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^{67}Gallium scanning in the diagnosis of liver disease

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SUMMARY ^{67}Gallium (^{67}Ga) citrate liver scanning has been carried out on 60 selected patients following a scan with a radioactive colloid preparation.

The ^{67}Ga scan correctly identified the site of primary liver carcinoma in 14 of 16 patients, including nine of 10 patients in whom the carcinoma arose in a cirrhotic liver, whereas a colloid scan positively identified the site in only four of these 10 cirrhotic subjects. Alpha-1-fetoprotein estimation was positive in eight of the 16 patients, including the two in whom ^{67}Ga scanning was negative. No positive ^{67}Ga scans were seen in 15 patients with cirrhosis but no primary liver cell cancer in whom a space-occupying lesion could not be excluded on colloid scan. ^{67}Ga citrate scanning appears to be the most reliable investigation available in the diagnosis of primary liver cell cancer. Uptake of ^{67}Ga in secondary metastatic tumours within the liver was less frequent, and appears to have much less value in the detection of these lesions and of bile duct carcinoma than in primary liver cell carcinoma.

The ^{67}Ga scan was positive in six out of six patients with pyogenic abscess either in the liver or adjacent to it. In four of these patients a preceding colloid scan had shown no definite filling defect in the liver.

Liver scanning with radioactive colloid preparations, usually ^{198}Au, ^{99m}Tc, or ^{113m}In, now has an established place in the diagnosis of hepatic space-occupying lesions (McAfee, Ause, and Wagner, 1965), but there are still several limitations to the use of these compounds which are taken up only by the reticulo-endothelial cells within the liver. There are two situations in particular in which further information from a liver scan would be of value: in the delineation of space-occupying lesions, particularly primary liver cell carcinomas, in the cirrhotic liver where colloid scans frequently show patchy uptake; and in identifying lesions peripheral to the liver which may be hard to differentiate from normal anatomical variants by conventional scanning methods.

^{67}Ga citrate was shown to be a potentially useful tumour scanning agent by Edwards and Hayes (1969) who showed the affinity of ^{67}Ga for soft tissue tumours in particular. It has also subsequently been shown to be selectively taken up into inflammatory lesions including pyogenic abscesses and sarcoidosis in many sites in the body (Lavender, Lowe, Barker, Burn, and Chaudhri, 1971; van der Schoot, van Marle-van der Groot, Groen, and de Jong, 1972; Lomas and Wagner, 1972; McKusick, Soin, Ghiladi, and Wagner, 1973).

Recently several reports have indicated that ^{67}Ga citrate is selectively taken up by primary liver cell carcinomas and may thus be very useful in their diagnosis (Lomas, Dibos, and Wagner, 1972; Suzuki, Honjo, Hamamoto, Kousaka, and Torizuka, 1971; Langhammer, Hor, Heidenreich, Kempken, and Pabst, 1972; Fogh and Edeling, 1972). It has also been shown to exhibit increased uptake in secondary malignant deposits within the liver, pyogenic liver abscesses, and in Hodgkin's disease affecting the liver (Turner, Gottschalk, Hoffer, Harper, Moran, and Ultman, 1973; Littenberg, Taketa, Alazraki, Halpern, and Ashburn, 1973).

This paper presents our experience of ^{67}Ga liver scanning in 60 patients used as an adjunct to routine radiocolloid liver scans. The object is to define more carefully its role and reliability in clinical practice.

Routine liver scans were carried out 20 minutes after the intravenous injection of 1-3 mCi of ^{99m}Tc sulphide or antimony sulphide colloid (Paton, Garcia, and Webber, 1966; Hawkins and McAlister, 1969) using a single or double head scanner or a gamma camera. The gallium scans were carried out in all cases on the double-headed scanner 48 hours after the intravenous administration of 2

