THE SURGERY OF HEPATIC TUMOURS

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THE tumours of the liver are both numerous and varied. So far, excision is the only means by which they may be cured. Although such operations are still uncommon, great strides have been made in this field during the past ten years. Surgical removal of a portion of the human liver is not, however, an utterly novel procedure. The first case was recorded in 1716 by Berta, who treated a madman with a self-inflicted knife wound of the right hypochondrium through which a part of the right lobe of the liver had prolapsed. On the day following the injury, Berta amputated the protruding portion and the patient recovered (Pettinari, 1957; Paolucci de Valmaggiore, 1955). Excision of a hepatic lobe had been successfully performed in the dog even earlier, by Zambeccari in 1680 (Jarcho, 1941). The first elective liver resection in man is attributed to Ohlshausen in 1882 and this was followed within a decade by many other reports (summarized by Keen, 1892, 1897, 1899), including those of Mayo Robson, Rushton Parker and Robert Jones in this country, Bastianelli in Italy, Langenbuch, Czerny, Eiselsberg and Hochenegg in Germany and Austria, and Terrillon and Doyen in France. In all, Keen tabulated records of 76 cases, including three of his own, with a known mortality of 15% in 74 of them. Thöle in 1913 brought the number up to 202 with 168 successes, while Warvi (1945) traced 223 fully documented resections for tumour and a further 347 references which were unobtainable, unproven or otherwise faulty.

The history of the subject falls into three periods. The first, up to the end of the nineteenth century, and covered by Keen's three reviews, is the primitive period. The indications for operation included anomalous lobes, gummata, echinococcal cysts, and tumours. In many cases an attempt was made to render the operation extra-peritoneal either by exteriorizing the liver before division, or else by stitching its cut margins to the abdominal incision at the end of the operation. The liver tissue was divided by various means, including scissors, cautery, and elastic rubber

ligatures. Hæmostasis was obtained by cautery, ligature and packing.

The second period, from Keen's last review (1899) to Warvi's paper (1945), may be described as the pre-anatomical period. Resections were carried out in one stage as intra-abdominal operations. Hæmostasis was usually secured by a chain of interlocking mattress sutures distal to which the liver could be safely incised, but the line of division took no account of the anatomical distribution of the vessels and ducts. One-stage intra-abdominal methods had been used by some surgeons even in the primitive period, notably among them being Langenbuch (1888), Voeltzkow (1889), Wagner (1890), Decès (1890), Tansini (1891) (all recorded by Keen, 1892).

In the third or modern period, covering only the last decade or so, liver surgery has been completely transformed by renewed anatomical studies using injection-corrosion methods. The knowledge so gained has led to the development of techniques of resection planned in conformity with the distribution of the vessels and ducts. This has coincided with improvements in anæsthetic methods, the surgery of access and the management of shock and metabolic disturbances while increased understanding of liver disease has led to the evolution of more refined methods of diagnosis. Modern surgical treatment of liver tumours frequently involves the removal of a half or more of the liver substance, and not only are such operations applicable to a greater number of cases than were the more limited excisions of earlier days; they also improve the prospects of cure.

As yet, few surgeons have recorded any really considerable personal experience of liver resection. Mention should be made of Pack (several reports), Brunschwig (1959) and Smith (1961).

This paper is based upon a series of 25 hepatic resections for various tumours occurring in a personal series of 47 hepatic resections performed by Professor V. Pettinari of the Clinica Chirurgica of the University of Padua (Table 1). Some of these cases have been described in detail elsewhere.

FIG. 1.—Cavernous hæmangioma of liver. Histological appearance. A, Case 23; B, Case 24.

(Pettinari, 1955a and b, 1957, 1959; Pettinari and Dagradi, 1960).

Pathology

The pathology of liver tumours has been very fully reviewed by Edmonson (1958), whose monograph should be consulted for further information. He recognizes the following primary tumours:

1. Adenoma:
 - (a) Liver cell.
 - (b) Bile duct cell (doubtful).
2. Carcinoma:
 - (a) Liver cell.
 - (b) Bile duct cell.
 - (c) Mixed liver and bile duct cell.
3. Miscellaneous:
 - (a) Hepatoblastoma.
 - (b) Mixed carcinoma and sarcoma.
 - (c) Mixed carcinoma of infancy and childhood, teratoma, combined carcinoma and sarcoma.
4. Hæmangioma, hæmangio-endothelioma, hæmangio-endothelial sarcoma.
5. Fibroma, lipoma, myxoma.
6. Sarcoma.
7. Rare or doubtful tumours; primary argentaffin tumours, adrenal rest tumours, squamous carcinoma.

We have treated four angiomas, three adenomas, five primary carcinomas, five carcinomas of the gall-bladder and one of the hepatic duct with extension into the liver, one carcinoma of the right kidney (hypernephroma) with direct infiltration of the liver, five carcinomas of the stomach with blood-borne hepatic metastases, and one metastatic malignant melanoma. The main features of these cases are shown in Table 1.

Angioma

This is the commonest benign tumour of the liver and many have been successfully resected (Macchitella, 1955). It may arise within the substance of the organ, at the surface, or even on a pedicle. 10% are multiple (Feldman, 1958), while size varies from less than 1 cm. across to enormous masses filling the abdomen and weighing up to 18,160 g (Major and Black, 1918). The majority are seen when about 7 to 10 cm. in diameter. Tumours causing symptoms, especially if the patient is under 40 years, are commoner in women (Schumaker, 1942), but in autopsy series males are affected more frequently (Edmondson, 1958). Symptoms may follow an increase in size and have been recorded during pregnancy (Ninard, 1950; Rubin, 1918). Possibly some endocrine cause favours enlargement and the

FIG. 2.—Hepatocellular adenoma (Case 22). (Above) Medium power view shows normal looking liver cells arranged in cords without portal tracts or lobal architecture and bounded by a fibrous capsule. (Below) High power of same.

appearance of symptoms in women between 20 and 50 years of age. Usually the angioma is cavernous in type and capillary forms are rare. Sometimes there are angiomas elsewhere, and occasionally the full Osler-Rendu syndrome is present (Brink, 1950; Smith and Lineback, 1954). Fatal intra-peritoneal hæmorrhage is the most important complication (11% of 103 patients—Niemann, 1957); pedunculated forms have been known to undergo torsion, and malignant change into a hæmangioblastoma is also seen.

