3,350,000/c.mm., haemoglobin 60%, colour index 0.89; white cells 9,400/c.mm.). Blood urea 67mgm./100 ml. Plasma proteins 4.6 G./100 ml. (A/G = 2.0/2.6). Blood cholesterol 200 mgm./100 ml. Serum colloidal gold reaction 000000. Plasma alkaline phosphatase 2,4 Bodansky units. The blood Wassermann and Kahn reaction strongly positive. Sternal marrow was fatty and somewhat hypoplastic; erythropoiesis was normoblastic. Laboratory investigations were repeated from time to time and the picture did not alter significantly except that the blood urea was at all other times within normal limits.

Paracentesis of the abdomen gave a slightly milky fluid the turbidity of which did not alter after shaking with ether; the protein content of the fluid was 0.4 G./100 ml. Further to exclude lymph duct obstruction, 100 mgm. Sudan III in 10 G. butter was given orally and paracentesis abdominalis repeated after 18 hours; no dye was present in the ascitic fluid. An incidental mild Flexner dysentery resolved on the exhibition of succinyl sulphathiazole.

Case F/2. (Continued)

Estimation of the plasma prothrombin gave an index of 92%. Liver biopsy was performed on 12.8.46 and again on 14.11.46. On both occasions satisfactory specimens were obtained and sections showed that, although the columns of liver cells were somewhat dissociated and the liver cells had a somewhat poor glycogen content, the liver generally appeared normal. There was no excess of bile pigment, no round cell infiltration of the portal tracts and no fibrosis. No spiro-chaetes were seen in sections stained by Levaditi's method.

The diagnosis of amyloid disease was excluded by the absence of amyloidosis of the liver as shown by specific staining of the biopsy material and by a negative Congo Red test. Treatment was by bed rest and a high protein (120 G.) diet with additional choline (10 G. daily); in view of the positive serological reactions, appropriate antispecific therapy was carried out.

By December, 1946, although the general condition of the patient had improved after an initial deterioration, ascites persisted and paracentesis of the abdomen was necessary about every third week. Proteinuria (1-5 parts Esbach) was continual and the plasma proteins remained low (4.55 G.; A/G = 1.02/3.53). The serological reactions were unchanged. He was sufficiently well to be discharged to a convalescent home on 11.1.47 with a tentative diagnosis of tertiary syphilis with portal thrombosis. His condition was maintained until readmission was necessitated on 6.3.47 because of abrupt increase in the abdominal swelling; examination showed no alteration other than increase in the systemic blood pressure (170/110 mm.) which subsided after a month in the wards and for which no adequate reason could be given. Laboratory investigations showed an improvement in the blood values (red cells 4,750,000/c.mm. and haemoglobin 95%) but an abnormal serum colloidal gold reaction (543,000) with a normal plasma alkaline phosphatase of 2.7 Bodansky units. The patient was shown to be in positive nitrogen balance. Fishberg's urinary concentration and dilution tests were carried out with normal result. A further course of antispecific therapy was given.

A third liver biopsy was carried out on 24.4.47 and the sections appeared normal; they were not stained for amyloidosis. A barium swallow examination showed no evidence of oesophageal varicosities.

Owing to the intractably nature of the ascites and the uncertainty of the diagnosis, laparotomy was advised. The operative notes (6.8.47) recorded (Diverticulosis of

Case F/2. (Continued)

the colon and jejunum. Right lobe of liver grossly contracted and deeply fissured by multiple scars) what appeared to be a gumma on the posterior aspect of the right lobe causing pressure on the upper part of the portal vein; the portal pressure was 210 mm. saline and the inferior vena caval pressure 130 mm. saline. The peritoneum generally was somewhat thickened.

Despite further antispecific therapy, the general condition deteriorated and paracentesis continued to be necessary every few weeks; in November, 1947, a further laparotomy was undertaken at which a Talma-Morrison operation was attempted and a Murphy button inserted. Post operative death occurred. At post mortem examination amyloidosis of the liver (1,100 G.) and the spleen (225 G.) was present. The liver was otherwise normal except for a gumma of the caudate lobe associated with gross fibrosis locally. Portal thrombosis was stated to be absent.

