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Incidence of primary carcinoma of the liver in the west of Scotland between 1949 and 1965

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Changes in the incidence of tumours are worthy of note as these may draw attention to factors concerned with aetiology. In recent years our attention has been drawn to the increasing frequency of primary carcinoma of liver in the west of Scotland. This change has been particularly notable in Glasgow Royal Infirmary where a marked rise in the number of fatal cases has been maintained since 1959. The cause is not apparent, but it is not associated with any corresponding increase in the prevalence of hepatic cirrhosis. Our original investigations were concerned only with necropsies carried out in Glasgow Royal Infirmary and a few associated hospitals in the east end of Glasgow from 1949 to 1963 (Manderson, Patrick, and Peters, 1965). This communication reports the findings of an extension of the study by two years, and to most of the general hospitals in the Scottish western region.

MATERIALS

Clinical and necropsy records of all primary liver cancer patients dying in Glasgow Royal Infirmary and associated hospitals within the period 1949 to 1965 inclusive were examined personally. The histopathology of every tumour was reviewed and all cases of doubtful histogenesis and of carcinoma arising in extrahepatic or large intrahepatic bile ducts were discarded. Note was made of the type of cirrhosis associated with malignancy. In this respect the term 'cirrhosis' is meant to imply fibrosis with loss of normal hepatic architecture and the replacement of normal parenchyma by hyperplastic nodules; minor degrees of hepatic fibrosis are therefore excluded.

Figures relating to the incidence of fatal primary liver cancer and hepatic cirrhosis during the same period were then obtained from the pathology departments of 12 other general hospitals in Glasgow and the west of Scotland, representing the great majority of the general hospital population in this area. Hospitals devoted to specialities such as paediatrics, obstetrics, and psychiatry were excluded.

Cases known to us only from liver biopsy are not included as the practice of this investigation has varied during the period of this study among the various hospitals from which information was obtained.

RESULTS

Figure 1 shows, in graphic form, the incidence of primary liver cancer and cirrhosis in Glasgow Royal Infirmary and in the other west of Scotland hospitals during the period under investigation. The notable increase in tumour cases in Glasgow Royal Infirmary since 1959 is clearly apparent. A similar, but less spectacular trend is seen in relation to the other hospitals and is significantly higher in the post-1958 period (Table I). By contrast, the incidence of cirrhosis has remained constant throughout the period of investigation. Indeed, there is a slight, but probably insignificant decrease in numbers in more recent years.

Before 1959 the incidence of primary liver cancer was low and no different in Glasgow Royal Infirmary from the other hospitals in this area. The incidence of hepatic cirrhosis has always been disproportionately high in Glasgow Royal Infirmary, although this hospital has no centre for the special investigation or treatment of such cases. This difference has been slightly more marked since 1959 (Table II).

Statistical analysis of our results also confirms a good correlation between the increasing incidence of liver cancer in Glasgow Royal Infirmary and in the other hospitals during the entire 17-year period covered in this investigation ($r = 0{\cdot}63$; $t = 3{\cdot}13$: $P < 0{\cdot}01 > 0{\cdot}001$).

All patients in this series were adults with ages ranging from 23 to 89 years (mean 58·7; SD 15·0). There has been no alteration in this wide age distribution or in the longevity of cirrhosis cases during the period under investigation, although the average age for all patients dying in Glasgow Royal Infirmary and subjected to post-mortem examination has been rising gradually, from 55·9 years in 1949 to 60·3 years in 1965.

Histological examination of all the Glasgow Royal Infirmary group cases showed that the great majority of these were of the hepatocellular type (Table III); examples of pure cholangiocarcinoma were notably uncommon in this series. Two cases of haemangio-