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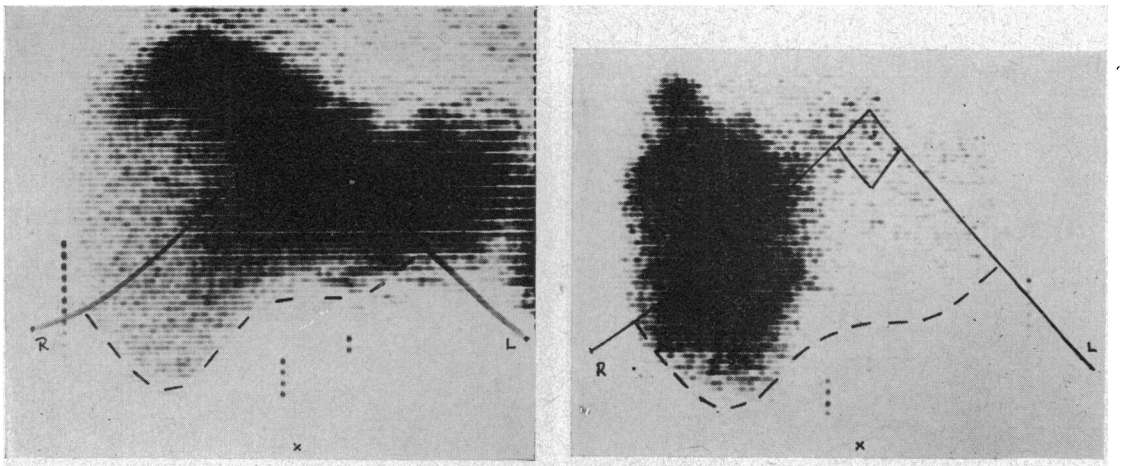

Fig 1a Fig 1b

Fig 1 *Primary liver cell cancer in non-cirrhotic liver.* (a) ^{99m}*Tc colloid scan.* (b) ^{67}*Ga scan.*

mCi ^{67}Ga citrate (Philips, Duphar, Holland), the channel width being 160-320 KeV.

Although 10-15% of an administered dose of ^{67}Ga is excreted into the intestine (Edwards and Hayes, 1970), no difficulties of interpretation of ^{67}Ga scans were encountered due to uptake from the bowel. No laxative preparations were given to help the ^{67}Ga to pass from the colon.

Each scan was reported on together with a previously obtained colloid liver scan by a physicist and a physician. Full clinical information was available about each patient at the time of reporting. No retrospective changes in the report have been made.

In all 60 patients a histological diagnosis was obtained within two weeks of ^{67}Ga scanning, either by Menghini needle biopsy of the liver, operative liver biopsy, or postmortem examination of the liver. The site of abscess was confirmed at laparotomy in five of the six patients reported.

Results

These are reported in table I.

PRIMARY LIVER CELL CARCINOMA

Sixteen patients with primary liver cell carcinoma received ^{67}Ga scans after conventional radioactive colloid liver scans. In 14 subjects a positive uptake

Diagnostic Group	*Technetium Scans*				*Gallium Scans*		*α Fetoprotein*
	Patients Studied	*Lesions*			*Positive*	*Negative*	*Positive*
		Definite	*Not Excluded*	*Absent*			
Primary liver carcinoma and cirrhosis	10	4	3	—	9	1	4
Primary liver carcinoma—cirrhosis	6	5	1	—	5	1	4
Cirrhosis	15	—	15	—	0	15	
Abscess	6[1]	2	3	1	6	0	
Acute hepatitis	3	—	2	1	0	3	
Secondary carcinoma	5	5	—	—	3	2	
Amyloidosis	1	1	—	—	0	1	
Bile duct carcinoma	3	3	—	—	0	3	
Hydatid disease	3	3	—	—	0	3	
Lymphoma	2	1	—	1	0	2	
Budd-Chiari syndrome	1	Caudate lobe uptake			0	1	
Normal	2	—	—	2	0	2	
Gallstones in common bile duct	2	—	—	2	0	2	
Congenital cysts	1	1	—	—	0	1	

Table I *Results of technetium and gallium scans and α-fetoprotein estimation in 60 patients*

