Introduction

Liver is often a site of a variety of diseases. A palpable liver during a routine clinical examination is an important finding and requires further investigations. The availability of non-invasive liver imaging procedures using nuclear, ultrasound, C.T. (and now MRI) techniques have immensely enhanced diagnostic accuracy in liver diseases. In this Chapter, a detailed description of routinely practised nuclear medicine procedures related to liver is given. Brief reference is also made to other imaging techniques, particularly ultrasonography, only for the purposes of comparison. Most of the information is based on our own clinical experience of past 30 years.

While examining a radionuclide image of liver, it should be kept in mind that it is basically a functional image and illustrates only those areas which have retained their function in spite of disease. The unique advantage of this image is that at the same time it also shows anatomical parameters i.e. size, shape, displacements, distortions, etc. The disease pattern seen on the radionuclide liver image may be described as diffuse (as seen in hepatitis, cirrhosis, fatty infiltration etc.) or focal (as in abscess, cyst, tumour etc.).

The visualization of spleen in a radiocolloid liver image provides additional valuable information about the functional status of the liver. In addition to liver scintigraphy, other useful nuclear medicine techniques applicable to liver include blood pool imaging, hepatobiliary study, immunoscintigraphy, and radioimmunoassay for tumour markers.

A list of radiopharmaceuticals commonly employed for the diagnosis of liver diseases is shown in Table I.
## TABLE I. RADIOPHARMACEUTICALS FOR LIVER IMAGING

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<td>$^{99}$Tc$^{m}$ Sulphur Colloid</td>
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<td>$^{99}$Tc$^{m}$ Tin Colloid</td>
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<td>$^{99}$Tc$^{m}$ Antimony Colloid</td>
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<td>$^{99}$Tc$^{m}$ Phytate</td>
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<tr>
<td>$^{99}$Tc$^{m}$ Iminodiacetic acid (HIDA)</td>
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<td>$^{99}$Tc$^{m}$ Paraisopropyl iminodiacetic acid (PIPIDA)</td>
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<td>$^{99}$Tc$^{m}$ Parabutyl iminodiacetic acid (BIDA)</td>
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<td>$^{99}$Tc$^{m}$ Diisopropyl iminodiacetic acid (DISIDA)</td>
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<td>$^{99}$Tc$^{m}$ Diethyl iminodiacetic acid (DEIDA)</td>
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<tr>
<td>$^{67}$Gallium (Tumour &amp; abscess)</td>
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<td>$^{111}$Indium labelled WBCs (Abscess).</td>
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<td>$^{99}$Tc$^{m}$ 'in vivo' labelled RBCs.</td>
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<td>$^{99}$Tc$^{m}$ 'in vitro' labelled RBCs.</td>
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<td>$^{99}$Tc$^{m}$ labelled human serum albumin.</td>
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Anatomy

Liver is a bilobed, large solid organ which occupies almost the whole of the right hypochondrium. A part of its left lobe occupies the epigastrium and extends into the left hypochondrium. The liver is divided into two parts by the falciform ligament. This division is also very often visible on the scintigram, but does not correspond to the actual anatomical division of left and right lobes based on their blood supply and biliary drainage. The right lobe also includes two other small lobes called caudate and quadrate lobes. The caudate lobe is situated on the posterior surface while the quadrate lobe lies on the inferior surface of the right lobe immediately medial to the gall bladder fossa. The quadrate lobe, if prominent, may be visible on the radionuclide image. The confluence of the portal vein, bile ducts and hepatic artery is called porta hepatis and this may show prominently as a focal defect at the junction of the right and left lobes. Similarly the confluence of the hepatic veins at the cephalic attachment of falciform ligament sometimes appears as a wedge shaped defect along the upper border of the liver. The liver is surrounded from all sides by a large number of other organs which may affect the shape of liver image in a radionuclide study. The important organs include the diaphragm, right lung, heart, rib cage, gall bladder, right kidney, intestines, biliary tract, stomach and pancreas.

The knowledge of the anatomy of biliary tract is necessary to interpret a hepatobiliary study. The two main hepatic ducts emerge from right and left lobes and join in the region of porta hepatis to make common hepatic duct which travels inferiorly and is joined by the cystic duct from the gall bladder to make common bile duct. The common bile duct further descends downwards up to 10-15 cm and enters the duodenum at ampulla of Vater where it is also joined by the pancreatic duct.

Gall bladder is a sac-like, pear-shaped structure which fills and empties through cystic duct. It is about 10 x 4 cm in size and is attached to the inferior surface of the right lobe, lateral to the quadrate lobe. It stores and concentrates bile and contracts to pour bile into the lumen of the duodenum. In acute cholecystitis, following a blocked cystic duct, the gall bladder is not visible in a hepatobiliary study. Intrahepatic gall bladder may produce a defect in the lower lateral part of the right lobe. In case of congenital biliary atresia, the obstruction at the level of hepatic duct is sometimes clearly visible in a hepatobiliary study. Similarly the point of obstruction in the common bile duct due to a calculus or external pressure can be detected.

In a radionuclide scan of liver, the spleen is also imaged due to its reticulo-endothelial system which normally phagocytoses the colloid particles. A normal spleen measures about 12 x 7 cm in size and is situated posteriorly in the left hypochondrium. It can not be palpated below the costal margin unless it is about three times enlarged. Very occasionally an accessory spleen or a double spleen may be detected in the scintigram. In the developing countries, the large spleens are seen in cirrhosis of liver and chronic myeloid leukaemia. Large malarial spleens are now not common in many of the South-East Asian countries.
Physiology

The two main types of liver cells relevant to radionuclide imaging are the hepatocytes, which constitute the major bulk of the organ (80-90%) and the macrophages (Kupffer cells) which constitute only 2% of the total mass. The Kupffer cells are distributed in the lining of the vascular sinusoids and effectively remove colloid particles from the circulation. The ultimate clearance of the colloid from the circulation depends on the function of macrophages, perfusion of the hepatic lobules, and size of the colloid particles. Hepatocytes are capable of concentrating chemical substances like HIDA, Rose Bengal and other dyes from the circulation and excrete them with the bile. Diseases which affect the function of the hepatocytes e.g., inflammations, fatty infiltrations, toxic substances, malignancies, fibrosis etc. also affect the uptake and excretion of these substances.

RADIO-COLLOID LIVER–SPLEEN IMAGING

The function of phagocytosis is common to both liver and spleen due to the presence of reticulo-endothelial cells (macrophages) in both the organs. Similar cells are also present in the bone marrow and to a small extent in the lungs. The Kupffer cells make about 65% of all macrophages in the body but would concentrate 80 to 90% of the total colloid particles from the circulation. There is some correlation between the particle size and the extraction of the colloid by these organs. Smaller particles go to the liver and smallest to the bone marrow. Spleen takes up the larger particles. Thus the variation in the particle size may alter the relative distribution of the radio-colloid injected.

Most commonly used radio-colloid for liver-spleen scintigraphy is $^{99m}$Tc Sulphur colloid. The usual dose is 2 to 5 mCi (75-185 MBq) and the estimated particle size is 0.3 to 1 micron. The uptake of radio-colloid in the liver depends on the overall perfusion of the organ and the functional integrity of Kupffer cells. In conditions affecting these factors, the uptake of $^{99m}$Tc colloid by the liver is diminished with corresponding increase in the uptake by spleen and bone marrow and infrequently by the lungs. This phenomenon is sometimes described as 'spill over'.

Technical Procedure

The patient's abdomen is carefully palpated. Xiphisternum, costal margins, liver and spleen borders (if palpable) and outlines of any mass palpable in connection with the liver or in its vicinity are marked on the skin of the patient using an ordinary ink marker. These skin markings should be done in the same position in which the patient is going to be scanned on the imaging device. The marking of mid-axillary line for the Right Lateral view may also be useful for aspiration or biopsy if required later.