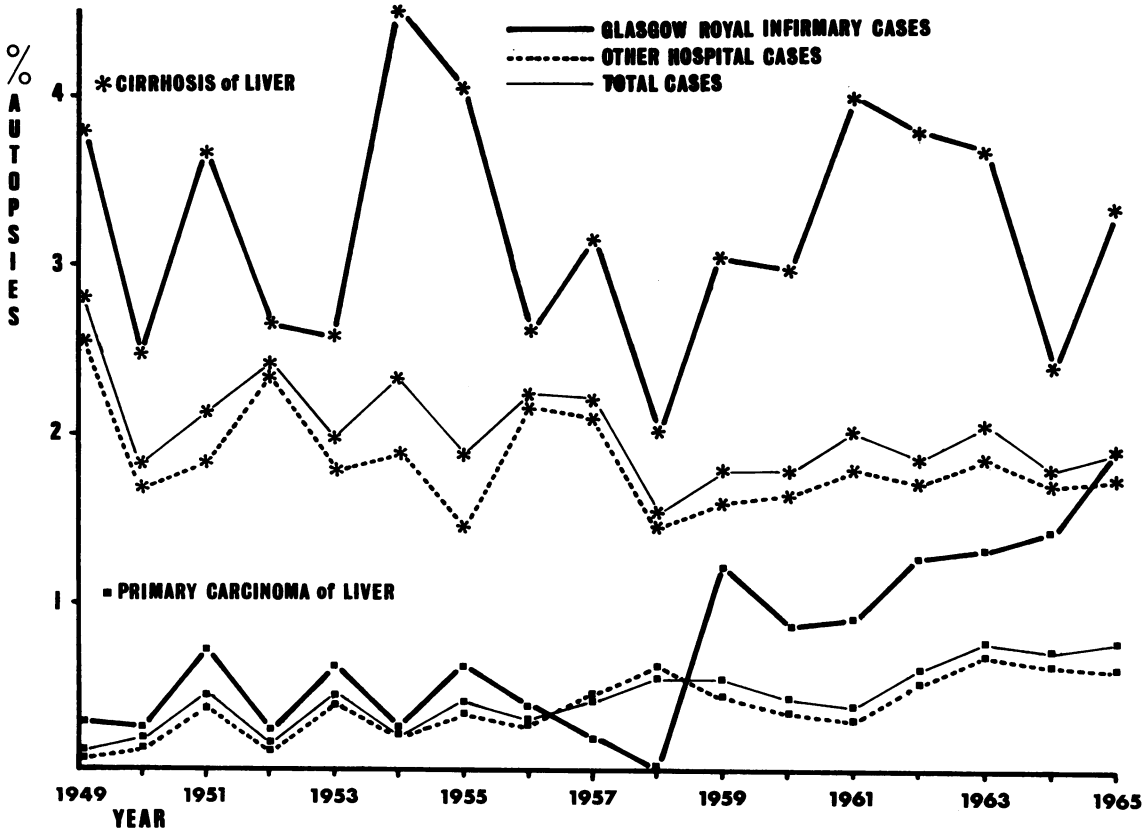

FIG. 1. *Incidence of primary liver carcinoma and hepatic cirrhosis in Glasgow Royal Infirmary and in other west of Scotland hospitals between 1949 and 1965.*

blastoma, both convincingly of hepatic origin, are included but no other rare hepatic tumour was found. A third primary haemangioblastoma of liver is included among the tumours from another Glasgow hospital. Table IV presents the association of other liver diseases with carcinoma in this same series. It will be seen that hepatic cirrhosis was present in about 75% of all cases but that the recent increase in carcinoma involved both cirrhotic and non-cirrhotic groups. Cirrhosis was generally of the coarse post-hepatitic or post-necrotic varieties as assessed histologically, but the majority gave no history of acute liver disease. Five patients had suffered from viral hepatitis many years before their terminal illness and five others had been treated for syphilis (four with arsenical compounds and one with penicillin). A substantial number had idiopathic haemochromatosis. Although cirrhosis was rarely of the fatty type, 12 patients could be regarded clinically as alcoholics and one other had suffered from severe war-time malnutrition.

Similar details could not always be obtained readily from the records of the other hospitals investigated. However, it seemed that in general, the majority of these liver cancer cases were likewise of the hepatocellular type and associated with hepatic cirrhosis.

DISCUSSION

The histological diagnosis of primary liver cancer can be a matter of considerable difficulty in poorly differentiated and atypical tumours. Even when a careful postmortem examination fails to reveal any other neoplasm, the possibility of metastatic deposits within the liver from some inconspicuous primary growth elsewhere in the body can never be excluded with certainty. This difficulty applies also

TABLE I

FATAL CASES OF PRIMARY LIVER CARCINOMA AND HEPATIC CIRRHOSIS IN GLASGOW ROYAL INFIRMARY AND IN OTHER HOSPITALS DURING THE PERIODS 1949-1958 AND 1959-1965