[1]Abscess in splenic bed

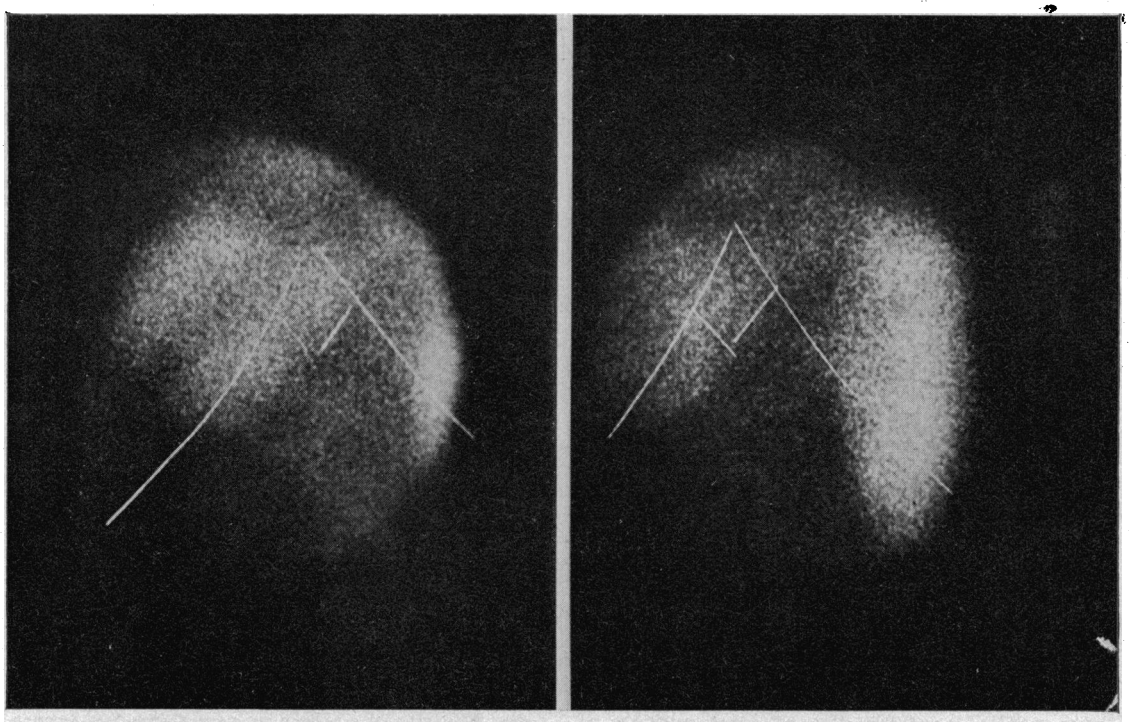

Fig 2a

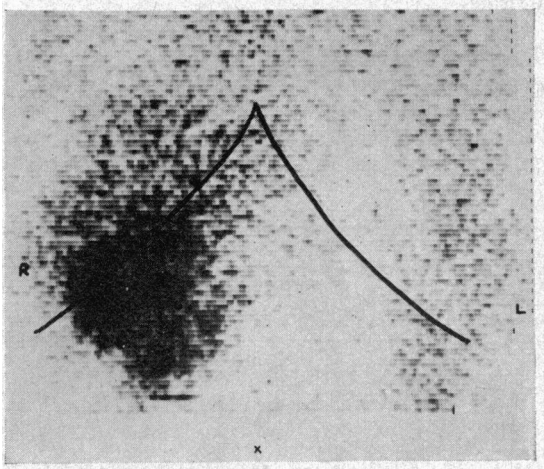

Fig 2b

Fig 2 *Primary liver cell cancer in cirrhotic liver.* (a) ^{99m}*Tc colloid gamma camera pictures, patchy hepatic uptake, and marked splenic uptake.* (b) ^{67}*Ga scan.*

of ^{67}Ga was seen, and was found to correspond to the position of the liver cell carcinoma in every case either at laparotomy, at necropsy, or by needle liver biopsy within two weeks of the ^{67}Ga scan (figs 1 and 2).

