

# CHOLESCINTIGRAPHY

## STELLINGEN

### I

Cholescintigrafie is een non-invasief en betrouwbaar onderzoek in de diagnostiek bij icterische patienten doch dient desalniettemin als een complementaire en niet als competitieve studie beschouwd te worden.

### II

Bij de acceptatie voor levensverzekeringen van patienten met hypertensie wordt onvoldoende rekening gehouden met de reactie op de ingestelde behandeling.

### III

Ieder statisch scintigram is een functioneel beeld.

### IV

The purpose of a liver biopsy is not to obtain the maximum possible quantity of liver tissue, but to obtain a sufficient quantity with the minimum risk to the patient.  
( Menghini, 1970 )

### V

Bij post-traumatische verbreding van het mediastinum superius is angiografisch onderzoek geïndiceerd.

### VI

De diagnostische waarde van een radiologisch of nucleair geneeskundig onderzoek wordt niet alleen bepaald door de kwaliteit van de apparatuur doch voornamelijk door de deskundigheid van de onderzoeker.

### VII

Ultra sound is whistling in the dark.

#### VIII

De opname van arts-assistenten, in opleiding tot specialist, in de C.A.O. van het ziekenhuiswezen is een ramp voor de opleiding.

#### IX

De gebruikelijke techniek bij een zogenaamde "highly selective vagotomy" offert meer vagustakken op dan noodzakelijk voor reductie van de zuursecretie.

#### X

Het effect van "enhancing" sera op transplantaat overleving is groter wanneer deze sera zijn opgewekt onder azathioprine.

#### XI

Gezien de contaminatiegraad van in Nederland verkrijgbare groenten is het gebruik als rauwkost ten stelligste af te raden.

#### XII

Met het ontstaan van een tweede maligniteit als complicatie van cytostatische therapie bij patienten met non-Hodgkin lymphoma, maligne granuloom en epitheliale maligne aandoeningen dient, vooral bij langere overlevingsduur, rekening gehouden te worden.

#### XIII

Bij operatieve behandeling van hyperparathyreoidie verdient het in het algemeen geen aanbeveling niet-pathologisch veranderde bijschildklieren te bioteren.

#### XIV

De argumenten om het vliegveld Zestienhoven open te houden zijn uit de lucht gegrepen.

Stellingen behorend bij het proefschrift "Cholescintigraphy"  
H.S.L.M.Tjen, Utrecht, 30 januari 1979.

# CHOLESCINTIGRAPHY

the clinical application of <sup>99m</sup>Technetium-diethyl-IDA  
to the investigation of the liver and biliary tract

## PROEFSCHRIFT

ter verkrijging van de graad van  
doctor in de geneeskunde  
aan de Rijksuniversiteit te Utrecht,  
op gezag van de Rector Magnificus  
Prof.Dr. A. Verhoeff,  
volgens besluit van het College van Decanen  
in het openbaar te verdedigen op  
dinsdag 30 januari 1979  
des namiddags te 4.15 uur

door

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geboren op 28 maart 1944  
te Venlo

Promotor: Prof. Dr. K.H.Ephraïm

Dit proefschrift kwam tot stand mede onder leiding van  
Dr.P.H. Cox ( Hoofd afdeling Nucleaire Geneeskunde van  
het Rotterdamsch Radio-Therapeutisch Instituut ).

Aan allen die mij geïnspireerd hebben.

## VOORWOORD

Het verschijnen van dit proefschrift biedt mij de gelegenheid allen te danken die ieder op hun eigen wijze hebben bijgedragen aan de totstandkoming ervan.

Het was een voorrecht om onder leiding van mijn promotor Prof. Dr. K.H.Ephraïm dit proefschrift te hebben kunnen voltooien. Voor de vele aangename besprekingen, adviezen en voor de kritische wijze van begeleiding ben ik hem zeer dankbaar. Dr. P.H.Cox en Dr. W.B. van der Pompe, die mij begeleid hebben bij mijn eerste Rotterdamse schreden op het nucleair geneeskundig pad, ben ik veel dank verschuldigd voor alle hulp en inspirerende gesprekken tijdens de bewerking van dit proefschrift.

