Summary and Conclusions

The *iron* content of the liver of a cirrhotic patient suffering from haemochromatosis was shown to be 50 times the mean value—9,100 compared with 183 $\mu\text{g./g.}$ In general, iron concentrations showed a wide spread, but no significant variation from disease to disease.

The liver content of *zinc* appears to be reduced in cirrhosis and carcinoma of the liver. Similarly with *cobalt*, but there are gross irregularities which may be due to the administration of substances such as vitamin B₁₂ which contain cobalt.

With *copper*, the most significant result of our investigations has been the discovery that in primary biliary cirrhosis the mean copper content of the liver is 30 times normal—220 $\mu\text{g./g.}$ as compared with 6.9 $\mu\text{g./g.}$ In Wilson's disease the mean copper content is 128 $\mu\text{g./g.}$ A preliminary test suggests that urinary copper excretion in primary biliary cirrhosis is markedly increased when penicillamine is administered. Interference with the excretion of copper by an obstruction to the bile-ducts does not appear to be the cause of the copper retention.

In two cases of cirrhosis in which *gold* had been administered therapeutically many years previously, the gold content of the livers, normally about 0.057 $\text{m}\mu\text{g./g.}$, was found to be 3,500 and 210 times this quantity. The first patient died of primary cancer of the liver.

Arsenic is another heavy metal known to induce cirrhosis. Four out of seven arsenical cirrhotics have developed cancer of the lung or skin.

These findings, so far fragmentary, suggest that the role of minute quantities of heavy metals in the aetiology of certain types of cirrhosis may be appreciable. Their part

in the causation of cancer of the liver remains to be investigated.

We are grateful to the physicians and surgeons of St. Bartholomew's Hospital and the Royal Marsden Hospital who have allowed us to use material from their patients, and to others, such as Dr. J. M. Walshe and Dr. E. M. Darmady, who have sent us pieces of liver; to Dr. F. Lees, who estimated the urinary copper excretion; and to Mr. M. A. Lambert and Mr. P. Ambrose, attendants in the post-mortem departments of St. Bartholomew's and the Royal Marsden Hospitals, and Mr. F. Lawrence, Officer at the Coroner's Court, Golden Lane, for their helpful and willing co-operation in the collection of specimens from all types of cases. Professor A. Wormald, F.R.S., and Professor W. V. Mayneord originally suggested analysis by activation, and Dr. R. A. Allen carried out the early tests for gold and arsenic.

REFERENCES

- Buchanan, W. D. (1962). *Toxicity of Arsenic Compounds*. Elsevier Publishing Co., Amsterdam, London, and New York.
 Bush, J. A., Mahoney, J. P., Markowitz, H., Gubler, C. J., Cartwright, G. E., and Wintrobe, M. M. (1955). *J. clin. Invest.*, **34**, 1766.
 Cameron, Sir R., and Hou, P. C. (1962). *Biliary Cirrhosis*, p. 156. Oliver and Boyd, London and Edinburgh.
 Cumings, J. N. (1951). *Brain*, **74**, 10.
 — (1962). *Proc. Nutr. Soc.*, **21**, 29.
 Gubler, C. J., Brown, H., Markowitz, H., Cartwright, G. E., and Wintrobe, M. M. (1957). *J. clin. Invest.*, **36**, 1208.
 Mahoney, J. P., Bush, J. A., Gubler, C. J., Moretz, W. H., Cartwright, G. E., and Wintrobe, M. M. (1955). *J. Lab. clin. Med.*, **46**, 702.
 Parr, R. M., and Taylor, D. M. (1963). *Phys. in Med. Biol.*, **8**, 43.
 Recommendations of the International Commission on Radiological Protection (1959). *Report of Committee 2*. Pergamon Press, London.
 Underwood, E. J. (1956). *Trace Elements in Human and Animal Nutrition*. Academic Press, New York.
 Vallee, B. L., Wacker, W. E. C., Bartholomay, A. F., and Hoch, F. L. (1959). *Ann. intern. Med.*, **50**, 1077.
 Walshe, J. M. (1956). *Lancet*, **1**, 25.

HEPATOMA IN CIRRHOsis

BY

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Primary carcinoma of the liver has attracted little attention in Great Britain although extensive studies have been made in tropical countries and in the U.S.A. Stewart (1931), in a review from Leeds of precarcinomatous lesions of the alimentary tract, found only 14 cases of primary liver carcinoma in a series of 12,800 necropsies over a period of 22 years (1910–31). However, Parker (1957) and reviewers in the U.S.A. (Macdonald, 1956; Benner and Labby, 1961) have suggested a higher incidence. Experience during the past two years has supported this view and has led to an examination of records for 23 years at St. Thomas's Hospital. The results of the present series have been compared with reports from Europe and the U.S.A. Comparison with studies from other countries has not been attempted.