Comment. Originally admitted as a case of ? nephritis, this patient presented a problem in diagnosis. The sudden appearance of ascites suggested portal thrombosis and the positive serological reactions indicated a causal or incidental syphilis. Initial liver biopsy studies showed normal appearances of the sections without amyloidosis; ultimate post mortem examination a year after the onset of the symptoms showed local syphilitic disease of the caudate lobe of the liver without apparent portal thrombosis; by this time amyloid disease had developed. The biopsies, carried out to assist diagnosis, failed to be of positive value except in excluding diffuse fibrosis and in excluding amyloidosis during the early part of observation.

Case F/3.

M. S., a married woman of 37 years, was admitted on 9.5.46 with a provisional diagnosis of cardiovascular syphilis. Of nervous disposition, she had always been readily fatigued, but lack of energy had become more compelling after the birth of her child in 1930. Breathlessness on exertion had been on insidious progress since about 1935. Since 1939 she had noticed that her ankles were occasionally swollen at night. In 1942 she was treated in bed for 6 weeks as a case of acute rheumatism with pain in many joints, principally the knees which were very tender. For four months prior to admission a persistent dry cough had disturbed her sleep, exertion-dyspnoea had further increased and swelling of the ankles had become constant. There had been no other illnesses apart from 'chorea' for which she had been treated in a large voluntary hospital for a year. There

Case F/3. (Continued)

were no points of interest in the family history.

On admission the patient was a poorly nourished nervous woman making slight abrupt movements of a choreiform nature. There was pallor with moderate cyanosis of the lips and was apparently breathless whether sitting or lying in bed. There was swelling of the ankles but induration prevented ready pitting on pressure; there was no oedema in the sacral area. The cervical veins were engorged. Clubbing of the fingers was present and there were rubbery mobile lymph glands palpable in the neck and in the right axilla. The pulse was regular and of average frequency; the blood pressure was 130/50 mm. The heart was enlarged to the left. There was a loud systolic murmur was present towards the apex and a short diastolic murmur in the aortic area; there was no thrill. The pulmonic second sound was accentuated. The spleen was enlarged to the level of the umbilicus and the lower edge of the liver was just palpable below the costal margin. Post-tussive rales were heard at both lung bases. Slight left facial paresis was present. There were a few pin-point haemorrhages at arterial bifurcations in the fundi. Physical examination was otherwise devoid of abnormality.

The urine contained protein + without other chemical or microscopical abnormality. The blood showed a moderate hypo-chromic anaemia; the white cells were 8,000/c.mm. and of average distribution except for a shift to the left of the Arneth count. The marrow was normoblastic. The blood sedimentation rate was 140 mm. in 1 hour (Westergren). Plasma proteins were 9.20 G.% (A/G = 2,53/6.70) with a positive Napier aldehyde test. Repeated blood cultures and a single marrow blood culture were all sterile. The Wasserman and Kahn tests were 'doubtful' on admission but gave 'negative' and 'doubtful' results respectively on repitition.

While the diagnosis was in doubt, treatment was symptomatic. Continuance of a low-grade irregular pyrexia together with transient microscopical haematuria led to the administration of a full course of penicillin as a possible case of bacterial endocarditis; no benefit accrued. Septic teeth were removed a few at a time and always under 'penicillin cover'. Some improvement in the general condition followed but the main features of pyrexia, splenomegaly, hyperglobulinaemia, valvular disease of the heart and occasional haematuria persisted unchanged. Ultimately the transient appearance of erythematous eruptions on the face and forearms led to provisional adoption of a diagnosis of lupus erythematosus disseminatus with Libman-Sachs endocarditis. Liver biopsy was carried out and sections showed that the

Case F/3. (Continued)

architecture of the organ was preserved and that there were mild fatty changes associated with depletion of the glycogen stores of the liver cells; slight round cell infiltration of the portal tracts was present and congestion in the centrilobular regions was apparent.

Three months after admission the general condition was sufficiently improved to allow discharge; three months later death occurred following haematemesis. The patient was not referred to hospital and no post mortem examination was carried out.

Comment. In this case, the diagnosis was apparently that of subacute lupus erythematosus with Libmann-Sachs endocarditis. Aspiration biopsy of the liver showed only the changes which may be seen in congestive cardiac failure of any causation.

Case F/4.

W. C., a grossly obese man of 64 years was admitted on 30.4.46 because of haematemesis with melaena which had occurred on the previous day for the first time in the patient's life. Pallor of his mucous membranes reflected the blood loss but there was nothing in the state of his past health or in the findings on physical examination to indicate a cause for the haemorrhage. He had had an unspecified 'dysentery' lasting for 5 weeks in 1938 whilst en routh home from India. He had suffered a mild flatulent dyspepsia on and off for many years. He had been an average but consistent consumer of beer and less often of spirits.