It takes about 10 to 15 minutes for the maximum accumulation of radioactivity after a radiocolloid injection, and this is the optimum time to commence imaging in most of the cases. In patients with impaired liver function or portal hypertension, the optimal
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concentration may be reached as late as 30 minutes after injection. The scanning is usually
done with patient in the lying position. If a rectilinear scanner is being used, this is the only
possible posture. When using this machine, the markings already made on the skin of the
patient are easily transferred to scan paper or X-ray film before starting the scan. A low
energy, medium focus, five inches focal length collimator is used. The information density
should be at least 800 counts/cm². Background subtraction of 5 to 10% may be used. The
'hot spot' is taken over the highest count rate on the liver in the anterior, right lateral, and
posterior views. If spleen is the organ of interest, 'hot spot' is taken over the spleen in the
left lateral and posterior views. Anterior, posterior and Rt. lateral views are obtained
routinely. If spleen is the organ of interest left lateral view should always be taken. Scan
is started from the level of the fourth intercostal space downwards to below all liver or spleen
activity.

While using a gamma camera both lying and standing positions can be utilized. The
advantage of standing position is that the up and down movement of the liver due to
diaphragmatic excursions is reduced. Such movements degrade the quality of the image and
small focal lesions may be obscured. A low energy, high resolution, parallel hole collimator
is used for the gamma camera and 500 000 to 1000 000 counts are collected for each image.
Counts below 300 000 would be unsatisfactory. The views to be taken are the same as
described for the rectilinear scanner. Skin markings can be transferred to the image by using
radioactive point sources or thin lead strip. 2 cm² pieces of lead may also be used to serve
as a reference marker for the size of focal lesions on the image.

In a gamma camera having a provision for taking counts over the region of interest
(ROI), the square of the ROI can be adjusted to the minimum and marked on the image.
With the help of a radioactive point source, skin markings can be transferred to the image
in the form of small mini-squares. If a discrete focal lesion is seen in the liver, its position
can be marked over the skin of the patient to facilitate biopsy or aspiration. A storage
oscilloscope (persistent scope), if available on the gamma camera, is very useful in
positioning the patient for different views.

Interpretation

The evaluation of a liver image should include:

(a) Size, shape and position of the liver. Upwards, downwards and lateral
displacement should be noted if present. Any deformity in the outline
due to external pressure caused by the pathology in the neighbouring
organs like lungs, heart, stomach, pancreas, kidneys, gall bladder,
biliary tract, intestines and ascitic fluid should be described. Degree of
hypertrophy or atrophy of the liver should be noted.

(b) The homogeneity of activity in the liver is described as uniform,
non-uniform, diffuse, mottled, decreased etc. referring to different
anatomical parts of the organ.
(c) Presence of focal defects is noted and their number, size, and exact anatomical location in the liver is described.

(d) Splenic image is carefully studied for size, site, density, deformity, and presence of focal lesions. The presence of visibility of bone marrow and relative distribution of colloid among liver, spleen and bone marrow is noted. Occasionally the radiocolloid may also be visible in the lung fields.

(e) Artifacts due to pendulous right breast or metallic articles on the body of the patient such as coins should also be kept in mind while interpreting a liver scintigram. Hot spots produced by slight extravasation of radioactivity at the site of injection at the ante-cubitus and contamination of bed or patient’s clothes by radioactive drops or spirit swab may be another source of artifacts.

The International Atomic Energy Agency (IAEA) in 1984, sponsored a three year regional coordinated research project on liver imaging in the South East Asian Countries, for which a standard liver scintigram report sheet was prescribed. This includes a comprehensive and convenient list of important points for the interpretation and description of a liver-spleen scintigram. This sheet can be requested from the Agency.

Normal liver scintigram

Radiocolloid image gives the best assessment of the size of the liver. It is difficult to give measurements for a standard ‘normal’ adult liver. The correct assessment of size comes with experience. Clinical examination of the patient improves this assessment but it should be always kept in mind that a palpable liver is not always enlarged. Conditions like chronic obstructive pulmonary disease, pleural effusion, tumours, subphrenic abscess, ascites, and laxity of the hepatic ligaments in the old age can make a normal liver palpable. On the other hand, an enlarged liver may not be palpable in cases of upward movement of right hemidiaphragm due to atelectasis or phrenic nerve paralysis.

The distribution of the radioactivity in a normal liver image is homogenous, gradually thinning out towards the left lobe. (Fig. 28.1.) Regarding the shape of the liver, various normal configurations have been described. A triangular outline due to less prominent left lobe; a prominent quadrate lobe; a tail-like projection extending downwards from the lower end of the right lobe (Riedal’s lobe), which may sometimes appear ‘detached’ from the right lobe due to deep impression of the lower coastal margin; and so on. Impressions of porta hepatis and falciform ligament may be seen at the junction of right and left lobes. Gall bladder may indent the inferior surface of the right lobe. Hepatic veins can notch the upper border of the hepatic image. Similarly enlarged heart and pericardial effusion produce a deep concavity along the upper border. In the posterior view, the right kidney often produces an impression on the right lobe and there is some masking of radioactivity in the liver tissue lying in front of the vertebral column. Spleen appears more prominent in this view as it is...
nearer to the detector of the imaging instrument. In cases of biliary obstruction, the dilated hepatic ducts may produce an appearance of focal defect at the junction of right and left lobes.

A normal liver may appear abnormal in the image due to extrahepatic causes e.g. displacement and compression by the abdominal masses, supra and subphrenic pathology and biliary disease.

Any deviation from the above description of a normal scan would indicate a strong possibility of a diseased liver. There are two main types of abnormalities which can be seen in the liver. These are (a) Diffuse or (b) Focal.

The diffuse abnormalities may manifest as hepatomegaly or atrophy of the liver. The image may show overall diminution of the uptake of the radioisotope irrespective of the size of the liver. The distribution of the radiopharmaceutical may be non-uniform with or without diminished uptake. A non-uniform uptake may be described, somewhat subjectively, in various ways, such as diffuse, patchy, mottled; occasionally a non-uniform uptake may mimic an appearance of multiple focal lesions, but such lesions do not show distinct boundaries.

The radiocolloid image is very sensitive for detecting the photon-deficient areas in the liver usually called focal defects. The smallest focal defect which can be detected in liver, using the modern gamma camera is about 1.0 cm in diameter. The detectibility also depends upon the location of the lesion. Rarely, focal hot spots may be visualized on the scan. This may happen in cases of Budd-Chiari syndrome (hepatic vein obstruction), focal nodular hyperplasia, and occasionally in superior vena caval obstruction where a bolus of activity injected into the basilic vein, can travel via collaterals and deliver a large amount of activity to the anterior mid-portion of liver.

Focal lesions can also be seen in the spleen, and one should not miss looking at the spleen critically in a radiocolloid liver image.

**DIFFUSE DISEASES OF LIVER**

**Cirrhosis**

Suspected cirrhosis of liver is a very important indication for radiocolloid liver scintigraphy. The typical picture in the advanced liver cirrhosis shows an atrophic, shrunken liver having markedly diminished radionuclide uptake with patchy, mottled appearance. The spleen is grossly enlarged and shows excessive radionuclide concentration. This phenomenon, where the normal liver-spleen ratio is reversed is called 'colloid shift' or 'spill-over', as the diseased liver is unable to accommodate sufficient quantity of colloid which is then shifted to or spilled over to spleen. (Fig. 28.2.) Additional confirmation of this condition is obtained by the visibility of spine, sternum and the pelvis in the scan and
occasionally the lungs as some colloid also spills over to the reticuloendothelial cells present in these organs.

In cases where the excessive intake of alcohol plays an etiological role, frequently the right lobe may be more damaged and appear smaller on the scan than the left lobe. The possible explanation for this being that the main stream of portal blood flow passes through the right lobe, and therefore more alcoholic damage to this lobe. In early cases of cirrhosis, the liver may appear enlarged or normal in size, although with diminished uptake, and spleen may be only moderately enlarged with positive 'spill-over' phenomenon. In long standing cases definite focal defects may appear indicating development of hepatocellular carcinoma for which cirrhosis is a predisposing condition.