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Met nimmer aflatende ijver en grote voortvarendheid werd door mej. M.W. van der Putten de tekst van het manuscript uitgetypt. De heren L.Ries en H.Vuik van de afdeling Medische Fotografie van het R.R.T.I. hebben op vakkundige wijze de tabellen, figuren en foto's verzorgd.

Zonder de inspanningen van mevr. Y.Swierstra-Leenders zou het laboratorium onderzoek zeker niet tot een goed einde zijn gekomen. De hulp van mevr. E.L.A.Vonk-Neele en mevr. M.Westerhout-Kersten bij het verzamelen van de literatuur was onmisbaar.

De voltooiing van dit proefschrift zou niet mogelijk geweest zijn zonder de morele steun en stimulerende belangstelling van mijn associés.

De inzet van de gehele afdeling Nucleaire Geneeskunde van het R.R.T.I. en de gehele afdeling Interne Geneeskunde van het S.F.G. is een grote steun geweest tijdens het bewerken van dit proefschrift.

U allen ben ik zeer erkentelijk.

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## CHAPTER I

### INTRODUCTION.

The past years have witnessed a remarkable upsurge of interest in liver disease the diagnosis of which has posed difficult problems for physicians in most fields of medicine. The currently available diagnostic methods, most of which have been developed or refined during the past three decades, ensure a high degree of diagnostic accuracy in liver disease. In the case of jaundiced patients there is a special need for a simple method to differentiate between a hepatocellular cause of jaundice and biliary obstruction.

At present there are several procedures which are used in an attempt to differentiate these conditions, but the lack of specificity of the biochemical tests on one side and jaundice as a limiting factor for radiological examination on the other side, make it still necessary to use more hazardous invasive techniques. Nevertheless in the clinical investigation of hepato-biliary disease there is room for a non-invasive method of investigating liver cell function and the functional capacity of the biliary system, with a minimum of inconvenience and risk to the patient.

The numerous reports on the use of radioisotope techniques to evaluate liver and biliary tract disease show the simplicity and ease of this type of examination in relation to other procedures.

The contribution of nuclear medicine to the investigation of an organ system can best be considered under two headings: function evaluation, as the evaluation of the physiological function of an organ and morphological imaging, defining the presence, position, size and shape of the organ as well as demonstrating

areas of increased or decreased radiopharmaceutical localisation within the organ.

The visualisation of the liver by means of scintigraphy following the administration of a suitable radiopharmaceutical has become a routine clinical procedure since Stirett et al ( 1953 ) used I-131 labelled human serum albumin for the detection of liver metastases.

The history of the dynamic investigation of liver function started in 1955 with the use of Iodine-131 labeled Rose Bengal by Taplin et al. However the problems of radiation exposure and the lack of sufficiently sensitive technical equipment limited their use and inhibited the development of clinically useful tests.

The limitations of existing techniques, particularly in differentiating severe hepatocellular disease from obstructive biliary tract disease has stimulated the search for better agents and techniques. New compounds, metabolized in the same way as iodinated Rose Bengal but with better physical and imaging characteristics together with the availability of computers for the analysis of the information obtained have stimulated interest in the investigation of liver function using radionuclides.

This thesis was triggered by the development and clinical trial of Technetium-99m labelled diethyl-acetanilido iminodiacetate ( diethyl-IDA ), a new radiopharmaceutical for the functional study of the hepato-biliary system.

The definition of the clinical role of a new technique or radiopharmaceutical is not an activity in which we in nuclear medicine have traditionally excelled.

The history of nuclear medicine is replete with examples of new procedures for which exaggerated or inappropriate claims were initially made, only to be later modified or withdrawn under the glare of the clinical spotlights. It is selfevident, although often forgotten, that the clinical role of any new diagnostic tests should be defined in relation to relevant existing procedures. A new test should provide either new information or at least the same information more reliably, more economically or preferably all of the above (Ronai, 1977).