Laboratory investigations were uninformative and full radiological examination of the gastro-intestinal tract failed to show evidence of a lesion in the oesophagus, stomach, duodenum or colon. There was no suggestion of a haemorrhagic diathesis. Liver biopsy was carried out and sections of the material appeared entirely normal.

Recovery from the blood loss was uneventful and the patient discharged. He continued well until 23.12.46 when recurrence of bleeding necessitated readmission. He passed through a phase of mental confusion resembling Wernicke's encephalopathy ultimately to improve without further incident. Radiological investigations were repeated without any lesion bbeing discovered and gastroscopy was performed also without result. A second liver biopsy was carried out, again the liver appearing normal apart from some slight fatty changes. On 6.4.47 further melaena resulted in readmission; recovery from the haemorrhage was again uneventful. Barium swallow

Case F/4. (Continued)

examination again failed to give evidence of oesophageal varices or of peptic ulceration.

Comment. The diagnosis in this case was felt to lie between peptic ulceration and oesophageal varicosities secondary to hepatic fibrosis. Radiological examinations were not fully satisfying owing to the gross obesity. The complete absence of any pathological changes in the liver as shown by biopsy specimens was taken as strong evidence excluding 'cirrhosis' and a probable diagnosis of peptic ulcer was recorded despite the failure of radiology and gastroscopy to demonstrate such a lesion.

Case F/5.

J. I., male aged 45 years, had suffered constant epigastric pain during the previous three years; for two years the pain had extended through to the back and to the left side of the abdomen, being described as 'dragging' in the latter site. There had been no significant previous illness but his mother had died in 1919 of a disease stated to be splenic anaemia.

The only abnormal finding on physical examination was gross splenomegaly, the organ extending below the umbilicus almost to the iliac crest. The red cells numbered 5,200,000 per c.mm., with haemoglobin 106%, M.C.V. 88 cu.μ, and white cells 9,600/c.mm. In the stained film the red cells showed marked anisocytosis and poikilocytosis; a few normoblasts were present. There was a slight shift to the left in the differential count of the white cells but no immature forms were seen. Reticlocytosis was absent. Fragility of the red cells in normal saline, bleeding time and coagulation time were all normal. Sternal puncture failed on two occasions to yield marrow tissue. The urine was clear. Apart from a slight increase in the serum calcium (11.5 mgm.) the blood chemistry was normal. Aspiration biopsy of the liver showed normal architecture with dilation of venous sinusoids in places by what appeared to be haemopoietic foci; fibrosis was absent. Radiological examination of the skeleton showed a widespread osteosclerosis most probably due to Albers-Schonberg disease.

Comment. Enlargement of the spleen in this case was no doubt due to extra-medullary haemopoiesis which was reflected also in the presence of foci of blood formation in the liver as shown by a liver biopsy specimen.

Case F/6.

E. K., aged 49 years, had worked in coal-mines between the ages of 15 and 30 years, since when he had worked as a steel moulder. For 25 years he had suffered winter

Case F/6. (Continued)

bronchitis and dyspnoea on exertion had insidiously appeared. Twenty years previously he had had left-sided pleurisy and six years previous to admission he had been confined to bed for 10 weeks with a nephritis presenting the features of the Type II (Ellis) group.

Five weeks before admission he had had a rigor accompanied by pain in the right scapular region and by increased frequency of micturition. Shivering and chest pain lasted only a few days but, despite medication by sulphonamides, irregular pyrexia persisted and diarrhoea appeared 10 days before admission. Examination showed his general condition to be poor with evidence of loss of weight. Resonance of the right side of his chest was impaired and coarse rales were present. He was pale, there was oedema of the ankles and slight clubbing of the fingers. The blood pressure was 155/100 mm. and the peripheral arteries were palpable; there was no other abnormality of the heart or blood vessels. The abdomen was somewhat tumid with guarding in the right upper quadrant, but no evidence of ascites and no evident enlargement of the liver or spleen. There was low irregular pyrexia.