Adenoma

By this term we understand a true tumour, showing a glandular structure typical of its organ of origin, of limited extent in time and space and exhibiting continuous growth. Published accounts in the past have been confused not only by the variety of names applied to liver adenomas but also by the variety of hepatic lesions to which the name adenoma has been applied. These have included frank carcinomas showing glandular pattern, nodules of regenerative hyperplasia in cirrhotic livers, and even anomalous lobes. Genuine adenomas are not rare. We saw three in the same time as our four angiomas, and Henson, Gray and Dockerty (1956) reported 13 compared

with 35 angiomas, though Edmondson (1958) found only six in a series including 176 angiomas. The tumour may occupy any part of the liver and is usually single. Some reported to be multiple, have probably been areas of nodular hyperplasia. The size is usually between 1 and 25 cm. across, about 10 cm. being a fair average. They are usually detected before middle age (our patients' ages were 7, 31 and 35). Some may be present at birth (Warvi, 1944) and undergo malignant change during childhood. Of the two histological types of adenoma recognized by Edmondson, we have only seen the liver-cell variety. Indeed, there is doubt whether the true bile-duct adenoma really occurs at all (Edmondson, 1958). Some of the cases reported as adenoma or cystadenoma of the bile ducts are probably examples of cystic malformation, which may ultimately become the seat of a cholangio-cellular carcinoma (Cruikshank, 1961). The liver-cell adenoma is a rounded, brownish tumour, consisting microscopically of normal-looking liver cells without lobular architecture and separated from the adjacent normal liver by a fibrous capsule. Being soft and bulky, it is liable to bleed either spontaneously or after minor injury, and such bleeding may be into the tumour substance or into the peritoneal cavity. This and the possibility of malignant change are the main dangers.

Primary Malignant Tumours

These constitute 1.2% of all malignant tumours in Europe, 2.5% in America, and 15-90% in Africa, Indonesia, China and Japan (Berman, 1951).

In Edmondson's series of 309 liver tumours, primary carcinoma (107 cases) stands second in frequency to angioma, liver-cell growths outnumbering bile-duct cell ones by approximately 3 : 1. Mixed liver and bile duct forms also occur as do mixed carcinoma and sarcoma. In children, hepatoblastomas, mixed tumours containing osteoid, and true teratomas are also seen (Froboese, 1952; Milman and Grayzel, 1951; Sheehan, 1930; and Williams, 1953). The maximum incidence is between 45 and 60 years of age (Behrend and Harberg, 1952), but liver tumours are also common in infancy. Steiner (1938) collected 77 cases under 16 years, 53% of them being under 2. Males predominate in the ratio 6 : 1 (Behrend and Harberg, 1952), and this predominance is even greater in infancy. The frequent correlation between liver-cell cancer and cirrhosis is well known and it is convenient to divide them into those occurring in a cirrhotic and those occurring in a non-cirrhotic liver. The significance of this correlation is not known but it is shown by all forms of cirrhosis, including such specific varieties

TABLE I
INDICATIONS, MAIN FEATURES AND RESULTS IN 47 CASES OF LIVER RESECTION

Serial No.	Diagnosis	No. of Cases	Sex	Age	Site	Operation	Course and Length of Follow-up	Known Deaths
1	Anomalous lobe	1	F	46	R. lobe	Local excision	Well 2/12	—
2	Rupture	1	M	24	R. lobe	Local excision	Died 5/7 post op.	1 (shock)
3	Sclero-necrotic nodule	1	F	43	L. lobe	Local excision	Cured	—
4	Subacute abscess (penetrating peptic ulcer)	1	M	52	Quadrante lobe	Local excision	Cured	—
5	Hypertrophic tuberculosis	1	F	51	L. lobe	L. lobectomy	Cured	—
6-9	Solitary cyst	4	M1 F3	29 45 63 64	L. lobe 1 R. lobe 3	Local excision 4	Cured 4	—
10-12	Polycystic liver	3	M2 F1	47 57 61	R. lobe 3	Local excision 3	Well (2 yrs.) 1 Fair 1 Dead 1/12 1	1 (liver failure)
13-17	Echinococcal cyst	5	M3 F2	7 18 32 39 50	R. lobe 4 L. lobe 1	Local excision 5	Well (2-4 yrs.) 5 (1 re-operated for further cysts after 4 yrs., now cured)	—
18-22	Cirrhosis	5	M3 F2	40 48 50 58 63	Total	Local excision 2 L. lobectomy 3	Well (up to 1 yr.) 3 Dead (4/7 and 4/7) 2	2 (liver failure)
23-26	Cavernous angioma	4	M1 F3	29 32 35	L. lobe 1 R. lobe 2 L. and R. lobes 1	Local excision 4 (1 double excision)	Unknown 2 Well (1 yr. and 5 yrs.) 2	—
27-29	Adenoma	3	M1 F2	7 31 35	R. lobe	Local excision 3	Well (3, 6 and 7 yrs.) 3	—
30-34	Primary carcinoma	5	M2 F3	35 35 45 57 64	L. lobe 4 L. and R. lobes 1	L. lobectomy 4 Extended L. lobectomy 1	Well (1, 1, 1 5/12) 3 Dead (9/7, 5/12)	2 (liver failure 1, recurrence 1)
35-39	Secondary extension from carcinoma of gall bladder	5	F5	51 59 65 65 66	R. lobe (gall bladder bed)	Local excision 4 R. lobectomy 1	Dead 5	5
40	Carcinoma of hepatic duct	1	M	50	R. lobe	Local excision	Well (18/12)	—
41	Carcinoma of R. kidney with direct infiltration	1	F	59	L. and R. lobes	Local excision	Dead (16/12)	1
42-46	Carcinoma of stomach (all blood-borne metastases)	5	M3 F2	58 62 65 66 66	R. lobe 5	Local excision 5	Unknown 1 Alive (18/12) 1 Dead (1, 2, 2)	3
47	Malignant melanoma	1	F	66	R. lobe	Local excision	Discharged alive No further information	—

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FIG. 3.—Primary carcinoma of the left lobe of the liver (Case 30). A, the excised lobe; B, histological appearance.

as hæmochromatosis. (Wilson's disease provides few examples, however, presumably because of the early decease of most sufferers.) Edmondson also noted that 35% of patients with carcinoma in a non-cirrhotic liver were chronic alcoholics.