The mechanism involved in producing diminished uptake of liver and spill-over to other organs seen on a radiocolloid scan involves:

(a) impairment of macrophage function
(b) diminished hepatic perfusion,
(c) replacement of liver parenchyma by fibrous tissue,
(d) shunting of blood from the liver to spleen and bone marrow,
(e) intrahepatic alteration in blood flow so that the blood is shunted away from the sinusoids which are lined by the macrophages.

In cirrhosis, widespread death of liver cells from many causes is accompanied and followed by progressive fibrosis, regenerative hyperplasia of surviving hepatocytes and distortion of liver architecture resulting in portal-systemic vascular shunts. Splenic enlargement is caused mainly by portal hypertension. The extreme degree of splenic enlargement is observed in advanced cirrhosis. The other important condition with comparable gross splenic enlargement is chronic myeloid leukaemia (CML). But in this disease, the most important finding on radiocolloid scan is normal relative uptake of radioactivity by liver and spleen and the 'spill-over' is therefore, not seen.

Using a gamma camera, we have done a short study of comparing the counts of small regions of interest (ROIs) of the same dimensions on the right lobe of liver and spleen. In normal individuals the average liver/spleen ratio was 4:1. Advanced cirrhotic cases showed exactly a reverse ratio. In cases of chronic hepatitis the liver/spleen ratio was 1:1.5. This technique can be applied in assessing the degree of impairment of liver function in quantitative terms to confirm the visual impression of diminished liver uptake.
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Other Diffuse Liver disorders

Other diffuse liver disorders leading to liver enlargement with or without non-uniform distribution of radioactivity in the liver include:

(a) Congestive cardiac failure,
(b) Lymphomas,
(c) Leukaemia,
(d) Amyloidosis,
(e) Sarcoidosis,
(f) Kala Azar,
(g) Malaria,
(h) Schistosomiasis,
(i) Acute and Chronic Hepatitis,
(j) fatty degeneration in diabetes.

Lymphomas may show as diffuse disease or as definite focal lesions.

FOCAL DISEASES OF LIVER

Amoebic abscess

In the developing countries, the amoebic liver abscess is still one of the common causes resulting in the appearance of a focal defect in a radiocolloid liver scan. However, in my experience of about 30 years in nuclear medicine in a developing country, I feel that there has been a gradual decline in the number of liver abscess cases during this long period. The reason for this is probably the gradual improvement in the living conditions and standards of personal and community hygiene in some of the developing countries. It is also likely that less number of patients are referred to nuclear medicine department, as many of them are referred for ultrasound examinations.

Amoebic liver abscess usually appears as a solitary, well-defined rounded focal defect mostly situated in the right lobe (Fig. 28.3). Less commonly the left lobe may be involved. Multiple abscesses of different sizes may occasionally be seen. Sometimes the location of the abscess is such that it produces obstructive jaundice through pressure on the main hepatic ducts. The exact site of the abscess can be ascertained by taking multiple views. It must be remembered that a focal defect on radiocolloid image is a non-specific finding. More information would be required to confirm that the lesion is an abscess. Ultrasonography is a convenient procedure to differentiate between solid and cystic lesions. Cystic lesion in a developing country could be an abscess or an hydatid cyst, although the latter is not as common as an abscess. The abscess is characterized by the presence of abdominal pain, pyrexia, nocturnal sweating, malaise and liver tenderness. This clinical picture is not seen in the hydatid cyst where the main complaint is enlargement of liver which may feel hard in the area of cyst. Amoebic abscess is often so insidious in its progress that clinical history is
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not very helpful in all the cases. It may also be remembered that in an early amoebic lesion where the disease is still in cellulitis phase and frank pus has not appeared the ultrasonography may give misleading information. The central area of the abscess (and cyst) is usually avascular. It is therefore, a routine at some centres to inject the radiocolloid when the patient is lying under the gamma camera and take sequential pictures after every 2-4 seconds for a dynamic blood flow study. A malignant lesion is usually hypovascular, but not completely devoid of perfusion as compared to the abscess or cyst.

Treatment with proper anti-amoebic drugs alleviates the patient’s clinical symptoms within one or two weeks. However, the cold area on the scan persists for a long time, even for several months. There is no point in doing follow-up scans every week or so. In any case, ultrasound scans are better for follow-up evaluation.

Pyogenic Abscess

Pyogenic abscess is seen less commonly in the developing countries. A pyogenic abscess is accompanied by acute symptoms of fever, malaise, sweating and pain in the right hypochondrium and higher mortality. There may be a large single abscess or multiple small abscesses. Timely treatment with antibiotics and aspiration, if required, often cures the disease.

Subdiaphragmatic Abscess

This is an uncommon condition where there is an abscess in the potential space between right hemidiaphragm and right lobe of the liver. Clinically, the patient shows all signs and symptoms of pyogenic infection but it is difficult to find the location of the abscess. The patient may complain of pain in the lower part of the chest on the right side. The radiocolloid liver scan may appear normal or there may be slight flattening of the upper border of the right lobe. The condition can be diagnosed by doing a liver and lung radiocolloid scan simultaneously. Patient is injected with $^{99}$Tc$^m$ sulphur colloid and $^{99}$Tc$^m$ Albumin macroaggregates and liver-lung area imaged in anterior, right lateral and posterior views. In case of subphrenic abscess, the cold gap between liver and lung is clearly outlined.

Hydatid cyst

Hydatid cyst is an helminthic infestation caused by a tiny tapeworm called Echinococcus granulosum for which dog and certain wild canines act as definitive hosts. The worm resides in the gut of these hosts. Animals like sheep, camel and other cattle are infested by ingesting the eggs from the pastures or water contaminated by the faeces of dogs. Men who live in close contact with dogs have a risk of getting infested. The embryo is liberated from the egg in the small intestine and gains access to the liver through portal circulation. The resultant cyst which is the larval stage of the worm, grows very slowly for years. It may ultimately calcify or rupture giving rise to multiple cysts. When the cyst has grown to a large size, it may produce pressure symptoms where it is located.
In nearly 75% of patients with hydatid disease, the right lobe of liver contains a single cyst. Multiple cysts are not very common. Hydatid cyst may also be found in lungs, brain or elsewhere. The treatment is essentially surgical. Cases of recurrence may be seen if some larvae escape to other parts of the liver. On clinical examination, the cyst feels hard and may be mistaken for a malignant growth. Calcification if present can be seen on radiological examination.

On a radiocolloid scan, the hydatid cyst appears as a 'cold' area (Fig. 28.4). The margins of the defect may be sharp and the shape more rounded as compared to an abscess or a tumour. Ultrasonography is a simple procedure to illustrate the cystic nature of the hydatid disease. Further confirmation may be possible through identification of daughter foci in the main cyst in the ultrasonogram. A blood pool or a perfusion study will exhibit a largely avascular nature of the defect. Intradermal (Casoni’s) test, complement fixation and immunofluorescent tests give support to the diagnosis in the presence of a long history and absence of signs and symptoms of an abscess. No attempt of confirming diagnosis with needle biopsy should be made in suspected hydatid cyst because of the risk of dissemination within and outside the liver.

Primary liver tumours

Hepatocellular carcinoma is a fairly common finding in some of the developing countries. It is the first or second commonest malignancy in the male population.

Cirrhosis of liver, a predisposing condition, increases the risk of primary liver cancer manifold. In a study done in Pakistan 12% of the cases of cirrhosis of Liver were found to be positive for cancer on radiocolloid scan and histological examination (needle biopsy). Liver cancer can, however, occur in an otherwise normal liver at any age. Regular use of oral contraceptives, which may produce hepatic adenomas, may be another causative factor. HBsAg positive sera helps in detecting high risk groups. On a radiocolloid scan, the liver cancer appears as a 'cold' area which is solitary in most of the cases but multiple primary lesions are also found. $^{67}$Ga study may produce a positive image of the cancerous area but it is not always outlined well and the appearance is non-specific. It is, therefore, not advised as a routine test. The better alternative is to do ultrasonography and make sure that the lesion is solid and proceed with needle biopsy for the exact diagnosis. High blood level of alpha-fetoprotein is a common finding but for diagnosis, it is still non-specific. Sequential estimations at regular intervals are supposed to be of prognostic value.