	1949-1958			*1959-1965*			*Comparison of Means for 1949-59 and 1959-65*	
	Total Cases	*Total Necropsies*	*Percentage Necropsies*	*Total Cases*	*Total Necropsies*	*Percentage Necropsies*	*t*	*P*
Liver cancer (Glasgow Royal Infirmary)	16	4,331	0·366	40	3,186	1·264	6·3915	<0·001
Liver cancer (other hospitals)	80	21,827	0·327	138	25,974	0·537	2·7373	<0·02>0·01
Cirrhosis (Glasgow Royal Infirmary)	135	4,331	3·133	104	3,186	3·289	0·4422	<0·7>0·6
Cirrhosis (other hospitals)	409	21,827	1·916	440	25,974	1·693	1·5386	<0·2>0·1

TABLE II

COMPARISON OF INCIDENCES OF PRIMARY LIVER CANCER AND CIRRHOSIS OF LIVER IN GLASGOW ROYAL INFIRMARY AND IN OTHER HOSPITALS

		Total Cases	*Total Necropsies*	*Comparison of Incidence*	
				χ^2	*P*
Liver carcinoma	Glasgow Royal Infirmary, 1949-58	16	4,331	0·001	>0·9
	Other hospitals	80	21,827		
Liver carcinoma	Glasgow Royal Infirmary, 1959-65	40	3,186	24·62	<0·05>0·02
	Other hospitals	138	25,974		
Cirrhosis	Glasgow Royal Infirmary, 1949-58	135	4,331	27·43	<0·05>0·02
	Other hospitals	409	21,827		
Cirrhosis	Glasgow Royal Infirmary, 1959-65	104	3,186	38·22	<0·02>0·01
	Other hospitals	440	25,974		

TABLE III

FATAL CASES OF PRIMARY LIVER CARCINOMA SEEN IN GLASGOW ROYAL INFIRMARY AND ASSOCIATED HOSPITALS, 1949-65, CLASSIFIED ACCORDING TO HISTOLOGICAL TYPE

Type of Primary Liver Tumour	*No. of Cases*
Hepatocellular carcinoma	56
Cholangiocarcinoma	4
Combined hepatocellular and cholangiocarcinoma	4
Haemangioblastoma	2

TABLE IV

FATAL CASES OF PRIMARY LIVER CARCINOMA SEEN IN GLASGOW ROYAL INFIRMARY AND ASSOCIATED HOSPITALS, 1949-65, CLASSIFIED ACCORDING TO ASSOCIATED LIVER DISEASE

Period	*Without Cirrhosis*	*With Cirrhosis*			
		Coarse Multilobular Cirrhosis	*Fine Fatty Cirrhosis*	*Pigmentary Cirrhosis (Haemochromatosis)*	*Total*
1949-58	3	8	3	5	16
1959-65	13	27	1	6	34

to the diagnosis of intrahepatic cholangiocarcinoma and we excluded one such case from our series when it became known that the patient had suffered from gastric carcinoma which had been resected some years before death, but with no local recurrence. Cholangiocarcinoma accounts for very few of our cases. Excluding the two haemangioblastomas, we are satisfied that the remainder all had features of hepatocellular carcinoma as described and illustrated by Edmondson (1958) in at least some part of their structure.

In studies of this kind, results may be influenced by the special interest of the investigators leading to the detection of a high proportion of early and inconspicuous lesions. However, in all Glasgow Royal Infirmary cases, with one exception, the tumours were large and readily apparent; the exceptional case comprised a small area of malignant change,

about 2 cm in diameter, on the anterior surface of a cirrhotic liver. A consistent standard of examination has been maintained, as the period covered in the investigation corresponds to that during which one of us (R.S.P.) has had the opportunity of examining personally the necropsy material of all cases of chronic liver disease in the parent hospital.

The majority of cases occurred in association with, and presumably as a sequel to, hepatic cirrhosis, but the overall incidence of cirrhosis, although relatively high among Glasgow Royal Infirmary necropsies, did not increase during the period under investigation. This hospital has no special centre for hepatic disorders and we are not aware that our interest in this subject has attracted extra cases of chronic liver disease.

From 1949 to 1965 the average age of patients from which our series is drawn has risen gradually. It is most unlikely that this could be the sole explanation of the sudden and sustained increase in the incidence of primary liver cancer in the latter part of this period. The tumour is by no means confined to the elderly, and the proportion of younger patients has not diminished in recent years.