Of the two patients with a negative ^{67}Ga scan one, who died of hepatic failure from poorly compensated cirrhosis, had a well circumscribed lesion 2 cm across in the centre of the right lobe of the liver which was found at necropsy. This is probably below the level of resolution of the scan, particularly in a cirrhotic liver. The second patient presented with obstructive jaundice, and a colloid scan showed a space-occupying lesion in the region of the porta

hepatis, suggestive of dilated bile ducts. At laparotomy the biliary tree was found to be filled with a gelatinous tumour thought to be a primary liver cell cancer.

Eight of the 16 patients who had primary liver cell carcinoma had positive tests for serum alpha-1-fetoprotein (counter immunoelectrophoresis) including both the patients with negative ^{67}Ga scans.

CIRRHOSIS

Fifteen patients with cirrhosis proven at biopsy in whom an intrahepatic space-occupying lesion could not be excluded on conventional colloid scan of the liver received a subsequent ^{67}Ga scan. In no case was there a local area of ^{67}Ga uptake suggestive of a lesion. No primary liver cell carcinomas have subsequently been discovered in these patients; serum alpha-1-fetoprotein was negative in every case.

ABSCESS

Among the six abscesses studied, two were intrahepatic, identified by a ^{99m}Tc colloid scan before ^{67}Ga scan. In one patient the abscess was on the inferior edge of the liver in relation to a ruptured empyema of the gallbladder (fig 3). Two other patients suffered from chronic subphrenic abscess. The sixth patient showed some indentation of the medial surface of the greatly enlarged liver posteriorly on colloid scan and a positive ^{67}Ga uptake to the left of the liver posteriorly. This was interpreted as an abscess arising in the bed of the spleen which had been removed one year earlier; laparotomy confirmed that this was the site of the abscess.

OTHER LIVER DISEASE

Positive uptake of ^{67}Ga has been seen in three of the five patients with secondary hepatic metastases from distant primary carcinomas (two squamous, one adenocarcinoma). All five patients had shown definite filling defects on colloid scan. No other positive ^{67}Ga scans have been seen. In particular, scans on three patients with bile duct carcinoma were negative as were those on three patients with acute hepatitis (one HbAg positive). ^{67}Ga was not taken up into or around four (three hydatid, one congenital) intrahepatic cystic lesions which were examined. There was no area of increased uptake of ^{67}Ga into the caudate lobe of the liver in a patient with the Budd-Chiari syndrome who showed marked uptake in this region on a ^{99m}Tc colloid scan.

Discussion

PRIMARY LIVER CELL CARCINOMA

^{67}Ga liver scans performed in conjunction with ^{99m}Tc colloid liver scanning were positive in 14 of 16 patients in the present series and in a further six of 29 in the published literature, thus ^{67}Ga scans have been correct in 40 of 45 (89%) patients with primary liver cell cancer. The reason for the two negative results is not clear. Probably the lesion in one patient was below the level of resolution of the scan. In the second patient no explana-