The use of contraceptive pills on a regular basis, although uncommon in developing countries, may be seen in young women in urban areas. This may give rise to asymptomatic hepatic cell adenomas incidently detected on a radiocolloid image as a focal defect due to lack of Kupffer cells. The tumour tends to regress with the discontinuation of pills. The hepatic cell adenoma should be distinguished from focal nodular hyperplasia of liver which is also common in women and appears as normal liver tissue in a radiocolloid image.
Metastatic liver disease

Primary malignancies of the gastro-intestinal tract are likely to give rise to early secondary deposits in the liver via portal circulation. Direct local extension from the gall bladder is also a common finding. Other more common primary malignancies Likely to produce metastatic liver disease are those of breast and lungs (Fig. 28.5). Lymphomas also involve liver at an advanced stage. The hepatic metastases in most of the cases appear as multiple lesions which may be discrete or infiltrative in type. However, a solitary lesion in the presence of a known primary malignancy indicates a strong possibility of a secondary deposit. Ultrasound examination may be done to ascertain the solid nature of the lesion.

Massive infiltration of liver by metastatic tissue may produce impaired reticulo-endothelial function causing colloid shift from liver to spleen. The sensitivity of radio-colloid scan to detect metastatic disease in the liver has been mentioned to be in the range of 75-80% as the small deep seated lesions are likely to be missed. The sensitivity will probably improve with the use of single photon emission tomography (SPECT) but its use in the developing countries is still limited.

Spleen Image

Reference to enlargement of spleen in cases of portal hypertension has already been made while discussing cirrhosis of the liver. In the tropical countries, repeated malarial infestation may be an important cause of splenomegaly but is not as frequently seen as before. A number of haematological disorders also produce splenic enlargement. A grossly enlarged spleen with moderate liver enlargement is quite a frequent finding in cases of chronic myeloid leukaemia. Hepatosplenomegaly may also be seen in patients suffering from lymphoma. It may be emphasized that the normal liver/spleen ratio of radiocolloid accumulation is not altered in splenomegaly due to reasons other than portal hypertension unless the liver is also damaged.

Focal defects in spleen is a rare finding which may be seen in cases of lymphoma. Haematoma as a result of injury to an enlarged spleen also appears as a cold area on a radiocolloid scan. We have not seen any case of cyst or abscess in the spleen.

Like liver, the spleen can also be displaced by mass lesions and other abnormalities in the neighbouring structures like stomach, pancreas, left lung, pleura, left kidney and masses in the abdomen.
LIVER AND GASTROINTESTINAL TRACT

PATTERN OF LIVER DISEASE IN PATIENTS IMAGED WITH RADIOCOLLOIDS

The information given below was presented in a meeting of Experts Group for the IAEA-RCA Regional Cooperative project on "Imaging procedures for the diagnosis of liver diseases" held at Seoul on 22 - 24 August, 1984. It is derived by analyzing the results of 1000 consecutive patients in whom radiocolloid liver imaging was done during July to October, 1983 at the Mayo Hospital, Lahore, Pakistan. Out of these 1000 patients 514 were imaged with a gamma camera and 486 with a rectilinear scanner.

Table II shows the age and sex distribution of these 1000 cases. About half of the patients (45%) are between the age 41 and 60, and the male to female ratio is almost same. Table III shows the disease-spectrum in these patients. Definite focal defects were found in 11.3% cases. A majority of the patients (46.9%) were those with Hepatomegaly of diverse origin. 18.6% cases had no abnormality. In the patients with definite focal defects malignancy was the most common (6.8%). Abscess was found in 3% and the cyst in only 1.4%. Spleen was enlarged in 31.3% of the images. Cirrhosis of liver is still fairly common. In 3.8% cases, it was not possible to say whether the abnormality seen is a true focal defect or is a diffuse low activity area.

This information describes a pattern of hepatic diseases in patients referred for imaging to a nuclear medicine department in one of the developing countries. It may not represent the pattern in all the developing countries of South East Asia but it still gives an overall picture of the types of liver diseases with their relative frequencies as seen in one of them.

**TABLE II. AGE AND SEX DISTRIBUTION OF 1000 PATIENTS REFERRED FOR LIVER IMAGING.**
AEMC, LAHORE, PAKISTAN.

<table>
<thead>
<tr>
<th>AGE</th>
<th>MALE</th>
<th>FEMALE</th>
<th>TOTAL</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 10</td>
<td>20</td>
<td>9</td>
<td>29</td>
<td>2.9</td>
</tr>
<tr>
<td>11 - 20</td>
<td>45</td>
<td>33</td>
<td>78</td>
<td>7.8</td>
</tr>
<tr>
<td>21 - 30</td>
<td>63</td>
<td>67</td>
<td>130</td>
<td>13.0</td>
</tr>
<tr>
<td>31 - 40</td>
<td>75</td>
<td>111</td>
<td>186</td>
<td>18.6</td>
</tr>
<tr>
<td>41 - 50</td>
<td>100</td>
<td>142</td>
<td>242</td>
<td>24.2</td>
</tr>
<tr>
<td>51 - 60</td>
<td>102</td>
<td>120</td>
<td>222</td>
<td>22.2</td>
</tr>
<tr>
<td>61 - 70</td>
<td>50</td>
<td>27</td>
<td>77</td>
<td>7.7</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>28</td>
<td>8</td>
<td>36</td>
<td>3.6</td>
</tr>
<tr>
<td>TOTAL</td>
<td>482</td>
<td>518</td>
<td>1000</td>
<td>100</td>
</tr>
</tbody>
</table>
### TABLE III. DISEASE SPECTRUM OF PATIENTS FOR LIVER IMAGING.

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>MALE</th>
<th>FEMALE</th>
<th>TOTAL</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>51</td>
<td>51</td>
<td>102</td>
<td>10.2</td>
</tr>
<tr>
<td>Abscess</td>
<td>19</td>
<td>11</td>
<td>30</td>
<td>3.0</td>
</tr>
<tr>
<td>Cyst</td>
<td>08</td>
<td>06</td>
<td>14</td>
<td>1.4</td>
</tr>
<tr>
<td>Subphrenic Abscess</td>
<td>01</td>
<td>0</td>
<td>01</td>
<td>0.1</td>
</tr>
<tr>
<td>Malignancy</td>
<td>34</td>
<td>34</td>
<td>68</td>
<td>6.8</td>
</tr>
<tr>
<td>Hepatomegaly; unif. upt.</td>
<td>212</td>
<td>257</td>
<td>469</td>
<td>46.9</td>
</tr>
<tr>
<td>Diffuse low upt. areas</td>
<td>44</td>
<td>48</td>
<td>92</td>
<td>9.2</td>
</tr>
<tr>
<td>Uncertain</td>
<td>18</td>
<td>20</td>
<td>38</td>
<td>3.8</td>
</tr>
<tr>
<td>Normal</td>
<td>95</td>
<td>91</td>
<td>186</td>
<td>18.6</td>
</tr>
<tr>
<td>TOTAL</td>
<td>482</td>
<td>518</td>
<td>1000</td>
<td>100</td>
</tr>
<tr>
<td>Spleen enlargem.</td>
<td>156</td>
<td>156</td>
<td>312</td>
<td>31.2</td>
</tr>
</tbody>
</table>

### COMPARISON OF NUCLEAR HEPATIC IMAGING WITH ULTRASONOGRAPHY

In most of the developing countries, the nuclear medicine facilities are scarce and workload immense. A considerable number of routine referral is for radiocolloid liver imaging. At the same time, there is a feeling that the information obtained by a nuclear liver image can also be obtained from ultrasound examination which is less expensive and also time-saving. In the developing countries therefore, if most of the load of liver imaging is shifted from nuclear to sonography, the nuclear facility can be spared for tests like detection of skeletal metastases, cardiac studies etc. which can not be done by non-nuclear techniques. The question to be answered is, how far an ultrasonographic examination can replace the nuclear radiocolloid liver imaging? The following Table IV summarizes the differences between these two imaging modalities:
TABLE IV. COMPARISON OF NUCLEAR WITH ULTRASOUND IMAGING OF THE LIVER.