A smaller number are found in normal livers, and some of these result from malignant change in a benign adenoma. Either lobe or both may be affected and the growth usually originates within the parenchyma but soon reaches the surface. It may be solitary and massive, multiple and nodular, or diffuse, infiltrating throughout the liver. Multi-nodular varieties may either arise multi-centrally, or they may arise by intra-hepatic metastasis from an originally single primary. The primary tumour may attain a considerable size before metastasis occurs. The colour varies, depending upon the combined effects of hæmorrhage, bile secretion and fatty degeneration. Bile-duct carcinoma is often harder and whiter because it contains more fibrous tissue. In the East, this form of cancer is sometimes associated with chronic cholangitis, due to clonorchis infestation of the bile ducts (Hou, 1956). Its association with cystic malformation of the bile ducts has already been noted.

Liver-cell growths in a non-cirrhotic liver may

sometimes attain large dimensions in the absence of metastatic spread. Edmondson records a massive carcinoma which was resected 18 months after diagnosis by biopsy and another, weighing 15 pounds, removed several years after the first appearance of a mass. On the other hand, multi-nodular growths, especially in cirrhotic livers, are usually fatal within three or four months of the appearance of symptoms. Distant spread may occur through any of the usual channels of dissemination; direct extension to the diaphragm or falciform ligament, lymphatic metastasis in the cœliac and pancreatic or pericardial groups of nodes, transcœlomic spread and venous embolism all occurring. Fortunately venous embolism usually occurs first in the portal branches, giving rise to intra-hepatic secondary deposits in the same liver segment as the primary tumour. Subsequent hepatic vein invasion, however, leads to pulmonary and other distant metastases.

Secondary Malignant Tumours

The main pathological facts about secondary tumour deposits in the liver are well known. From the point of view of liver resection, it is helpful to classify such tumours as follows:

1. Tumours arising by direct invasion (especially from gall-bladder, bile ducts, stomach and colon).

2. Peritoneal implants.
3. Lymphatic metastases, especially at the hilum.
4. Blood-borne metastases (via portal vein: gastro-intestinal tract and derivatives, or via hepatic artery: breast ovary, bronchus, kidney, etc.).
 - (i) Solitary, and localized multiple deposits.
 - (ii) Generalized multiple deposits.
- (a) Synchronous metastases.
- (b) Metachronous metastases.
5. Freakish metastases—retrograde growth of tumour thrombi, retrograde lymphatic permeation, etc.

Local Spread

Direct spread does not necessarily indicate an advanced stage of the disease. Such deposits often extend over the surface of the liver without great penetration in depth, and provided that both the primary tumour and the affected portion of the liver are technically resectable, total removal may be perfectly possible.

Carcinoma of the Biliary Tract

The spread of gall-bladder cancer to the liver is almost invariable and occurs early. It was found in 36 of Jones's 50 cases (72%) (Jones, 1950) and 33 of Glenn and Hays, 68 patients (48%) (Glenn and Hays, 1954). It occurs both by direct extension and through lymphatic channels, there being a close connection between the lymphatics of the gall-bladder and those of the liver (Fazio, 1952; Ottaviani, 1932). These connections involve not only the superficial lymphatics of the liver and gall-bladder, but also those on the hepatic surface of the gall-bladder and within the adjacent liver parenchyma. Lymph node involvement in the portal fissure is found in 50% of cases. The likely extent of liver invasion as suggested by the anatomical studies of Ottaviani includes the whole of the quadrate lobe and a moderate amount of the right lobe along the lateral border of the gall-bladder fossa. Gans and Bax (1955) show an even larger territory, including the right and left paramedian lobes (in Couinaud's terminology) and part of the right lobe.

In general, the same remarks apply to intra-hepatic spread from carcinoma of the bile ducts. Again this takes place both by direct extension and through the lymphatics and is both early and frequent.

Carcinoma of Stomach and Colon

Direct spread of carcinoma of the stomach to the liver, usually the left lobe, is also common,

occurring with approximately the same frequency as blood-borne metastasis (Raven, 1955).

Similar considerations apply to growths of the hepatic flexure of the colon with spread to the adjacent liver, for which liver resections (generally of part of the left and right lobes) may be combined with right hemicolectomy.

Other Visceral Carcinomas

Few examples of liver resection combined with nephrectomy for intra-hepatic spread from carcinoma of the right kidney have been recorded. Case 19 is an example. It required local excision of part of the left and right lobes. The operation, though difficult, was followed by satisfactory recovery, the patient was discharged in two weeks and survived for 16 months.

Blood-borne Metastases

We have operated upon five metastases from carcinoma of the stomach and one from malignant melanoma. The incidence of liver metastasis from growths in various sites in the gut has been analysed by Raven (1955). In summary, he found that out of 818 patients, liver metastases were present on clinical or visual assessment in 176 (21.5%), and partial hepatectomy was either carried out or would have been feasible in 32 of these (3.9%).