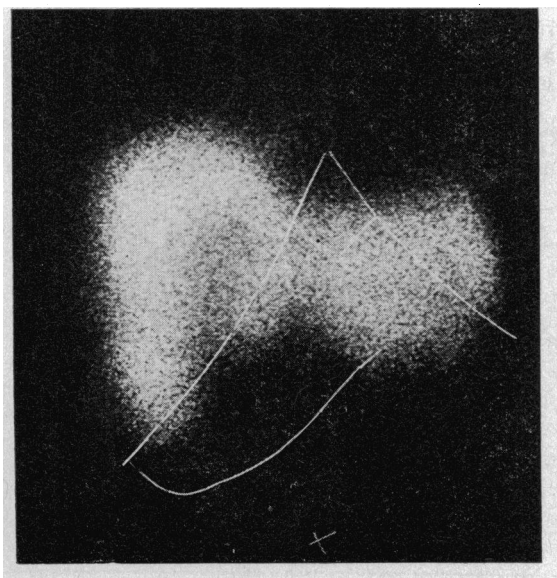

Fig. 3a

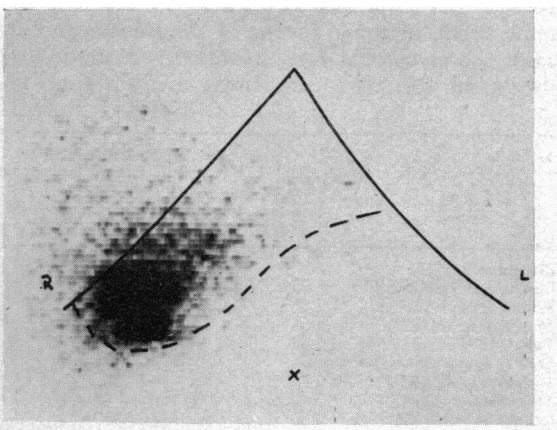

Fig 3b

Fig 3 *Liver abscess contiguous with ruptured empyema of the gallbladder.*
(a) ^{99m}*Tc colloid gamma camera picture*
(b) ^{67}*Ga scan*

tion can be offered. The serum alpha-1-fetoprotein was positive in both these patients: thus either the ^{67}Ga scan or the serum alpha-1-fetoprotein estimation was positive in every patient in the present series.

One of the most difficult problems in liver scanning is the detection of primary liver cancer in the presence of a cirrhotic liver. This is because hepatic uptake of colloid is patchy in the cirrhotic liver and in many cases space-occupying lesions cannot be excluded as a result of the scan (fig 2).

When the results in this study are added to published reports only one false-positive ^{67}Ga scan has been recorded in 45 (2%) of ^{67}Ga scans carried out on cirrhotic livers with no evidence of primary liver cell cancer (table II). This seems an acceptably low 'false positive' rate. Radiocolloid ^{67}Ga scanning in combination with alpha-1-fetoprotein estimation is a satisfactory and reliable method in the diagnosis of primary liver cell cancer.

OTHER INTRAHEPATIC MALIGNANCY

The uptake of ^{67}Ga in intrahepatic secondary metastases from other primary sites seems to be unpredictable; three of the five patients studied showed uptake of ^{67}Ga in areas reported as showing space-occupying lesions on ^{99m}Tc sulphide colloid scans. A review of other series shows that secondary deposits give positive ^{67}Ga uptake within the liver in about half (51/89) of the recorded cases (table II).

No positive uptake of ^{67}Ga was seen in three patients with bile duct carcinoma in whom a hilar defect had been shown by colloid scan. This is perhaps not surprising as the actual lesion may be quite small, although in one of the three reported cases the carcinoma had extended throughout the liver, and bile duct carcinomas are scirrhous in nature; fibrous lesions do not appear to take up ^{67}Ga well at any site in the body. Suzuki *et al* (1971) and Lomas *et al* (1972) both report positive uptake of ^{67}Ga in single bile duct carcinomas. This group clearly needs further evaluation.

PYOGENIC LIVER ABSCESS

Many intrahepatic pyogenic abscesses are satisfactorily demonstrated as filling defects on conventional colloid liver scans, but abscesses or inflammatory lesions at the edge of the liver have been more difficult to detect. Subphrenic abscess, for example, may produce an abnormality in the outline of the liver which resembles a variant in the normal shape of the liver. Four of the six abscesses reported fell into this group (fig 3). The high uptake of gallium in abscesses may be of particular use in the diagnosis and localization of such lesions on the edge of the liver or in organs close to it. A survey of the literature to date reveals 15 positive scans in hepatic abscess and no negative scans. Littenberg *et al* (1973) and Grove, Madewell, Rapp, Pinsky, and Johnson (1973) have demonstrated the value of ^{67}Ga scanning in abscesses not only within the abdomen but also in other sites in the body. Lomas and Wagner (1972) have demonstrated high ^{67}Ga uptake in empyema of the gallbladder.