<table>
<thead>
<tr>
<th></th>
<th>Nuclear</th>
<th>Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>more expensive</td>
<td>less expensive</td>
</tr>
<tr>
<td>Spatial resolution</td>
<td>2 cm or larger</td>
<td>can detect smaller lesions</td>
</tr>
<tr>
<td>Differentiation between cystic vs solid</td>
<td>not possible</td>
<td>possible</td>
</tr>
<tr>
<td>Skills and training required</td>
<td>modest</td>
<td>highly skilled and experienced doctor required</td>
</tr>
<tr>
<td>Liver size estimation</td>
<td>excellent</td>
<td>less satisfactory</td>
</tr>
<tr>
<td>Radiation exposure</td>
<td>within permissible limits</td>
<td>nil</td>
</tr>
<tr>
<td>Imaging in the presence of dressings, drains, plasters, open wounds etc.</td>
<td>possible</td>
<td>Impossible</td>
</tr>
</tbody>
</table>

Previously the ultrasound examination of the liver suffered from the presence of ‘rib-shadowing’ rendering a part of the liver ‘invisible’ to the transducer, but now with the advances in the design of transducers and availability of sector scanners the entire liver can now be ‘seen’. One can even scan through the intercostal spaces.

The International Atomic Energy Agency under its Regional Cooperation Agreement (RCA) program for Asia Pacific Region has started a regional cooperative research project in 1989 comparing the efficacy of ultrasonography with nuclear imaging for the detection of focal and diffuse liver disease. Our institute (INMOL Lahore) is also one of the participants in this study.

Although it will take another two or more years for the final results of the IAEA’s project to come but in the meantime, we have been collecting information on patients who have undergone both radiocolloid and ultrasound imaging and have analyzed results in 196 patients up to now which is as follows.
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<table>
<thead>
<tr>
<th>Total number of Patients</th>
<th>196</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) Focal lesion positive cases</td>
<td>142</td>
</tr>
<tr>
<td>(combining nuclear and ultrasound images)</td>
<td></td>
</tr>
<tr>
<td>Nuclear image detected</td>
<td>126</td>
</tr>
<tr>
<td>missed</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>142</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>88%</td>
</tr>
<tr>
<td>Ultrasound detected</td>
<td>134</td>
</tr>
<tr>
<td>missed</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>142</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>94%</td>
</tr>
</tbody>
</table>

This means that nuclear imaging missed 16 out of 142 cases of focal defects which were detected by ultrasound imaging while ultrasound missed 8 out of 142 cases of focal defects which were detected by the nuclear image.

| Diffuse liver disease positive | 44 |
| Nuclear scan detected | 32 |
| missed | 12 |
| Total | 44 |
| Sensitivity | 72.7% |
| Ultrasound detected | 40 |
| missed | 4 |
| Total | 44 |
| Sensitivity | 90% |
LIVER AND GASTROINTESTINAL TRACT

This means that 12 out of 44 cases missed by the nuclear imaging are detected by the ultrasound and 4 out of 44 missed by the ultrasound were detected by the nuclear imaging.

(a) Cases normal both on nuclear and ultrasound imaging = 10

(b) Ultrasound examination revealed that 26 cases who were positive for focal defect both on ultrasound and nuclear imaging were cystic in nature.

(c) In 12 cases, where nuclear scan showed only solitary lesion, the ultrasound revealed multiple lesions.

(d) The cases of diffuse disease which were missed by the nuclear image were mainly those with congestive cardiac failure and biliary obstruction in which the ultrasound scan showed congested vessels and dilated hepatic ducts.

From the above observations, it appears that ultrasonography is superior to nuclear imaging for the detection of focal defects and diffuse liver disease (Figs. 28.6 A and B and 28.7 A and B). There is, however, a small percentage of cases missed by the ultrasound and detected by nuclear imaging. It may, however, be prudent to see the final results and recommendations of the above mentioned multicentric trial initiated by IAEA.

HEPATOBILIARY IMAGING.

The chemical substances which follow the route of bilirubin in liver and biliary passages, can be used with a suitable radioactive label to study the function of hepatocyte and the biliary system. In fact, the first compound recognized as a possible liver imaging radiopharmaceutical was a hepatobiliary agent, the $^{131}$I labelled Rose Bengal, a fluorescent halogenated dye. The other dye used for this purpose was Bromosulphthalein (BSP). As compared to the colloids, these dyes had the disadvantage of rapid excretion and constantly changing levels of activity in different parts of the liver even during the course of examination, especially with the rectilinear scanner, resulting in poor images. Later on, with the development of gamma cameras $^{123}$I labelled Rose Bengal and BSP were revived for studying hepatobiliary function but by that time $^{99}$Tc labelled compounds had established their superiority for use with the gamma camera.

These new imaging agents are iminodiacetic acid (IDA) analogues which provide high quality images of the biliary system. The first IDA derivative used widely was the dimethyl IDA also called hepatobiliary IDA or HIDA. Approximately 85% of this compound is excreted by the liver and 15% by the kidneys. In cases of liver damage, a larger fraction is excreted through the kidneys. However, acceptable biliary images can be obtained with serum bilirubin levels as high as 5-7 mg/dl. The other derivatives of IDA devised later include paraisopropyl IDA (PIPIDA), parabutyl IDA (BIDA), diisopropyl IDA (DISIDA) and
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diethyl IDA (DEIDA). DISIDA is probably more suitable because of its high biliary excretion.

Procedure

About two hours fasting before the test is usually advised. Prolonged fasting renders the gall bladder akinetic and filled with viscous, static bile which inhibits the entry of HIDA in the gall bladder and therefore poor visualization of gall bladder. Similar thing happens in patients on total parenteral nutrition or patients of chronic alcoholism.

The patient is given 3 - 5 mCi (100 - 200 MBq) of \(^{99}\text{Tc}^m\) labelled IDA intravenously. Sequential images of anterior abdomen are taken with a gamma camera, at 10 minutes intervals for one hour. The first image taken five minutes after injection may be useful to outline the liver as the radioactivity is passing through it.

As the study proceeds, the radioactivity passes from the liver towards porta hepatis and hepatic ducts may be (Fig. 28.8) visualized. Simultaneously the common bile duct and the cystic duct become visible. The gall bladder, normally, fills up within half an hour after injection. At about the same time, the loops of duodenum are also visualized. Clearance of activity from the liver starts within 10-15 minutes and at the end of the study the liver is hardly visible and the gall bladder still shows prominently. At this point, the patient may be given a standard fatty meal as in cholecystography to demonstrate contraction and emptying of the gall bladder.

In those cases, where the overall liver function is poor the study can be continued for a longer period as there may be a delayed visualization of various structures. If the liver function is grossly impaired the radiopharmaceutical is excreted mainly through the renal system and both kidneys and urinary bladder show up prominently. This also happens in cases of biliary atresia. In such situations, the activity in the right kidney may be mistaken for the gall bladder, but presence of the left kidney image in the scan picture should avoid such a confusion.

The IDA hepatobiliary study gives useful information in a number of clinical conditions like acute cholecystitis, chronic cholecystitis, gall stones, biliary tract obstruction, jaundice, bile leak, congenital biliary atresia (Fig. 28.9) and choledochal cysts.