The question of surgery cannot arise if such deposits are present throughout the whole of the liver, but when only one is found, or when there are two or three confined to one anatomical segment of the liver, resection should be considered. It is worth while to distinguish between a synchronous metastasis (seen at the time of the operation for the primary growth) and a metachronous one (first discovered some time after the primary growth has been removed). A large solitary metachronous growth may well be presumed to be truly single since any emboli passing from the primary growth to the liver must have been transmitted before the primary growth was removed and if one deposit has had time to attain a large size the others would also have done so.

Clinical Features and Diagnosis

The manner of presentation and the means by which a diagnosis was reached in our cases are shown in Tables 2, 3, 4 and 5.

The discovery of a palpable tumour is undoubtedly the crucial step in diagnosis. In all ten patients in whom no tumour was found clinically, the true diagnosis was made only at laparotomy (Nos. 23, 24, 26, 36, 37, 42, 43, 44, 45 and 46 in Table 1). In the remainder the mass was recognized as a liver tumour in all but two—Nos. 35 and 40—and in five cases—Nos. 32,

TABLE 2
BENIGN TUMOURS

Case No. (Age and Sex)	Presenting Complaint	Mode of Diagnosis	Histology	Positive Investigations (i.e. showing abnormality)	Negative Investigations (i.e. normal result)
ANGIOMA					
23 (F. 29 yrs.)	Dyspepsia due to gall stones.	Accidental discovery at cholecystectomy.	Cavernous angioma.	Cholecystography (no function).	—
24 (F. 32 yrs.)	Dyspepsia due to gall stones.	Accidental discovery at cholecystectomy.	Cavernous angioma.	Cholecystography (stones)	—
25 (F. 35 yrs.)	Hepatic tumour noticed for 8 days.	Site demonstrated by investigations. Nature revealed by aortography. Confirmed at laparotomy.	Cavernous angioma.	Ba. meal and cholecystography (displacement). RPP. Aortography.	L.F.T.
26 (F. 52 yrs.)	Dyspepsia due to gastric ulcer.	Accidental discovery at gastrectomy	Cavernous angioma.	Ba. meal—lesser curve ulcer.	—
ADENOMA					
27 (F. 31 yrs.)	Many years symptomless tumour R.U.Q. Recent increase to size of adult head.	Site demonstrated by investigation. Nature suspected at laparotomy.	Hepato-cellular adenoma.	Ba. meal and retrograde pyelogram showed displacement. Anaemia.	L.F.T. Casoni.
28 (F. 35 yrs.)	5 yrs. large mass in R.U.Q. increasing to size of adult head. Periodic attacks of colicky pain. Recent increase of pain with dyspepsia and vomiting. Previous laparotomy. Lesion thought to be inoperable retroperitoneal tumour.	Site demonstrated by investigations. Nature suspected at laparotomy.	Hepato-cellular adenoma.	Ba. meal. Cholecystography and pyelography showed displacement.	L.F.T. Casoni.
29 (M. 7 yrs.)	4 yrs. intermittent mild pyrexia with diffuse abdominal pain.	Palpable mass in R.U.Q. size of a fist. Site demonstrated by investigations. Nature suspected at operation.	Hepato-cellular adenoma.	RPP.	No bruit, L.F.T. Casoni. Ba. meal.

Abbreviations:

R.U.Q. = Right upper quadrant C.M. = Costal margin
L.F.T. = Liver function tests R.P.P. = Retroperitoneum
R.P. = Retrograde pyelogram

TABLE 3
PRIMARY MALIGNANT TUMOURS

Case No. (Age and Sex)	Presenting Complaint	Mode of Diagnosis	Histology	Positive Investigations	Negative Investigations
30 (F. 35 yrs.)	4 mths. heaviness L.U.Q. with diarrhoea and occasional pyrexia. Recent appearance of rapidly growing tumour L.U.Q.—hard and irregular, with weight loss. R. lobe of liver also enlarged 1 finger breadth below C.M.	Clinical diagnosis of liver tumour.	Hepato-cellular carcinoma.	Ba. meal showed displacement of stomach.	Cholecystogram.
31 (M. 64 yrs.)	Jaundice 13 yrs. previously, 5 mths. distension after food, heaviness in R.U.Q.; constipation. Abdomen asymmetrical. Large irregular tender mass L.U.Q. with hard and soft areas. R. lobe 4 fingers enlarged.	Clinical diagnosis of liver tumour.	Cholangio-cellular adenoma.	L.F.T. Ba. meal—stomach displaced. RPP—spleen enlarged x10. In front of spleen, separate from it, mass with distinct wavy outline, probably part of L. lobe of liver.	Hb. Serum total proteins.
32 (M. 45 yrs.)	Sudden epigastric and R.U.Q. pain 10 days before admission. Disappeared in 2 days leaving heavy feeling. Liver enlarged to umbilicus, L. lobe hard and irregular and tender. Abdominal asymmetry with venous network in hypogastrium.	Clinical diagnosis of malignant liver tumour.	Hepato-cellular carcinoma.	L.F.T. Serum electrophoresis. Ba. meal—displacement of stomach. R.P.P. Aortogram. Splenoportogram.	Cholecystogram.
33 (F. 57 yrs.)	2 mths. heaviness, especially after food, progressive weakness, evening pyrexia, weight loss 5 kg. 1 mth., epigastric tumour. Abdomen protuberant. Epigastric mass, size of an orange. Firm. R. lobe enlarged 4 fingers.	Clinical diagnosis of malignant liver tumour.	Hepato-cellular carcinoma.	L.F.T. Serum electrophoresis. Ba. meal—displacement of stomach. Cholecystogram. RPP.	—
34 (F. 35 yrs.)	Few mths. mild pyrexia and R.U.Q. pain. R.U.Q. tender with fist-sized tumour.	Clinical diagnosis of liver tumour.	Cholangio-cellular carcinoma.	Cholangiogram.	Ba. meal. L.F.T.