In Rotterdamsch Radio-Therapeutisch Instituut investigation of patients with disturbances of liver function using the above mentioned radiopharmaceutical is performed since october 1976. With the help of the computer functional images are constructed from data obtained in the dynamic study of the hepatobiliary system.

In the department of internal medicine of St.Franciscus Gasthuis in Rotterdam the routine clinical examination of patients with liver function disturbance encompasses this procedure. This study aims to define the place of this functional investigation in regard to other methods in patients with disturbed liver function.

For this purpose the study attempts to answer the following questions:

1. What is the contribution of a dynamic radio-isotope liver investigation to the diagnosis in case of patients with liver function disturbance associated with jaundice?
2. Is it possible to differentiate, in an early phase of the illness, between medical and surgical jaundice and thereby avoid more invasive and risky examinations?

3. What does a dynamic liver investigation contribute to the diagnosis in patients with liver function disturbance without jaundice?
4. In this connection: what is the relation between the data obtained and the recovery rates of patients with liver disease. Can the dynamic liver investigation be used as measure for the prognosis of liverdisease?

In this thesis a survey is given of the techniques routinely used in the clinical investigation of liver and biliary tract disease including the various investigations in nuclear medicine. The preparation and bio-kinetiques of Technetium-99m labelled diethyl-acetanilido iminodiacetate is described in detail. A description of the methods in use in our institute and the reproducibility of the results as revealed by a retrospective study in patients, completes this presentation.

## CHAPTER II

### THE LIVER AND BILIARY TRACT.

reviewed from Lichtman, 1953; Mountcastle, 1968; Netter, 1967;  
Schiff, 1969; Siegenthaler, 1973; Sherlock, 1975.

#### 2.1. *The liver.*

The liver plays an important role in the intermediate metabolism and storage of carbohydrates, the metabolism of fats and amino-acids and the synthesis of proteins. It serves as a depository for numerous vitamins, enzymes and hormones. A large number of chemical syntheses are carried out by the liver. Bile is secreted into the bile passage, synthesized from bile-salts and bile pigments. The liver is the largest organ in the body with a weight in an adult of 1200 - 1500 gm. comprising one fiftieth of the total body weight. It is located in the upper part of the abdomen where it occupies the right hypochondriac and the greater part of the epigastriac region.

A part of its surface is associated with the diaphragm. The location of the liver is dependent on the position of the body and varies with respiration. The topography is altered with some diseases and can be changed by displacement of the organ due to thoracic processes which may push the liver downwards ( Villemin, 1951 ). In contrast to the multilobulated liver of many mammals, the human liver is a compact and continuous mass of parenchyma. There are two anatomical distinct lobes, divided conventionally by the line of insertion of the falciform ligament. The right lobe is larger than the left lobe and has on its posterior-inferior surface two smaller lobes: the caudate and the quadrate lobes. The whole organ is covered by the fibrous capsule of Glisson.



In the porta hepatis which is situated on the visceral surface of the right lobe, the branches of the hepatic artery and portal vein enter the liver and the common bile duct leaves the liver. At this point the capsule of Glisson enters into the liver following the blood vessels and biliary ducts.

The mammalian liver is made up of polygonal prisms, each representing a defined unit known as a lobule. Hepatic lobules were already described by Malpighi in 1666 and Mascagni in 1819. A more definite concept of hepatic lobulation as basic architecture was introduced by Kiernan in 1833. He described the hexagonal lobule centered around the radicles of the hepatic veins. Running through the center of the lobule along its longitudinal axis, is the central vein. At the periphery are situated the branches of the portal vein ( intra-lobular vein ), the interlobular bile ducts, branches of the hepatic artery and the lymphatics, which form a network about the portal vein and its branches.

Many authors however questioned the existence of the classic hexagonal lobule ( Mall, 1906; Arey, 1932; Elias, 1949; Rappaport, 1954, 1958 ). Rappaport described acinar units. He demonstrated that a lobule is centered about a terminal portal venule and adjoined at its periphery by one or more hepatic veins ( Rappaport, 1973 ). Scanning electron microscopy of the liver confirmed this finding ( Grisham, 1976 ).