Material and Method

The case records and necropsy reports of primary liver carcinoma for the years 1940–62 have been studied. There were 39 cases of carcinoma (35 male, 4 female), 10 of which had been personally observed during life, and 157 cases of cirrhosis (115 male, 42 female). These figures

do not reflect the experience of a unit with a special interest in liver disease. In each case the diagnosis has been confirmed by necropsy and subsequent histological review by one of us (H.S.). The investigation has been restricted to malignant hepatoma and cholangioma, excluding carcinoma of the hilar bile-ducts, and a small number of rare tumours (malignant haemangioma, sarcoma, hepatoblastoma). Cirrhosis has been accepted only where nodular regeneration with diffuse fibrosis or post-necrotic scarring was present (Fifth Pan-American Congress of Gastroenterology, 1956). Primary biliary cirrhosis, fibrosis due to chronic biliary obstruction, and cardiac cirrhosis have been excluded. A further nine cases of primary carcinoma diagnosed in life through biopsy have been omitted since necropsy was not performed.

Results

Data on the incidence of primary carcinoma of the liver and cirrhosis are presented in Tables I to V. Results from other studies are also included in Tables I and II.

Clinical Features.—The detection of malignant change in cirrhosis is notoriously difficult, and experience in this series has not brought to light any special features diag-

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nostic of the condition. The many symptoms and signs described in hepatoma are of course often present in cirrhosis alone. However, a combination of circumstances, together with an appreciation of the frequency of primary carcinoma, may suggest the correct diagnosis. A patient known to have cirrhosis may develop upper abdominal pain, particularly over the liver, and different in character from ulcer pain. The general condition deteriorates unexpectedly; the liver paradoxically may enlarge and occasionally masses or a friction rub may be found. The downhill course is rapid, death usually occurring within six months.

The diagnosis in the present series was made as follows: needle biopsy in 5 cases, laparotomy in 7, and necropsy

in 27. In six cases needle biopsy failed to disclose the tumour.

Biochemical Changes.—The two most commonly reported abnormalities in hepatoma are a high serum alkaline phosphatase and an elevated α_2 -globulin. In the present series the alkaline phosphatase exceeded 30 units (King-Armstrong) in about half the cases. Provided that other causes are excluded, a raised figure may suggest hepatoma but is not diagnostic, since high levels are occasionally found in uncomplicated cirrhosis. The electrophoretic pattern was that usually seen in cirrhosis—namely, an increase in the gamma-globulin fraction. A raised α_2 -globulin would no doubt be more helpful in the absence of cirrhosis (Otaki *et al.*, 1960).

Pathology

The majority of primary hepatic carcinomas occurring in this country arise from liver cells rather than from the intrahepatic biliary system. In the present series 20 of the 22 cases identified as liver-cell cancers were associated with cirrhosis, and the malignant change was a multicentric process which originated as regenerative hyperplasia. Most of the tumours secreted bile and were often macroscopically bile-stained. Growth had usually extended into both the hepatic and portal veins, and this explains the frequency with which clot was found in these vessels at necropsy. Macroscopic thrombosis of the portal vein should suggest the presence of malignant change in a case of cirrhosis. Hepatoma should not be excluded on the macroscopic appearances alone, since section will often reveal unsuspected areas of growth. The microscopical appearances of the liver-cell tumours showed considerable variation, including large hyperchromatic and multinucleate cells, often with polyploidy in addition to numerous ordinary mitoses, and spindle cells. In most cases there was secretion of bile which escaped into immature canaliculi. In four cases many of the nuclei of both tumour and normal liver cells were occupied by eosinophilic bodies resembling inclusions. No correlation was found between the histological varieties of growth and the prognosis; neither could any aetiological significance be attached to the presence of inclusions. With one exception (a deposit in the femur) distant metastases were limited to the lymph nodes of the porta hepatis and to the lungs.

Of the 13 cases of malignant cholangioma only seven were associated with cirrhosis. Where cirrhosis was absent the tumour occurred as a solitary mass of pale tissue largely confined to one lobe of the liver. Microscopically the cholangiomas were well differentiated and consisted of non-secreting tubular growths resembling the small interlobular bile-ducts from which they had developed. In one instance this tumour arose multicentrically from bile-duct hamartomas.

In four cases the tumour presented a mixed appearance and it was not possible to determine the site of origin.

Discussion

Primary carcinoma of the liver is a rare tumour in temperate zones. The present series shows an incidence of 0.53% of all necropsies, which although high is in general agreement with reports from Europe and the U.S.A. (Table I).

It is accepted that the majority of primary liver cancers originate in cirrhotic livers, but the frequency of malignant change in cirrhosis is difficult to assess. The concept of the pathology of cirrhosis has differed between observers.