Acute cholecystitis

Acute cholecystitis is almost always associated with obstruction of the gall bladder neck or cystic duct by a gall stone or an intestinal parasite like a round worm. Occasionally, obstruction may be by mucus or rarely by a neoplasm. HIDA hepatobiliary study is ideal for (Fig. 28.10) investigating the patency of the cystic duct. If the gall bladder is outlined in the study, the patency of the cystic duct is proved beyond doubt. HIDA is so sensitive for the diagnosis of this condition that intravenous cholangiogram for this purpose is now considered unnecessary.
Although the non-visualization of gall bladder in a HIDA study in the presence of clinical signs and symptoms of acute cholecystitis establishes the diagnosis, some rare situations should be kept in mind where the non-visualization could also be due to few other reasons. As already mentioned a patient fasting for more than 12 hours has his gall bladder filled with bile and therefore the radioactive bile after HIDA injection cannot enter unless the gall bladder contracts and expels the stored bile. This can be achieved by giving an injection of Cholecystokinin (CCK) along with HIDA. However two other situations still remain in which CCK fails to contract gall bladder. These include cases with chronic alcoholism and/or pancreatitis and those who are on total parenteral nutrition. In these situations the ultrasonography can help in diagnosis by demonstrating a full gall bladder corresponding to the clinically tender area in the right upper abdomen. Sonography is also capable of detecting calculi, but the presence of calculi alone is not sufficient to prove the diagnosis of acute cholecystitis.

Although there are no specific findings in a HIDA study characteristic of chronic cholecystitis, a few important points can be briefly mentioned which are very often associated with chronic gall bladder disease:

(a) Delayed visualization of the gall bladder, i.e. one hour or more after injection of HIDA.

(b) Delayed biliary to bowel transit time.

(c) Filling defects within the gall bladder due to stones.

(d) Suboptimal contractile response of a filled gall bladder to cholecystokinin.

Biliary Atresia

In jaundiced neonates, it is important to differentiate between congenital biliary atresia and neonatal hepatitis, so that biliary atresia could be corrected by timely surgical intervention. If HIDA hepatobiliary study shows a patent biliary passage, biliary atresia is ruled out. In cases of atresia, the exact site of obstruction can be seen sometimes at the level of hepatic duct, as it emerges at the Porta hepatis. In such cases, the radioactivity is ultimately excreted through the urinary system and both kidneys and the urinary bladder are outlined in the scan.

The hepatobiliary study is the most convenient, sensitive, and non-invasive test for detection of bile leakage after trauma or a surgical procedure. After an intravenous injection of the radiopharmaceutical (5 mCi or 200 MBq), the abdomen is imaged for at least two hours. Delayed pictures may be taken at 12 hrs and 24 hrs. Presence of radioactivity outside liver and biliary system would confirm pathological extravasation. Ultrasonography and CT imaging may reveal abnormal fluid collection in the area but cannot detect the exact nature of the fluid.
Blood Pool Imaging of Liver

It may be useful to find out the state of perfusion of a focal defect seen on a radiocolloid liver scan. While cysts and abscesses are devoid of blood supply, the neoplastic focal defects may show varying degree of perfusion. However, the absence of perfusion does not necessarily prove that the lesion is non-neoplastic because a neoplastic focal defects may also appear avascular in a blood pool scan due to central necrosis. Hemangiomas, on the other hand, show as hypervascular areas in the blood pool scan.

If a computerized gamma camera is available for the study, information on perfusion of different parts of the liver can be obtained as a part of the routine radiocolloid imaging. For this purpose, the patient is positioned under the gamma camera before injecting the radiocolloid. The radioactivity over the liver is recorded continuously, immediately after the injection as the blood carrying the bolus of radiocolloid appears in the liver. Later on, the static radiocolloid uptake images are taken as usual. Drawing the regions of interest (ROIs) over the focal defects in the perfusion phase and radiocolloid uptake phase it can be assessed whether the focal defect appearing in the radiocolloid phase is vascular or avascular. Time-activity curve can also be generated on these ROIs to get better understanding of the perfusion of the lesion.

Alternatively, a blood pool agent can be used to study the vascularity of the area corresponding to the focal defect in the radiocolloid image. For this purpose, the most convenient technique is the 'in vivo' of red blood cells using $^{99}$Tc as a label.

A sterile solution of 1.2 mg stannous chloride and 1.8 mg of pyrophosphate stabilized at a pH around six is injected intravenously. $^{99}$Tc, at least 10 mCi (400 MBq), is injected i.v. half an hour later. This results in 'in vivo' of RBCs. We have used this technique successfully for investigating focal defects in the liver. The other possibilities are to use $^{99}$Tc labelled human serum albumin or in vitro labelled red blood cells.

$^{67}$Gallium imaging

Gallium localizes non-specifically in soft tissue tumours and inflammatory lesions. It is expensive and difficult to obtain in the developing countries. Its physical characteristics are not ideal for in vivo imaging; low energy photons (91 keV) not suitable for optimal intrinsic resolution and the high energy photons (394 keV) difficult to collimate. Its relatively slow excretion through the intestine, often interferes with accurate Imaging of abdominal and pelvic lesions.

$^{67}$Ga scintigraphy is useful in detecting sites of acute infections as well as other inflammatory and granulomatus processes. It is useful especially in detecting pulmonary inflammatory diseases, abdominal and pelvic inflammations and in inflammatory diseases of the skeleton.
LIVER AND GASTROINTESTINAL TRACT

$^{67}$Ga scintigraphy is also useful as a diagnostic procedure for tumour detection, staging and monitoring the effect of therapy. The tumours usually detected with $^{67}$Ga are lymphomas, lung carcinoma, primary hepatic carcinoma and malignant melanoma. Gallium scintigraphy is neither very sensitive nor very specific but occasionally it might provide some useful information. However, it has no significant role in routine diagnostic work up of a patient with a space occupying lesion in the liver.

A more specific and sensitive method for imaging inflammatory disease is by radiolabelled white blood cells, which is described extensively in Chapter 27.

SPECT vs conventional imaging of the liver

With the developments in ultrasonography and computerized axial tomography the value of radionuclide liver imaging is significantly reduced as the sensitivity of the detection of liver lesions by isotopic methods has been reported to be 75% and 85% whereas these other imaging modalities claim accuracies of 90% or better. Single photon emission tomography has been found to improve the detectability of liver lesions (Fig. 28.11).

Liver is a large solid organ with complex internal scatter patterns. Liver imaging with SPECT needs attenuation correction and a high resolution collimator. Sensitivity of SPECT for liver focal defects is as high as 92% in some of the reported series.

Since the size of a liver lesion is a useful parameter to a clinical oncologist, the system that provides this information is advantageous. Lesion reduction is a volumetric phenomenon, not necessarily measured accurately in only two dimensions. It is possible to determine the volume of liver lesions from SPECT data. This type of study is very helpful in monitoring established liver lesions in patients on chemotherapy. SPECT, not only provides improvement in the detectability of liver lesions, but also gives exact measurement of the volume of such lesions.

GASTROINTESTINAL TRACT

Gastro-oesophageal Function

Radionuclide techniques can be employed for studying the function of oesophagus, stomach and any abnormalities at the gastro-oesophageal junction. Using an appropriate radiopharmaceutical and a computerized gamma camera a number of useful tests can be performed quite conveniently. The commonly performed tests include: gastric emptying rate, oesophageal transit time, and detection and quantification or gastro-oesophageal reflux. In performing these studies non-absorbable radiopharmaceuticals such as $^{99}$Tc$^{m}$ sulphur colloid or $^{99}$Tc$^{m}$DTPA (diethylene triamine penta-acetic acid) are used.
Gastrointestinal Bleeding

Since 1960, we have been using $^{51}$Cr labelled red blood cells for measuring the amount of blood loss in the stools in suspected gastrointestinal bleeding by a simple technique. Using an activity of 100 $\mu$Ci $^{51}$Cr, 5 to 10 ml of red cells of the patient are labelled in vitro, and re-injected immediately. The patient is asked to take two identical empty dry milk tins of about half a litre capacity and collect 24 hours stools in one of these tins. Next day the tin containing the stools, closed with a tight lid, along with the empty tin is handed over by the patient to the hospital staff.