The plates of liver cells are separated from one another by the sinusoids. The lining of the hepatic sinusoids is composed of an irregular alternation of two kinds of cells connected by many intermediate forms. One of these two lining cells are fixed macrophages, the phagocytic stellate cells of Von Kupffer which may contain phagocytosed material ( Hampton, 1958 ).

### 2.1.1. *The blood supply of the liver.*

The importance of blood flow for hepatic function has long been appreciated and much attention has been given to methods of measurement.

Abnormalities of the hepatic circulation cause reduced hepatocyte uptake capacity ( Goresky, 1973 ).

The liver circulation is characterized by its dual blood supply. It receives blood from the hepatic artery and the portal vein, which latter transports blood that has already passed through the capillaries of the gastro-intestinal tract and the spleen. The terminal vessels of the hepatic artery enter the portal fissure and follow the branches of the portal vein quite closely. The distribution of the vascular tree is just like the biliary tree within the liver and is strictly segmental. The hepatic arterial and the portal venous streams meet in the lateral portions of the liver lobules, where they enter the sinusoids. This mixed blood proceeds through these wide channels to the center of the lobule and enters the branches of the hepatic veins. After a short course it joins the inferior caval vein ( Segall, 1923; Hjortsjö, 1948 ) Gillfillan, 1950; Elias, 1952 ).

By means of the Fick principle reliable estimates of the flow through the liver are possible ( Bradley, 1945; Caesar, 1961; Rees, 1964; Neumayer, 1964; Winkler, 1965; Mackenzie, 1976 ). Bradley ( 1945 ) used infusion of bromsulphalein for the estimation of blood flow. Some what better is the estimation of blood flow by means of indocyanine green as described by Caesar ( 1961 ) but a disadvantage is the instability of these compound in plasma. Radionuclides have also been used to estimate blood flow: <sup>131</sup>I-Rose Bengal was used by Winkler (1965).

In 1962 Ueda used  $^{198}\text{Au}$  for the determination of the ratios of flow through the hepatic arterial and portal vein. Pabst et al. ( 1962 ) found the clearance of radioactive gold to be useful for measuring liver blood flow.

Rees ( 1964 ) and Mackenzie ( 1976 ) described the use of  $^{133}\text{Xenon}$  for this purpose.

### 2.1.2. *The liver cell.*

The liver cells are arranged more or less regularly in columns extending radially from the central vein to the periphery of the lobule. In adults fine bile canaliculi run between the hepatic cells and form a condensation of the membrane of the hepatic cells ( Elias, 1949 ). The structure and function of the hepatocyte is mostly polarized: materials are absorbed from the blood at the sinusoidal surfaces and bile constituents are secreted at the surfaces exposed to the bile canaliculi ( Novikoff, 1960 ). Damage to the liver cell can therefore impair its function in two directions each independent of the other. The cytoplasm of the liver cell presents an extremely variable appearance which reflects to some extent the functional state of the cell.

The extensive use of electron microscopy correlated to cytochemical and histochemical analysis has resulted in a new dimension in the understanding of liver disease, in that disorders of organelles of the cells are being recognized. The absorptive and secretory surfaces of the liver cell are increased by the microvilli, projected into the lumen of the bile canaliculi and peri-sinusoidal tissue space ( Fawcett, 1955 ; Novikoff, 1960 ). The mitochondria are the main and probably exclusive sites of oxidative phosphorylations (Novikoff, 1960); glycogen synthesis also occurs there.

In 1918 Cowdry stressed already that mitochondria are much more sensitive indicators of cell damage than are nuclei. This statement has been confirmed by others ( Altmann, 1955; Manelidis, 1958 ).

The endoplasmatic reticulum is a system of submicroscopic tubuli and flattend vesicles in the cytoplasm. It is possible to distinguish between a rough or granular reticulum and a smooth or agranular reticulum. The first is responsible for the synthesis of albumin and some globulins including fibrinogeen ( Miller, 1954 ). It has a high content of R.N.A. The latter has great importance for glycogenesis as pointed by Porter ( 1957, 1959 ). Further it is the site for bilirubin conjugation and detoxification of many drugs and other foreign compounds ( Remmer, 1967 ).