TABLE I.—Incidence of Primary Carcinoma of Liver at Necropsy in Europe and U.S.A.

Authors	Years Reviewed	Total No. of Necropsies	Incidence of Primary Carcinoma
Stewart (1931)	1910–31 U.K.	12,800	0.11% (14)*
Wilbur <i>et al.</i> (1944)	1898–1942 U.S.A.	11,045	0.44% (49)
Spat and Grayzel (1948)	—1946	4,731	0.23% (11)
Berman (1951)	1900–47 Europe	248,053	0.14% (361)
	1916–43 U.S.A.	108,632	0.27% (296)
Macdonald (1956)	1917–46	15,491	0.34% (53)
	1947–54	7,623	0.72% (55)
Edmondson and Steiner (1954)	1918–53	48,900	0.20% (100)
Halpert and Erickson (1955)	1949–54	1,400	2.00% (28)
Parker (1957)	1919–55 U.K.	17,732	0.30% (53)
Present series	1940–62	7,366	0.53% (39)

* Number of cases in parentheses.

TABLE II.—Incidence at Necropsy of Cirrhosis Alone and With Primary Carcinoma

Authors	Total No. of Necropsies	Incidence of Cirrhosis	Incidence of Primary Liver Carcinoma in Cirrhosis
Stewart (1931)	12,800 U.K.	2.10% (269)*	3.35% (9)*
Wilbur <i>et al.</i> (1944)	11,045 U.S.A.	4.22% (466)	5.8% (27)
Macdonald (1956):			
1917–46	15,491	8.65% (1,340)	2.98% (40)
1947–54	7,623	13.9% (1,062)	3.96% (42)
Hall <i>et al.</i> (1953)	16,600	4.71% (782)	2.68% (21)
Halpert and Erickson (1955)	1,400	10.0% (140)	13.6% (19)
Parker (1957)	17,732 U.K.	1.04% (184)	16.3% (30)
Present series	7,366	2.13% (157)	19.1% (30)

* Number of cases in parentheses.

TABLE III.—Incidence of Primary Carcinoma in Cirrhosis by Five-year Periods, 1943–62, in the Present Series

Years	Total Necropsies	Incidence of Cirrhosis	Incidence of Primary Carcinoma in Cirrhosis
1943–7	1,028	1.35% (14)*	14.3% (2)*
1948–52	1,672	2.69% (45)	11.1% (5)
1953–7	2,181	1.93% (42)	19.0% (8)
1958–62	2,249	2.36% (53)	28.3% (15)

The years 1940–2 are omitted. Figures for this period are: necropsies, 236; cirrhosis, 3; hepatoma, 0.

* Number of cases in parentheses.

TABLE IV.—Relationship of Tumour Cell Type to Variety of Cirrhosis

	Post-necrotic Scarring	Diffuse Fibrosis	No Cirrhosis
Hepatoma	11	9	2
Cholangioma	5	2	6
Mixed	—	3	1

TABLE V.—Incidence of Active Chronic Peptic Ulcer at Necropsy

	Total No. of Cases	Gastric Ulcer	Duodenal Ulcer	Incidence of Ulcer
Cirrhosis alone	127	6	12	14.2%
with hepatoma	30	4	3	23.3%

Where the term embraces minor disturbances in the liver the incidence of malignant change is low, while if the diagnostic criteria are stringent the incidence appears higher (Parker, 1957). For this reason the results in Table II cannot strictly be compared, and serve only to give a general impression. Adopting the same criteria as the present series, Sherlock (1958) found an incidence of carcinoma in cirrhosis of 14%.

Table III shows that malignant change has been recognized more frequently in successive five-year periods, although undue emphasis should not be placed on this increase owing to the small number of patients studied. The incidence of primary liver carcinoma in cases of cirrhosis at necropsy for the last five years was 28.3%. Thus a tumour which is rare in the whole population is common in relation to a small group of patients with cirrhosis. Appreciation of the frequency of the condition will be more likely to suggest the diagnosis than a search for or reliance upon diagnostic signs and tests.

The apparently high incidence of malignant change may be due either to a real increase or to improved methods of recognition. We are not in a position to decide this point.

A feature of interest is the association of peptic ulcer with cirrhosis and hepatoma. Active chronic peptic ulcer occurs in 4 to 8% of all hospital necropsies (Watkinson, 1960). A greater incidence in cirrhosis is well recognized, figures as high as 19.5% being quoted (Lipp and Lipsitz, 1952). In the present series 14.2% of patients dying with cirrhosis were found to have chronic peptic ulcers. Macdonald and Mallory (1958) showed the incidence in hepatoma to be higher (16%) and in the present series the incidence of chronic peptic ulcer in those dying of hepatoma was 23.3%. No explanation for this is offered, but from the clinical standpoint the association may be of some importance, since further investigation of upper

abdominal pain in cirrhosis may be abandoned when an ulcer is demonstrated unless it is appreciated that cirrhosis, hepatoma, and ulcer may often coexist.