TABLE 4
SECONDARY MALIGNANT TUMOURS—DIRECT EXTENSION TO LIVER

Case No. (Age and Sex)	Presenting Complaints	Mode of Diagnosis	Histology	Positive Investigations	Negative Investigation
CARCINOMA OF GALL BLADDER					
35 (F. 65 yrs.)	Many yrs. biliary dyspepsia. Recent increase in symptoms with continuous pain, weight loss and weakness. Hard liver, edge palpable.	At operation (contracted gall-bladder containing stones.	Solid undifferentiated carcinoma	Cholecystogram.	Ba. meal.
36 (F. 59 yrs.)	Typical history of cholecystitis.	At operation.	Solid carcinoma.	Cholecystography (large solitary stone).	—
37 (F. 66 yrs.)	Symptoms of cholecystitis for yrs. Recent increases in frequency and severity with fever and wasting.	At operation.	Solid carcinoma.	—	—
38 (F. 51 yrs.)	Biliary colic 3 yrs. before, but X-rays negative. Recent recurrence of R.U.Q. pain with wasting and tumour size of fetal head. Venous network across lower abdomen.	Clinical diagnosis.	Adeno-carcinoma.	Electrophoresis. L.F.T. R.R.P.	—
39 (F. 65 yrs.)	Many yrs. biliary dyspepsia, 2 yrs. R.H.C. tumour, 5 mths. fever and weight loss (10 kg.); hard, irregular painless liver edge with ovoid, stony, hard mass.	Clinical diagnosis.	Adeno-carcinoma.	Electrophoresis. L.F.T. Haematocrit 34.7%. Ba. meal—displacement of duodenum. Cholecystography and cholangiography. R.R.P.	—
CARCINOMA OF BILE DUCT					
40 (M. 50 yrs.)	Biliary colics, 3 yrs. with dyspepsia. Symptoms worse 2 mths. with weight loss (5 kg.). Mass palpable. Jaundice first appeared after admission.	At operation.	Cholangio-cellular carcinoma undifferentiated.	Cholecystogram (no function), 2 calcified shadows.	Electrophoresis. L.F.T. Ba. meal.
RENAL CARCINOMA					
41 (F. 54 yrs.)	Haematuria 3 times in 6 mths. R. renal tumour palpable.	Clinical diagnosis (renal carcinoma with probable spread to liver).	Undifferentiated renal carcinoma.	I.V.P. R.P. P.R.P.	—

TABLE 5
SECONDARY LIVER TUMOURS (BLOOD-BORNE METASTASES)

Case No. (Sex and Age)	Presentation	Mode of Diagnosis	Histology
42-46 (M. 66 yrs.) (F. 68 yrs.) (M. 65 yrs.) (M. 58 yrs.) (F. 62 yrs.)	All presented with clinical features of carcinoma of stomach verified by investigations and at operation.	Solitary metastasis 2-3 cm. across in R. lobe discovered at operation in all.	Confirmed histologically.
47 (F. 40 yrs.)	Rt. eye removed following injury 8 yrs. previously, 8 mths. swelling R.U.Q. 3 wks. pain and further swelling following lifting strain.	Clinical diagnosis of sub-capsular rupture (Ba. meal showed displacement) large necrotic haemorrhagic melanomatous tumour in R. lobe found at operation, unroofed and drained.	Confirmed histologically.

33, 38, 39 and 41—a complete pre-operative diagnosis could be made with reasonable confidence. Often there is no difficulty on clinical grounds in deciding that the tumour is hepatic in origin, but there are one or two misleading features which may give rise to difficulty. Keen (1899) described several cases in which there was a band of resonance between the tumour and the costal margin which led to diagnostic error. Sometimes, too, no distinct tumour is palpable, the whole liver appearing to be enlarged. Liver tumours may also be simulated by other upper abdominal swellings, most notably pancreatic cysts, though bulky swellings of the kidneys, spleen, stomach and omenta may also cause confusion.

Sometimes it is the presence of complications

which brings the patient to hospital. Superficial tumours may bleed into the peritoneal cavity, pedunculated ones may undergo torsion and benign ones are liable to malignant change.

Angioma

Angioma seems to be the liver tumour most likely to be correctly diagnosed, or at any rate suspected pre-operatively, particularly if large. Of 35 cases reported by Henson and others (1956b) 24 were discovered during a laparotomy performed for some other condition, while the other 11 were explored for symptoms thought to be due to the angioma. In three of our patients the angioma was a chance finding at laparotomy. The fourth presented with an enormous mass. Once a liver tumour has been recognized there are several clinical and radiological features which should arouse suspicion that it is an angioma. Sometimes variations in size may be provoked by ingestion of food, adrenalin injections, or local applications of heat or cold. (Successive radiological examinations provide a more sensitive index of such variations than clinical examination.) Either splenoportography or aortography may demonstrate the lesion as a coiled mass of vessels and in older patients calcification may be visible. Attacks of pain, sometimes colicky in nature, also occur. The risk of hæmorrhage, either spontaneous or traumatic, is quite considerable, as Niemann's figures (already quoted) prove.

Liver-Cell Adenoma and Carcinoma

These tumours have no characteristic symptoms as our cases show: the benign adenomas indeed often cause no symptoms at all. In nine of the 13 cases of Henson and others the tumour was discovered accidentally at operation. Of our three, all had a palpable mass, and in two symptoms were also present. In carcinoma the onset is often misleading with dyspepsia, pallor, weakness, wasting, pyrexia, or merely the presence of a symptomless lump. Clinical evidence of liver dysfunction, jaundice and ascites are usually late to appear. Slight or sub-clinical jaundice was present in a fifth of Edmondson's patients, but in none of ours. Fever is common and was found in all our cases, while hepatomegaly is invariable. The liver is usually firm and irregular and sometimes a venous hum may be heard over it. There may be evidence of other clinical conditions known to be associated with liver-cell carcinoma, such as cirrhosis or clonorchis infestation of the bile ducts. Splenomegaly is occasionally found (once in our series) and hæmatemesis may occur (particularly with liver-cell growths). Sometimes there is portal hypertension, which may be due

FIG. 4.—Benign adenoma of right hepatic lobe outlined by retroperitoneal pneumography (from Brearley, 1960).

to the presence in the tumour of numerous arterio-venous anastomoses, or to compression of the portal trunk as in our own Case 32, shown by splenoportography (Fig. 6), or to thrombosis of the portal vein (Hou, 1956).