Other intracellular structures are the lysosomes: pericanalicular dense bodies adjacent to the bile canaliculi ( Essner, 1960 ), the nucleus containing D.N.A. and the golgi apparatus, which is also situated near the canaliculi and plays a role in the secretion of ingested material ( Palay, 1958 ).

## 2.2. *The biliary system.*

The biliary system commences with the intercellular bile capillaries and canaliculi which empty into the smallest bile ducts. Ellinger and Hurt ( 1929 ) first visualized the bile capillaries with fluorescence microscopy. The bile capillaries form an intercommunicating network within the center of the liver cell plates and appear to lie within grooves in them, though they actually constitute a part of them.

The network of bile canaliculi drains to the smallest intra-lobular bile ducts, the cholangioles. In the portal tracts the cholangioles communicate with the smallest interlobular bile ducts. When the ducts become wider due to confluence of the smaller ones and approach the hilus, their epithelium becomes high columnar and mucus producing. The right and left lobar ducts which leave the liver in the porta hepatis become the right and left hepatic ducts and fuse to form the common hepatic duct with a length of 2 - 3 cm. After the common duct is joined by the cystic duct on its right side, it forms the common bile duct.

The normal internal biliary duct pressure is regulated by the secretory pressure of the liver, the distensibility of the gallbladder and the resistance of the choledochal and ampullary sphincters ( White, 1975 ). Recent studies have shown that there is no peristalsis in the common bile duct, only a milking action of the several sphincter muscles at its distal end ( Daniel, 1972; Hand, 1973 ). The physiological regulation of the flow of bile into the duodenum can be thought of as the result of a balance between two types of pumps and one major resistance ( Hallenbeck, 1967 ). The principal resistance to bile is provided by the sphincter of Oddi. Neural and hormonal stimuli can increase the flow of bile by contracting the gallbladder and relaxing the sphincter of Oddi ( Admirand, 1973).

### *2.3. The gallbladder.*

The gallbladder is a pear-shaped, hollow structure, closely attached to the posterior surface of the liver. It consists of a fundus, a body and a neck which progresses into the cystic duct.

It shows marked variations in shape and size and is frequently the site of pathological processes which change the size and thickness of the wall. The major functions of the gallbladder are to concentrate and store bile and to deliver it to the duodenum during meals. When stimulated by cholecystokinin the gallbladder also delivers the concentrated bile through the cystic duct into the common bile duct and the intestine ( Ivy, 1930 ). The mechanism of concentrating bile is an active process in and through the wall of the gallbladder which absorbs fluid and electrolytes ( Ostrow, 1969; Wheeler, 1971 ).

### CHAPTER III

#### BILE FORMATION AND SECRETION OF ORGANIC COMPOUNDS IN BILE.

Bile is produced in man at the rate of 15 ml per kg. body weight in 24 hours ( Koster, 1936; Cameron, 1958 ). Total bile flow is largely determined by the flow of the blood through the liver ( Brauer, 1954 ). Bile flow varies with the portal blood flow, although sudden interruption of the latter decreases, but does not stop bile flow. In first instance the relationship between blood flow and bile production is controlled by hepatic cell function. The total amount of what is produced as bile is defined by bile secretion in the canaliculi, in the ducti and by the biliary system ( Javitt, 1971 ). Bile acids induce bile flow, i.e. they induce fluid movement during their secretion into the biliary canaliculi ( Sperber, 1965; Wheeler, 1961; Hofmann, 1977). Sperber ( 1965 ) and Wheeler ( 1961 ) proved that the initial phase of the formation of bile is the active transport of bile-acids from parenchymal cells into the bile canaliculi. The osmotic effect of these substances results in a flow of water and solutes into the bile canaliculi. The total amount of bile that finally reaches the duodenum is further dependent on the entero-hepatic cycle of the bile acids ( v.Berge Henegouwen, 1974; Hofmann, 1977 ).