The urine contained protein, blood and granular casts; the specific gravity tended to be low and fixed about 1.006 to 1.010. Radiological examination of the lungs showed appearances consistent with a chronic inflammatory process in the right lung, consistent with chronic tuberculosis. The abundant purulent sputum was examined repeatedly for Myco. tuberculosis without avail; latterly a yeast-like organism was isolated which proved to be Monilia albicans. This fungus was shown to be pathogenic for laboratory animals. Blood examination showed hypochromic anaemia (red cells 2,830,000/c.mm., haemoglobin 49%) with a white cell count of 12,000/c.mm. (neutrophils 90%). The blood sedimentation rate was 105 mm. Westergren. Examination of sternal marrow showed there to be an excess of plasma cells, but no other significant abnormality was observed. Nitrogen retention was present (blood urea 57-123 mgm.). Blood culture and blood Wassermann reaction were negative.

Before the tests of pathogenicity on the yeasts had been carried through, diagnosis was felt to be that of chronic phthisis accompanied by amyloidosis. An intravenous congo red test was, however, negative. Liver biopsy was carried out and sections showed no histological abnormality; no deposits of amyloid substance were shown by appropriate staining.

Despite treatment, deterioration was progressive and death occurred three months after admission. Post mortem examination confirmed the chronic granulomatous nature

Case F/6. (Continued)

of the pulmonary lesions and the findings in the kidneys were consistent with the clinical diagnosis of type II nephritis. There was no evidence of amyloidosis.

Comment. Considerable difficulty in diagnosis attended this case and the ultimate opinion was that of moniliasis of the lungs associated with a chronic form of nephritis. Aspiration biopsy of the liver proved of value in aiding exclusion of amyloidosis.

Case F/7.

A. C., a warehouseman of 61 years, was admitted with a history of recurring haematemeses on the preceding day. There was no previous dyspepsia. Examination showed a man of good general condition; the blood pressure was 170/95 mm. and the liver edge was palpable about an inch below the costal margin. There were no other physical abnormalities and the haemoglobin value was 100%. Occult blood was present in the faeces for 10 days after admission (guaiac test).

Recovery was uneventful on a peptic ulcer regime with ascorbic acid. Investigations were then carried out to determine the cause of the haemorrhage. Barium examinations showed no abnormality of the oesophagus, stomach or duodenum apart from spasticity of the duodenal cap. Cholecystography demonstrated the presence of a calculus in a 'non-functioning' gall-bladder. Biochemical results included plasma alkaline phosphatase 4.4 Bodansky units, serum colloidal gold reaction 200000 and prothrombin index 92%.

In view of the hepatomegaly and the absence of evidence of peptic ulceration, liver biopsy was performed. Sections showed no histological abnormality.

Comment. In this case of haematemesis there was no guide clinically as to the cause of the blood loss and radiological investigations were equally fruitless. Liver aspiration biopsy served to exclude diffuse fibrosis of the liver as the primary lesion. A probable diagnosis of peptic ulceration was therefore accepted.

Case F/8.

Mrs. J. H., a housewife of 35 years, was admitted to a surgical ward because of pain below the left ribs following a sharp blow. She gave the history that a recent pregnancy was thought to be plural owing to the size of the abdomen. After delivery, however, a large mass remained palpable in the abdomen.

Examination revealed gross splenomegaly, the organ

Case F/8. (Continued)

extended below the umbilicus, and the presence of soft mobile enlarged glands in the neck. Blood examination showed a white count of 3,600/c.mm. with red cell and haemoglobin values within normal limits. A differential count showed neutrophil polymorphonuclears 60%, myelocytes 3.4%, lymphocytes 33.4%, monocytes 2% and unidentifiable cells 1.2%. As the question of subleukaemic leukaemia was raised, sternal puncture was performed and the marrow found to be hypercellular although of normal fat content. A differential count on this preparation showed neutrophil polymorphs 12%, metamyelocytes 10%, mtelocytes 14% and premyelocytes 2%. Normoblasts (25%) and lymphocytes (17%) accounted for the major part of the rest. Myeloblasts were slightly in excess of 1%.

A diagnosis of chronic subleukaemic myeloid leukaemia was adopted and liver biopsy carried out for academic reasons. Sections showed normal lobular architecture with mild fatty changes in the centrilobular zones. There was no evidence of leukaemic infiltration.

Comment. In this case of subleukaemic leukaemia biopsy study of the liver was carried out for academic purposes and showed only fatty changes; the infiltration of the organ so conspicuous a feature in post mortem material from cases of myeloid leukaemia was absent.