Radiology

A plain film may confirm the suspicion of a liver tumour by showing displacement of the gas shadows of the stomach and colon, and barium studies may usefully supplement this. Occasionally calcification will be seen in the tumour.

Retroperitoneal insufflation performed according to the technique used in Padua (Brearley, 1961) yields a considerable amount of useful information. A small quantity (about 500 ml.) of air or oxygen is introduced into the pre-sacral space and then by adjustment of the patient's posture it is induced to pass into the upper abdomen. The movements of the gas are controlled by periodic screening, and by changes of posture. By this means it is possible to outline all the surfaces of the liver, demonstrating the relation between the tumour and the adjacent

FIG. 5.—Angioma of liver, aortographic appearance, arterial phase. Dye has not yet entered the tumour. Displacement and elongation of an arterial branch in the right lobe well shown.

organs. Areolar planes which fill with air are free of malignant infiltration, while areas which cannot be filled are probably invaded, so that a fair indication of operability is also obtained.

Hepatic arteriography may show displacement and interruption of the vessels (Fig. 6) or zones of increased vascularity, seen particularly in secondary deposits (whose blood supply is derived entirely from the hepatic artery).

We inject the contrast medium by puncturing the aorta at the level of the 12th thoracic vertebra. Serial films are taken at 1 and 2 seconds (arterial phase), 3, 4, 6 and 8 seconds (parenchymal phase) and 11, 13, 15 and 18 seconds (venous phase). We prefer this to selective arteriography by catheterization because it shows the anatomical arrangement of the hepatic artery and any possible anomalies of number or distribution (not infrequent in our experience) which may be important when surgery is contemplated.

Splenoportography may show sharp interruption or distortion of the intra-hepatic vessels, large avascular areas, and in the presence of massive growths, compression or blockage of the portal trunk, leading to the development of anastomotic channels (as in Case 32). In the absence of splenomegaly it is wise to defer this investigation until near the time of operation in case of damage to the spleen.

Retrograde injection of medium into the catheterized hepatic veins (Servello and Dalla Palma, 1954) may show similar appearances or the medium may pass into irregular cavities in the tumour parenchyma.

Laboratory Tests

Although the common liver function tests and especially those flocculation reactions thought to be connected with the α and β globulins are often disturbed, there is no characteristic pattern peculiar to liver tumours. We have found electrophoresis of the serum proteins extremely helpful however. Usually an increase is found in the α and β globulins, especially the α_2 fraction (Rafski, Weingarten, Krieger, Stern and Newman, 1950; Seibert, Seibert, Atno and Campbell, 1947). Two of our primary tumours showed marked elevation of the α_2 fraction, while the β globulin appeared to be increased more markedly in the presence of secondary tumours. Often these changes are accompanied by a considerable reduction of the albumin (Fig. 7).

Other possible findings in malignant tumours include thrombocytosis (Feasby, 1945) and hypoglycaemia (Thompson and Hilferty, 1952; Edmondson and Steiner, 1954). This is attributed to mopping up of glucose by the neoplastic cells which grow rich in glycogen, to such an extent that the normal liver may become depleted and unable to maintain the normal blood glucose (McFadzean and Yeung, 1956). In children there may be decalcification of the skeleton (hepatic osteomalacia) and hyperlipaemia (Hansen, Zeigler and McQuarrie, 1940) which may lead to excessive accumulation of lipoids in the reticulo-endothelial cells.

Radioactive Isotope Methods

Both Rose-bengal (which is taken up by the

FIG. 6.—Primary carcinoma left lobe of the liver (Case 32).

A, Aortography, arterial phase. Normal vasculature in right lobe. There is an absence of branches passing to the left.

B, Splenoportogram. Absence of branches to the left. Compression of the distal splenic and proximal portal vein.

parenchymal cells) and colloidal gold (which is taken up by the reticulo-endothelial cells) may be made radioactive and when administered intravenously both are concentrated in normal liver but not in tumour tissue. Scanning of the liver

will then disclose zones of absent or diminished radioactivity corresponding to the sites of the tumours. We have no experience of this method which is still in the experimental stages, but it appears to be highly promising (Friedell, Mac-

FIG. 7.—Primary carcinoma of liver (Case 33). Histological appearance of the tumour at low, medium and high powers. Inset shows (below) serum protein electrophoretic strip and (above) densitometer scanning.

Intyre and Rejali, 1957; Fee and Fedoruk, 1960; Helander, Jonsson, Larsson, Lindbonn and Odman, 1958).

The information collected by these means is usually sufficient to sustain a pre-operative diagnosis, or at any rate to determine the need for laparotomy. In genuine doubt and difficulty, needle biopsy of the liver (which is generally quite harmless even in cases of tumour) and peritoneoscopy will offer additional information.

Treatment

General considerations

Some tumours which appear to the naked eye to be benign prove on histological examination to be malignant. Others may undergo malignant change later, or give rise to fatal hæmorrhage. All should therefore be removed, irrespective of whether they have been diagnosed pre-operatively or discovered inadvertently at laparotomy. Since even a small hæmorrhage greatly increases the difficulty, excision should be undertaken as soon as possible.

Of the frankly malignant tumours, the diffuse forms, both nodular and infiltrating, are plainly beyond surgical cure, but this does not exclude all multiple tumours; if the nodules result from portal embolism they will all lie in the same anatomical segment as the primary growth and this type of spread often precedes the appearance of more distant metastases in lymph nodes, lungs or diaphragm. The propagation of tumour

thrombus through the hepatic vein to the vena cava or right atrium is very rare (Edmondson, 1958), as is retrograde spread in the portal vein.