It is possible that length of survival in hepatic cirrhosis is a factor in the development of malignant change, and this could explain the relatively high incidence of malignancy in haemochromatosis with cirrhosis (Popper and Schaffner, 1957). It is often very difficult to assess the duration of chronic liver disease, and most cases of cirrhosis which we have seen, although classifiable as post-hepatitic or post-necrotic, were, in fact, cryptogenic. No patient with cirrhosis complicated with carcinoma had been subjected to portocaval anastomosis or other special therapeutic measures which might have influenced survival. However, it will be noted that the increasing incidence of the tumour appears to include those less common cases which arise in the otherwise normal liver.

Most cases of carcinoma in this series could be classified as hepatocellular. While this is in keeping with the experience of others, we saw relatively few examples of the cholangio-cellular variety. Bras (1961) has suggested that cholangio-cellular carcinoma is a distinct tumour which does not have the same geographical incidence as the commoner hepatocellular type. Nevertheless, it is thought that the aetiology of these two tumours may be similar (Edmondson, 1958) and both histological features can be present in the same specimen. None of the four Glasgow Royal Infirmary cases of cholangiocellular carcinoma was associated with hepatic cirrhosis, and none had a history of previous chronic biliary infection. We have included haemangioblastoma (haemangioendothelial sarcoma) of liver because of the known association of this condition with hepatic cirrhosis (Edmondson, 1958), and one of our two cases did show this association.

The relationship of hepatocellular carcinoma to hepatic cirrhosis is generally accepted, although in a few series of cases it has not been striking (*eg*, Thompson, Hackley, and McGinnis, 1957; Nelson, de Elizalde, and Howe, 1966; Nett and Gilbert, 1966). The relatively high incidence of cirrhosis in Glasgow Royal Infirmary might explain the numbers of hepatocellular carcinoma cases in that hospital, but not the changing incidence in recent years. It seems that the tumour may be associated with any type of cirrhosis and in some reports it has been predominantly of the fatty or alcoholic variety (*eg*, Parker, 1957; Eppstein, 1964). Our findings are similar to those of most recent observers who describe liver cancer as a complication predominantly of coarse multilobular cirrhosis (Gall, 1960; Miyai and Ruebner, 1963; Sagebiel, McFarland, and Taft, 1963; Patton and Horn, 1964; San Jose, Cady, West, Chomet, and Zimmerman, 1965). Post-hepatitic and post-necrotic varieties may be recognized, but in our experience this subdivision was sometimes uncertain on morphological grounds, while the clinical history was usually uninformative.

It is well known that the incidence of liver cancer varies widely in different parts of the world. Where it is common there may be some readily detected predisposing factor, such as liver fluke infestation in South China (Hou, 1956). There are now a number of reports of a gradually increasing incidence of the disease from places where, until recently, it has been regarded as a relatively rare disease. Some of the latter reports originate in the USA (*eg*, MacDonald 1957), where the cases may be drawn from a mixed racial population. However, there are recent accounts of a similar trend from parts of Scandinavia (Glenert, 1961; Ohlsson and Norden, 1965). Likewise, our present report is concerned with patients who were all indigenous to the west of Scotland and so our findings cannot be explained by recent changes in the population pattern due to immigration.

No convincing explanation has been offered for the increasing incidence among white populations. Walter, Hanauer, and Kent (1966) attributed their cases to viral hepatitis. No such relationship is readily apparent in our experience, but this might be worthy of epidemiological study. Cases of alcoholic liver disease have shown an increase in the west of Scotland in the past decade, but the association of typical alcoholic cirrhosis with cancer was very unusual; nevertheless, several patients in our series did have a history of alcoholism without the typical hepatic manifestations. From his study of liver cancer in the Bantu, Higginson (1963) suggested that

two liver-damaging factors may be concerned with aetiology, an initiator or predisposing agent acting in childhood and associated with malnutrition, and a promoter such as viral hepatitis which is effective at a later date in the production of both cirrhosis and carcinoma. Therefore it may be important to bear in mind in any consideration of the changing incidence of liver cancer that the pathogenesis may depend on several agents, any one of which by itself need not be carcinogenic.

SUMMARY

Primary carcinoma of the liver has been investigated from the necropsy records of most general hospitals in Glasgow and the west of Scotland. This has revealed a gradual increase in the incidence of the disease during the period 1949 to 1965 inclusive. In the case of Glasgow Royal Infirmary there has been an abrupt and sustained rise in the incidence since 1959. These changes are not associated with any corresponding increase in the numbers of fatal cases of hepatic cirrhosis and the explanation for the phenomenon is not known.

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