OTHER INTRAHEPATIC SPACE-OCCUPYING LESIONS

No positive uptake of ^{67}Ga was seen in the defects shown by colloid scanning in the three patients with hydatid disease or in a subject with congenital hepatic cysts. Lomas *et al* (1972) and Littenberg *et al* (1973) report no uptake of gallium in four cases of amoebic abscess while Grove *et al* (1972) report no uptake in intrahepatic cysts in a further three patients. These

Series	*Primary Liver Cell Carcinoma*		*Secondary Carcinoma in the Liver*		*Bile Duct Carcinoma*		*Lymphoma in Liver*		*Pyogenic Liver Abscess*		*Other Intra-Hepatic Lesions*		*Cirrhosis*		*Acute Hepatitis*	
	+ve	−ve	+ve	−ve	+ve	−ve	+ve	−ve	+ve	−ve	+ve	−ve	+ve	−ve	+ve	−ve
Present series	14	2	2	2	0	3	0	2	6	0	0	4	0	15	0	2
Lomas and Wagner (1972)	11	1	7	5	1	1	2	0	4	0	0	2	1	10	0	1
Suzuki *et al* (1971)	7	2	6	10	1											
Manfredi *et al* (1973)	4		20	11									0	10		
Fogh and Edeling (1972)	2		4	2									0	4		
Dvorak and Montez (1973)			6	3												
Lavender *et al* (1971)							1	0							0	3
Littenberg *et al* (1973)									3	0			0	4		
Langhammer *et al* (1973)	1															
Turner *et al* (1973)							1	0								
Winchell *et al* (1970)	1															
Larsen *et al* (1971)							1	0								
Grove *et al* (1973)									3	0	0	3		1	0	1
Trapp *et al* (1971)			6	5			7	1								
Kramer *et al* (1973)							1									
Total	40	5	51	38	2	4	13	3	16	0	0	9	1	44	0	7

Table II *Survey of the results of ^{67}Ga-citrate liver scanning obtained in 15 published series*

results taken together indicate that there will not be a high proportion of 'false positive' gallium scans in these lesions although clearly further evaluation is necessary in this group.

HEPATIC UPTAKE OF GALLIUM

Gallium is thought to be taken up by liver cells rather than by the reticuloendothelial system. Haubold and Aulbet (1973), using differential centrifugation, have shown that ^{67}Ga is taken up almost exclusively in the lysosomal fraction of rat liver cells and in a similar fraction of cells from an affected lymph node in a patient with sarcoidosis. We have confirmed the uptake of gallium in the cytoplasm of hepatic cells of a primary liver cell cancer using autoradiography. The reason for increased accumulation of gallium in these lesions is at present unknown.

There are two types of result which are regarded as being positive. More frequently the lesion, whether neoplastic or inflammatory, is indicated by an area of markedly increased uptake on the gallium scan while the remainder of the liver shows by comparison little uptake of gallium (fig 1); in the second group there is moderate uptake of gallium throughout the liver and a definite defect on a conventional scan is filled in by the ^{67}Ga scan. Presumably this difference is partly due to the avidity with which the lesion has taken up ^{67}Ga relative to the rest of the liver. This second type of positive scan is similar to that reported with ^{75}Se-selenomethionine scanning in primary liver cell cancers (Ben-Porath and Kaplan, 1969; Eddleston, Rake, Pagaltsos, Osborn, and Williams, 1971).

DRAWBACK TO ^{67}GALLIUM SCANNING

The half life of ^{67}Ga is 78 hours, and, unlike some other scanning agents, this precludes its constant availability within the hospital. It must be ordered either at regular intervals or when needed. In addition the optimum time for scanning appears to be 48 hours after injection of the ^{67}Ga. There may therefore be a delay of several days between ordering a gallium scan and carrying it out. Because the ^{67}Ga scan is thought to be particularly valuable in the diagnosis of liver abscess where speed may be important in diagnosis, this delay is a disadvantage in its use. Nevertheless, in view of the low incidence of false positive scans and of false negative results in selected patients, ^{67}Ga scanning is a valuable additional tool in the diagnosis of liver disease.

The cost of the ^{67}Ga used in a scan in a centre where the scans are regularly carried out is at present about £18 ($44). This compares with about £2 for the ^{99m}Tc sulphur colloid.

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