In the case of secondary malignant deposits arising by direct extension, removal of the affected portion of the liver is simply a complementary part of radical resection and for reasons already given it is usually sufficient to divide the liver 2 or 3 cm. beyond the visible limits of the tumour. In the case of gall-bladder cancer, the necessary extent of the excision is still debated. Simple removal of the gall-bladder and its bed is certainly inadequate as our own and many others' long-term results show. Pack (1961) describes an operation which involves removal of the central portion of the liver, leaving the left anatomical lobe and the lateral portion of the right lobe, but he does not exactly indicate whether he has himself performed it.

Of blood-borne metastases there is no doubt that the best results are to be looked for among the solitary, massive, metachronous deposits, but large, single metastases or well-localized clusters seen at the time of the primary operation are well worth removing. Such masses do not necessarily require a very wide excision and all five of our cases treated in this way survived beyond one or two years.

Note on Rare Tumours

Among the rare tumours of the liver, fibroma, neuro-fibroma, neurinoma, lipoma and myxoma

call for little comment. Of greater interest are the carcinoid tumours. There are a few of these on record in which careful search has failed to disclose any extra-hepatic primary site of growth (Edmondson, 1958; Hartmann, 1920; Peyron, Corsy, Surmont, Robert and Gleize-Rambal, 1924; Stanley, 1958; Cruickshank, 1961). These may have arisen primarily in the liver, since argentaffin cells are found in the intra-hepatic bile ducts. The majority of hepatic carcinoids, of course, are secondary deposits from a primary growth in the gut or occasionally the bronchi. Both primary and secondary deposits are slow-growing and the main threat to life comes from the carcinoid syndrome. This occurs when there are substantial deposits either in the liver or outside the portal system altogether, and is thought to be due to the release of serotonin into the general circulation (Pernow and Waldenström, 1954). Serotonin released by a primary tumour in the gut is destroyed by monoamine oxidase in the liver and the severity of the symptoms is more or less proportional to the mass of active tumour tissue elsewhere. The implications of these facts are obvious. Secondary deposits should be excised whenever possible. Even if the primary growth is inoperable or not all the liver metastases can be resected, removal of those which are amenable to surgery will reduce the total secreting mass with corresponding benefit. Successful resections of carcinoid tissue in the liver have been reported by Hartmann (1920), Ogilvie (1953), and Wilson and Butterick (1959).

Surgical Principles

The importance of pre-operative replenishment of the blood volume and the body stores of protein and vitamins is now universally recognized: no operation calls more for more preparation than a hepatic resection. The liver is unique among the organs of the body in that removal of a portion of its substance leads to active regeneration of the remainder, so that the original weight of the organ is regained in about a fortnight's time. This process has been very fully studied in the rat (Harkness, 1957; Dagradi, De Candia and Bellini, 1958; Dagradi, Bellini, De Candia and Crucitti, 1958) and there is ample evidence to indicate that the human liver behaves similarly (Pack, Miller and Brasfield, 1955). In the rat subjected to a 70% resection, the weight of the residual liver has approximately doubled in about 36 hours, trebled in about five days, and has regained the original weight in about 14 days. This requires enormous quantities of protein and it has been shown experimentally that in protein-starved animals regeneration is hindered (Brues, Drury and Brues, 1936; Vars and Gurd, 1947).

FIG. 8.—The liver from below showing the principal plane and the main branches of the portal vein.

FIG. 9.—The liver from in front showing the principal plane and the main hepatic veins.

There is also experimental evidence in favour of vitamins A and B, liver extracts and, if required, vitamin K. Simultaneous replacement of blood lost at operation is also essential.

Anæsthesia

We have used light hypothermia in five cases and have been greatly impressed with its advantages. Coagulation defects have not been a problem nor has ventricular fibrillation, which is unlikely to develop in a non-cardiac operation conducted at a body temperature above 30° C. The field is quiet and comparatively bloodless and in the event of hæmorrhage from the liver, temporary hæmostasis by hilar compression may be

FIG. 10.—The liver from below showing line of section for left lobectomy and its relation to the arcade of the left branch of the portal vein.

FIG. 12.—The liver from below showing line of section for extended right hepatic lobectomy and its relation to the branches of the portal vein.

FIG. 11.—The liver from in front showing the line of section for left lobectomy and its relation to the left hepatic vein.

FIG. 13.—The liver from in front showing the line of section for extended right lobectomy and its relation to the left hepatic vein.

maintained for periods exceeding 15 minutes (the maximum which is considered to be safe at normal body temperature). Shock due to reflex disturbances is much reduced, less anaesthetic agent is required, and analgesia persists for about 24 hours after operation, reducing the need for sedative drugs.

Surgical Technique

Access. Excision of the left half of the liver can be carried out through the abdomen and a vertical mid-line incision is usually adequate. In case of difficulty it may be extended upwards by excision of the xiphoid and mobilization of the costal margin, and if that is not enough the lower part of the sternum may be split. Removal of

the right half requires a right-sided thoraco-abdominal incision at about the level of the 8th rib. If there is doubt about the form the resection will take, a transverse epigastric incision can be used, extending it into an intercostal space to remove the right half of the liver or converting it into an inverted 'T' to deal with the left half. An operable tumour may be removed in one of three ways: enucleation, local excision, and anatomical resection.

(1) **Enucleation.** This is a suitable for a few benign tumours, especially if they are superficially placed and have a well-developed capsule. Angiomas occasionally lend themselves to the method as do the rarer connective tissue tumours.