Two ml of patient's blood is taken and added to the empty tin with some saponin to haemolyze the blood. The tin containing stools is weighed on a small balance. The other tin, now containing two ml blood is placed on the same balance and water added to it slowly till it weighs the same as the other tin containing the stools. The lid is tightly closed and tin is shaken few times to make a homogeneous solution of the haemolyzed blood. The radioactivity of the two tins is measured by a scintillation counter in identical geometrical conditions. Counts of the stools compared with the blood counts. The exact volume of blood present in the 24 hours stools can be calculated by a simple equation.

$$\text{Blood loss in mls.} = \frac{\text{CPM of stools } \times 2}{\text{CPM of blood}}$$

Two ml blood sample is taken as this volume gives reasonable counts on the scintillation counter. Thus simply by looking at the counts obtained from the 24 hours stools one can find out at a glance whether there is any excessive blood loss present. The exact volume is then calculated.

This simple test, although quite useful for measuring total blood loss in stools in 24 hours, does not give any information about the exact site of bleeding in the gut for which an imaging technique is needed.

It is important to locate the site of gastrointestinal bleeding before a decision for an active intervention. The radiopharmaceutical generally used for detecting lower G.I. bleeding is $^{99m}$Tc sulphur colloid. It is routinely available in the nuclear medicine departments because of its use for radiocolloid liver imaging. The other important advantage which it has over the intravascular blood pool agents (e.g. $^{99m}$Tc labelled RBCs) is its rapid clearance from circulation by the reticuloendothelial system of liver and spleen resulting in very low tissue background activity providing excellent contrast between background and extravasated radioisotope at the bleeding site.

The radioactivity in the liver makes it difficult to detect any bleeding sites in the upper abdomen, but even with the blood pool agents the liver activity is quite high because of the vascularity of liver. The procedure requires a dose of 10 mCi (400 MBq) of $^{99m}$Tc sulphur colloid to be injected intravenously with the patient placed under the gamma camera. A large
field-of-view camera which can cover the whole abdomen at a time and a low energy
collimator are necessary. 300 000 to 500 000 count images are obtained every two minutes
for 15 minutes. A bleeding site is seen as a hot spot in the image. If the study is continued,
the activity may be seen travelling distally along the intestine with peristaltic movements. A
carefully performed study has a high degree of sensitivity with a low false negative rate.
Because the sulphur colloid is cleared from the circulation within 15 minutes, only that
bleeding can be detected which occurs within 15 minutes of injection.

For detecting intermittent bleeding, the intravascular blood pool agents should be used
and patient imaged intermittently for 24 hours after the injection. As the sensitivity of this
procedure is low, larger amounts of blood should extravasate for detection as compared to
the radiocolloid technique.

Meckel’s diverticulum

Meckel’s diverticulum is a developmental anomaly which is in the form of a small sac
like protrusion from anterior mesenteric border of the ileum about three feet proximal to the
ileocecal valve. This diverticulum is lined with ectopic gastric mucosa. This occurs in about
2% of the population and in most of the cases remains symptomless. Occasionally
haemorrhage, intussusception and volvulus may occur in this abnormal sac. These
complications are accompanied by bleeding. The bleeding can be demonstrated by the
radionuclide tests already described. The presence of ectopic gastric mucosa can be
demonstrated by the 99mTc pertechnetate imaging. About 1-2 mCi (37- 54 MBq) of the
radiopharmaceutical is injected intravenously and abdominal images are obtained sequentially
every five minutes. Any spot of radioactivity appearing in the intestinal area should be
interpreted with reference to gastric activity. A positive scan usually shows a focal area of
increased activity in the right lower quadrant of the abdomen. Barret’s disease (gastric
mucosa at the distal end of the oesophagus) can also be demonstrated by this technique.

Gastric Emptying

Gastric emptying can be studied either with liquids or with solids. The liquids leave the
stomach faster than the solids. For the study of liquid phase about 500 μCi of 99mTc sulphur
colloid or 99mTc DTPA is dissolved in half a glass of milk and given to the patient to drink
after overnight fasting. For solid phase study, the same amount of radio-pharmaceutical is
mixed with about 150 grams of solid diet like mashed potatoes and given to the patient to eat.
Radioactivity is recorded over the stomach for one hour with the patient lying supine under
a computerized gamma camera. A region of interest over the stomach is fixed and time
activity curve generated. The results are usually expressed as “T½ emptying” or the time
taken by the gastric radioactivity to reduce to half the original value.

The technique is frequently useful in finding out the state of gastric mobility in systemic
diseases like diabetes mellitus and scleroderma and following surgical procedures such as
vagotomy.
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Gastro-oesophageal reflux

The same dose of radiopharmaceutical is used in liquid form as prescribed for the gastric emptying procedure. The radioactivity is recorded with the help of a gamma camera over the gastro-oesophageal junction, with the patient lying supine. The study may continue for half an hour. Continuous recording on a computerized gamma camera or repeat images at fixed intervals may be obtained. The simplest procedure would be to see the appearance of radioactivity in the distal part of the oesophagus in the images taken. Pressure may be applied over the stomach to provoke reflux. Using regions of interest over the lower oesophagus and stomach the amount of reflux can be expressed in quantitative terms as percentage of the gastric contents observed in the oesophagus. (Fig. 28.12).

Oesophageal transit.

The oesophageal transit time may be prolonged in diseases like achalasia, scleroderma, diffuse idiopathic oesophageal spasm and other non-specific motor disorders of the oesophagus. This parameter can be measured by using $^{99}$Tc™ sulphur colloid or $^{99}$Tc™ DTPA in liquid form in the same dose as for gastric reflux. The patient drinks, in one swallow, the radioactive liquid while lying supine under a computerized gamma camera. In normal subjects the radioactivity rapidly traverses the oesophagus and is not visualized by 4-10 seconds after deglutition. In patients with motor disorders the activity can be seen in the oesophagus for a long time in spite of repeated attempts to swallow (successive dry swallows). In such cases, the study should be prolonged and actual transit time determined, which may be as long as 15-30 seconds.

Immunoscintigraphy for colorectal cancer

The presence of carcinoembryonic antigen (CEA) in the colorectal cancer makes it possible to localize such tumours with immunoscintigraphic technique by using $^{99}$Tc™ labelled anti-CEA antibodies. This procedure has been found useful in the following situations.

(a) In cases of apparently curative resection of the colorectal cancer, the rise in the serum levels of CEA precedes clinically evident relapse by several months. Scintigraphy using labelled anti CEA antibodies may detect the recurrent sites at an early stage.

(b) In cases of recurrence, the immunoscintigraphy may reveal an extensive disease and save the patient from second laparotomy.

(c) Recurrence in the scar may be detected and removed.

(d) An apparently benign rectal polyp may give a positive image and resected extensively like a malignant lesion.
LIVER AND GASTROINTESTINAL TRACT

During the last few years, the anti-CEA colorectal scintigraphy has been fairly standardized and kits are now commercially available.

RADIOIMMUNOASSAYS

Tumour markers

Tumour markers are chemical substances mostly proteins, which are associated with the presence of certain specific tumours in the body. These substances are usually present in the serum of normal subjects in low quantities. With the appearance of specific tumours, and secretion of these substances in large quantities by the tumour cells, the serum levels of these tumour markers rise above the normal values. Regression of the tumours results in their return to normal values. Any increase in the level of a particular tumour marker after the patient has been successfully treated would indicate relapse. There are two important tumour markers related to gastro-intestinal tract and the liver malignancies which can be measured by RIA technique. These include the carcinoembryonic antigen and Alpha-fetoprotein.