Summary

The incidence of primary carcinoma of the liver at necropsy was studied over a period of 23 years (1940-62) at a London teaching hospital.

Among 7,366 necropsies there were 157 cases of cirrhosis and 39 cases of primary hepatic carcinoma.

The incidence of malignant change in cirrhosis was 19.1% over the whole period. Analysis by five-year periods showed an apparent increase to 28.3%. Active chronic peptic ulcer occurred in 14.2% of cases with cirrhosis and in 23.3% of those with primary carcinoma of the liver.

Malignant change in cirrhosis appears to be common.

We are indebted to the physicians of St. Thomas's Hospital for permission to study patients under their care.

REFERENCES

- Benner, E. J., and Labby, D. H. (1961). *Ann. intern. Med.*, **54**, 620.
 Berman, C. (1951). *Primary Carcinoma of the Liver*, p. 5. Lewis, London.
 Edmondson, H. A., and Steiner, P. E. (1954). *Cancer*, **7**, 462.
 Fifth Pan-American Congress of Gastroenterology (1956). *Lancet*, **1**, 377.
 Hall, E. M., Olsen, A. Y., and Davis, F. E. (1953). *Amer. J. Path.*, **29**, 993.
 Halpert, B., and Erickson, Ethel E. (1955). *Cancer*, **8**, 992.
 Lipp, W. F., and Lipsitz, M. H. (1952). *Gastroenterology*, **22**, 181.
 Macdonald, R. A. (1956). *New Engl. J. Med.*, **255**, 1179.
 — and Mallory, G. K. (1958). *Amer. J. Med.*, **24**, 334.
 Otaki, A., Read, A. E., Stubbs, J., and Sculthorpe, H. (1960). *Brit. med. J.*, **2**, 256.
 Parker, R. G. F. (1957). *Proc. roy. Soc. Med.*, **50**, 145.
 Sherlock, Sheila (1958). *Diseases of the Liver and Biliary System*, 2nd ed., p. 571. Blackwell, Oxford.
 Spatt, S. D., and Grayzel, D. M. (1948). *Amer. J. Med.*, **5**, 570.
 Stewart, M. J. (1931). *Lancet*, **2**, 565.
 Watkinson, G. (1960). *Gut*, **1**, 14.
 Wilbur, D. L., Wood, D. A., and Willett, F. M. (1944). *Ann. intern. Med.*, **20**, 453.

INFECTION DUE TO MYCOBACTERIUM AVIUM

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Disease due to *M. avium*, the avian variety of the tubercle bacillus, has been regarded as very rare in man (Feldman, 1938). Only two well-established cases have so far been reported in Britain (Bradbury and Young, 1946; Furniss *et al.*, 1961), but since *M. avium* closely resembles certain of the "anonymous" mycobacteria in its cultural and biochemical properties, it was decided to investigate anonymous strains collected by the Tuberculosis Reference Laboratory during the last 10 years. The study was confined to 16 isoniazid-resistant thermophilic strains, taken at random from a series of 18 incriminated as pathogens. The case reported by Furniss *et al.* is also described, because the strain belonged originally to the series being surveyed (Case 4).

Material and Methods

The strains in the present series were classified presumptively as pathogenic because of their repeated isolation either from pus in cervical adenitis or from sputum in patients with pulmonary disease in the absence of other pathogens. In each case in which it was possible, histological examination of resected or post-mortem material

supported the diagnosis of mycobacterial infection. Strains were stored at 4° C. but subcultured every three months on Löwenstein medium before their examination as a group in 1962-3.

Strains 40529 and 35445 were submitted for identification by laboratories in England, but the remainder were recovered in the routine work undertaken for Wales.

Fowl Inoculations.—The main experiment employed 16 8-week-old Rhode Island Reds, housed separately. All fowls were shown before use to be tuberculin-negative to 0.05 mg. of avian P.P.D. injected into the wattle. Those which survived 12 weeks were retested. A fully grown culture in Dubos medium was inoculated into a pectoral muscle and intraperitoneally in a dose of 0.5 ml. (about 0.25 mg.) by each route except with strain 35445, for which the dose was 1 ml. Certain additional fowls were inoculated similarly but given 0.002 mg. intravenously as well. Fowls in the main series which survived 12 weeks were killed after their tuberculin test and examined by the methods used for those dying spontaneously. Impression films and sections were made of lung, liver, spleen, and kidney, and portions of these organs were pooled for