(2) *Local removal.* Although old-fashioned and of limited usefulness, this method should not be scorned altogether. It is applicable to peripherally situated, circumscribed tumours and those having a pedicle or situated at the tip of a long prolongation of liver tissue, such as a Riedel's lobe. Haemorrhage may be overcome by a combination of interlocking mattress sutures, transfixion ligation of major vessels, absorbable sponge, and during the actual excision, judicious compression of the liver substance between the fingers of an assistant or in an emergency temporary hilar compression. A wedge-shaped incision beginning at the liver margin is the usual form which the operation takes. Special attention must be paid to dangerous areas, particularly the fissure of the ligamentum teres where the left branch of the portal vein curves round to supply the quadrate lobe. Resection too far to the right at this point divides the arcade and deprives the quadrate lobe of its blood supply. Similarly, the left hepatic vein follows the same plane more deeply in the liver substance and a line of section to the right of its course will deprive the same area of its venous drainage leading to congestion and secondary haemorrhage (Figs. 10 and 11).

(3) *Anatomical Resection.* This method applies to the liver, the principle already well established in lung surgery, of removing segmental units after first ligating and dividing their vascular and ductal connections. For detailed information on the vascular anatomy of the liver the original accounts of Elias and Petty (1952), Gans (1955), Couinaud (1957) and Hobsley (1958) should be consulted. The picture which emerges is of a liver whose internal arrangement bears little relation to the lobes of classical anatomy which are limited by superficial indentations of no structural significance. The main division is into right and left halves separated by a plane (the principal plane of the liver) intersecting the inferior surface along a line from the fundus of the gall-bladder, crossing the bifurcation of the portal vein, to the left border of the inferior vena cava. On the superior surface the line of intersection joins the same end-points, more or less by the shortest route. The two halves are the separate territories of the right and left branches of the portal vein, hepatic artery and bile duct. The middle hepatic vein runs between them in the principal plane, receiving tributaries from either side (Fig. 9). The quadrate lobe and part of the caudate lobe are therefore constituents of the left half, while the caudate process belongs to the right. Both halves may be further divided into segments (four are usually recognized on each side). On the right side this is of little practical interest since the segmental hila lie deep in the liver and the superficial boundaries cannot be marked

out precisely. For this reason it is usually more satisfactory when confronted with a lesion of the right half requiring only local removal, to perform a wedge excision. On the left side, however, removal of the anatomical left lobe (i.e. that part of the left half lateral to the falciform ligament) is a perfectly satisfactory undertaking (Figs. 10 and 11). Using much the same line of section excision of the right half may be extended to include the paramedian part of the left lobe (Figs. 12 and 13).

The left and right hepatic veins which run through the centres of their respective halves resemble the middle vein, in that they lie in planes separating different portal territories—the lateral and paramedian segments of each liver half. On the left side this corresponds with the plane of the falciform ligament. Variations in the venous drainage are well illustrated by Reifferscheidt (1957), and useful hints on their recognition are given by Lloyd Davies and Angell (1957). There are also several short, thin veins running from the liver to the vena cava where these two structures lie in contact with one another.

The forms of anatomical resection which were in favour are four: right hemihepatectomy, left hemihepatectomy, extended right hemihepatectomy and left hepatic lobectomy. Removal of either or both of the anterior segments of the left lobe is also perfectly feasible, but the central hepatectomies described by Pack (1961) and Couinaud (1957) do not attract us, nor do other forms of segmental excision of parts of the right lobe. The points of division of the portal structures and hepatic veins in these various operations are shown in Figs. 8 to 13. Further details of operative technique are given by Pettinari (1957) (who first carried out a left lobectomy with previous hilar ligation in 1940), Smith (1958 and 1961), Raven (1949), Lloyd Davies and Angell (1957), Lortat-Jacob and Robert (1952) (who first performed right hemihepatectomy in 1951), and many others.

Results

Hepatic resection has never been as dangerous an operation as is generally supposed. Of the 76 cases collected by Keen in 1899, 63 recovered, 11 died, and the outcome was unknown in two. Of Pettinari's 47 cases (Table 1), among 29 with non-malignant conditions there were four post-operative deaths (one shock—resection for traumatic rupture; three liver failure—two cirrhotic and one polycystic liver), while among the patients undergoing operation for benign tumours there were no deaths at all.

The long-term result of operation for malignant tumours is influenced by many factors, of which

the selection of cases is perhaps the most important. There are few series of any size followed up for any length of time available for comparison. Brunschwig (1953), out of 22 patients had seven who survived for periods between 4 months and 5 years. Reifferscheid (1957) collected reports of 21 patients with primary carcinoma of the liver. There were three post-operative deaths, and of the other 18, 13 survived for periods between 1 and 7 years. Of Smith's nine right hemihepatectomies or hepatic lobectomies, for primary and secondary tumours, there were one operative death and three deaths from residual malignant disease (one at 6 months and two at 18 months), while five had survived for periods of 2 years, 2 years, 3 years, and 4 years. One of the 3-year survivors had evidence of residual disease, but the remaining four were well. Of our five primary carcinomas, there were one post-operative death and one late death from recurrent disease. The other three are alive and well after 17 months, 1 year and 1 year. In none of these patients was the liver cirrhotic.

The operations for carcinoma of the gall-bladder are particularly disappointing, all five patients

having died, one at the conclusion of a right lobectomy and the remaining four at varying intervals following cholecystectomy with local hepatic resection. These results further demonstrate the inadequacy of combining a purely local form of hepatectomy with cholecystectomy. Pettinari (1957) tabulated 67 cases treated in this way and of 27 who were followed up only six survived for periods between 1 and 7 years (the 7-year survivor was reported by Glenn and Hayes, 1954). Better results may be expected from right hepatic lobectomy (which includes the gall-bladder) and Smith (1961) has a patient so treated who is alive and well after 3 years.

Of our remaining eight patients with metastatic tumours, only two are known to have survived as long as 18 months. Considering the nature of their lesions, this is hardly surprising, for metastatic melanoma, carcinoma of the stomach with synchronous blood-borne liver secondaries, hypernephroma directly infiltrating the liver, and primary carcinoma of the bile ducts are unhelpful conditions from the start. The survival of even two suggests that liver resection is worth undertaking in such cases whenever it is feasible.

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