Carcinoembryonic antigen (CEA)

This antigen is a glycoprotein with a molecular weight of approximately 180,000, which is produced in appreciable amounts by the fetal large intestine. In adults, the CEA may be present in serum in small quantities usually not exceeding 4 ng/ml, but in the presence of certain malignancies the serum concentration may rise to high levels. The malignant tumours of gastro-intestinal tract and other sites such as pancreas, ovary, breast, lung and uterus may be associated with excessive serum levels or CEA. Very high levels of CEA are often an indication of spread of tumour to the liver.

CEA levels in serum may be raised in a number of non-malignant conditions. For instance about 14% of chronic cigarette smokers have elevated serum levels of CEA. Patients with some non-malignant tumours may also have raised levels. 15 - 20% of subjects with inflammatory disorders such as ulcerative colitis, Crohn’s disease, pancreatitis, acute and chronic liver diseases and lung infections show elevated serum levels of CEA. In spite of the fact that raised serum CEA is not specific to malignant tumours, very high concentrations e.g. above 20 ng/ml are highly suggestive of malignancy.

The CEA test is not useful as a screening procedure to detect cancer in general population or in an otherwise asymptomatic person. However, the CEA test is now well-accepted as the best non-invasive test which may be used to assist in the management of patients with colorectal, breast, lung and other cancers.

The CEA serum assays by radioimmunometric techniques are being widely used even in the developing countries by using commercially available kits. Whenever possible the patients must be given the benefit of this useful investigation. It is possible to reduce the cost of these assays by using bulk reagents.
CHAPTER 28

Alpha-fetoprotein (AFP)

Alpha-fetoprotein is a specific fetal serum alpha-globulin which consists of a single polypeptide chain and is composed of 96% protein and 4% carbohydrate. Initially during the fetal life the AFP is produced by the yolk sac and the fetal liver. By 13 weeks of gestation, the fetal plasma concentrations of AFP reach peak level of approximately 3000 µg/ml which is totally derived from the hepatic origin. Subsequently the AFP levels decline and reach a level of approximately 80 µg/ml at birth, and 0 - 20 ng/ml at the age of two years. This level is maintained for the rest of the life.

Elevated levels of AFP are found in many patients of hepatocellular carcinoma and teratoma of the testis or the ovary. Measurement of the serum AFP levels can be useful in the diagnosis and as a baseline information in these patients in following the response to treatment, which if successful results in decrease in AFP levels in serum. Similarly any rise of the AFP levels during follow-up would indicate a relapse or an uncontrolled disease.

AFP is not entirely specific to hepatocellular carcinoma and teratoma as elevated AFP levels have been seen in liver cirrhosis and viral hepatitis probably associated with liver regeneration. However, persistently elevated level in excess of 1000 ng/ml are strongly suggestive of presence of hepatocellular carcinoma or teratoma.

Hepatitis B surface antigen

Hepatitis B surface antigen (HBsAg) is a 22 nm particle, which can be produced by the virus in the human body in large amounts. It is the outer coat of Hepatitis B virus (HBV) and is probably not infectious as such. Nevertheless, finding of HBsAg in the blood is regarded as an indicator of the presence HBV. All patients, who receive blood containing HBsAg, do not develop hepatitis, but the risk that they will develop hepatitis is very high. This close association between detection of HBsAg in the blood and the transmission of hepatitis B led to the realization that all blood to be transfused should be screened for HBsAg. Thus a lot of work was done to develop the assay procedures for the detection of HBsAg. Since the use of screening procedures, the incidence or transfusion induced hepatitis has dropped sharply. Moreover it has been established that a sensitive screening test like Radioimmunoassay (RIA) can result in a very significant decrease of transfusion hepatitis.

There are several methods, which are employed for screening HBsAg from blood. Most commonly used are:

1. Latex agglutination
2. Red Cells agglutination
3. Enzyme Immunoassay
4. Radioimmunoassay

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Radioimmunoassay is considered to be the most sensitive assay for the detection of HBsAg, and is based on the principle that $^{125}$I conjugated to anti-HBs can act as a good indicator for the presence of HBsAg in the antigen - antibody reaction. In this method anti-HBs is coated on to a solid phase e.g. polystyrene beads. This is done by dipping the beads overnight in anti-HBs solution buffered at pH 9.5. The specimen to be tested for HBsAg is poured on to the anti-HBs coated beads in a tube and incubated overnight at room temperature. After the incubation the beads are washed and $^{125}$I labelled anti-HBs is added and incubated again for one to two hours depending upon the method used. At the end of this, the beads are washed again and binding of $^{125}$I is measured by a gamma counter. The number of counts are directly proportional to the amount of HBsAg present in the sample tested. This is known as Sandwich method.

Routine screening of the patients with HBsAg resulted in the discovery that many people have HBs in their blood. These people are healthy and are asymptomatic carriers of HBsAg. Test should be repeated to confirm the presence of HBsAg in their blood. If the antigenemia lasts for more than six months and the persons are found positive for HBsAg in two serum samples obtained six months or more apart, they should be considered as HBsAg chronic carriers.

It has been found that the numbers of HBsAg chronic carriers are high among the following groups:

1. Drug Abusers
2. Homosexuals
3. Patients in renal dialysis and oncology units
4. Recipients of blood transfusions
5. Recipients of organ transplants
6. Persons in lower socioeconomic areas.

Though the male population has been found to be positive for HBsAg twice as often as female population, it is essential that if the pregnant female is found positive for HBsAg, her neonate should be vaccinated within seven days after delivery so that the infant be protected.

In dialysis centres, separate machine should be used for HBsAg positive patients, so that cross contamination be avoided.

HBsAg chronic carriers should be given the following instructions:

1. The blood of the person should be checked every 6-12 months.
(2) The person should be told NOT to donate blood.

(3) The person should not handle blood or blood products and his blood should be considered infectious and all precautions should be taken to prevent the spread of the infection.

Although HBV (Dane Particles) has been shown to have other serological markers such as anti-HBs, anti-HBc, HBeAg and anti-HBe, and the tests for these markers are also available, these markers are not used in the routine screening of the blood for hepatitis B.

It is worth mentioning here that an association exists between the presence of HBsAg carrier state and cirrhosis of liver and to the eventual development of Primary Hepatocellular Carcinoma. It has been found that the rate of development of Primary Hepatocellular carcinoma is much higher among the people, who are HBsAg chronic carriers than those who are negative for HBsAg.
Fig. 28.1 Normal radiocolloid spleen / liver scan. Anterior, right lateral and posterior views.
Fig. 28.2  Radiocolloid liver scan showing Cirrhosis of the liver. Note the shrunken liver and marked 'spill-over' to the spleen and visualization of the bone marrow.
Fig. 28.3  Radiocolloid liver scan of a patient with large liver abscess.
Fig. 28.4 Radiocolloid liver scan of a large hydatid cyst.
Fig. 28.5 Radiocolloid liver scan showing multiple metastases from primary lung cancer.
Fig. 28.6 A. Radiocolloid liver scan shows no evidence of a focal defect.

Fig. 28.6 B. Ultrasound examination of the same liver showing a focal lesion.
Fig. 28.7 A. Radiocolloid liver scan of a case of breast cancer showing a focal defect in the upper medial part of the right lobe which was considered to be a metastatic deposit.

Fig. 28.7 B. Same patient. Ultrasound scan shows the lesion to be cystic.
Fig. 28.8 A normal hepatobiliary study using $^{99m}$Tc - HIDA.
Fig. 28.9 Hepatobiliary study in an infant with biliary atresia. Note satisfactory liver uptake and non-visualization of the gall bladder, bile ducts and duodenal loops. The entire activity is excreted through the kidneys.
Fig. 28.10 Hepatobiliary study showing a non-functioning gall bladder in a case of acute cholecystitis.
Fig. 28.11: SPECT imaging of liver. The small lesion seen in the Coronal section was not detected in the planar images. Biopsy of lesion shows hepato cellular carcinoma.
Fig. 28.12 Gastro-oesophageal reflux study showing the filling of the lower half of the oesophagus with the regurgitant radioactive meal.