Much of what we know about the secretion of bile originates from observing the livers of animals following the administration of fluorescent dyes ( Grafflin, 1947; Mendeloff, 1949; Hanzon, 1952 ). Hanzon ( 1952 ) described the behaviour of the dye sodium-fluorescein:

- within 3-10 seconds after i.v. injection the dye appears in the blood plasma of the hepatic sinusoids, then in the Kupffer cells and after 15-32 seconds traces of the dye are found within the liver cell.

Bile canaliculi contain the dye 26-27 seconds after it reaches the sinusoids. In 30-60 minutes the liver cells are cleared of the dye, although it can be detected in the canaliculi as long as two hours after injection.

In the last years kinetic analysis has been carried out with radioactive tagged substances ( Boyer, 1974; Cowen, 1975 ). When the excretion of bile is abruptly interrupted by mechanical obstruction of the bile ducts, bile continues to be formed and is absorbed from the liver at first through the lymphatics and later by the blood vessels of the liver ( Hanzon, 1952 ). Hanzon suggests a leakage from the bile canaliculi into the blood, either between or through the liver cells. Leakage most often develops in injured liver cells of which the permeability has been altered because of the raised pressure in bile ducts. However the toxic action of a high concentration of bile acids may be important. In prolonged biliary obstruction there is an astonishing degree of biliary hyperplasia and liver cell atrophy, perhaps due to chemical irritation, that commences within a few days of obstruction ( Cameron, 1958 ).

Organic substances can enter the bile by diffusion, secretion or filtration. Mechanisms by which many substances enter the bile are closely associated with the mechanism of bile formation ( Wheeler, 1961 ). Extracellular fluid to cell transfer may consist of active transport, facilitated by diffusion, pinocytosis or a combination of these processes. Accumulation within the cell often results from binding to cell components and it is possible that active transport contributes to the accumulation ( Schanker, 1968 ). The nature of the transfer process is determined by the kind of organic compound.



Two kinds of substances are present in hepatic bile.

1. Those which are found in concentrations that differ slightly from those found in plasma; they represent a protein free ultrafiltrate of plasma formed by the liver cells. The chief examples are  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cl}^-$ , creatinine, glucose and cholesterol (Cameron, 1958).
2. Others such as bilirubin and p-aminohippurate, are much more strongly concentrated in bile than in plasma and reach the bile by an active secretory mechanism. In addition bile acids are secreted after their synthesis by liver cells.

ad 1. The organic compounds which appear in bile in a concentration similar to or smaller than in plasma include lipid-insoluble molecules, highly lipid soluble weak electrolytes and a miscellaneous group of organic ions. Studies of the hepatic uptake and biliary excretion of lipid-soluble drugs are complicated by the fact that most of these substances are metabolized by the liver (Smith, 1966). Large, lipid-insoluble molecules enter the bile via restricted diffusion or filtration (Sperber, 1959). Large insoluble molecules could enter the liver cells either by diffusing through pores in the cell membrane, or by being taken up by some non-specific transport process such as pinocytosis (Cahili, 1953; Schanker, 1961). An alternative pathway for these substances from extracellular fluid to bile would be through intracellular spaces (Sperber, 1959). When this latter pathway may be open to all substances it is to a degree dependent on the size of molecules.

ad 2. The compounds which appear in bile in a concentration greatly exceeding that of plasma, are transferred against a sizable concentration gradient and have to pass at least two membranes between plasma and the bile: a substrate must

penetrate a liver cell before it can be secreted into bile. Therefore there is strong evidence that plasma-to-cell and cell-to-bile transfer takes place by a process of active transport. Mendeloff ( 1949 ) showed an accumulation of Rose Bengal in hepatic parenchymal cells. The cellular accumulation of fluorescein appears to be highly dependent on temperature variations, therefore this characteristic might be accepted as evidence that accumulation results mainly from active transport. Some investigations have shown that secreted compounds as bromsulphalein and procaine amide ethobromide are bound to components of liver tissue ( Solomon, 1963; Priestly, 1966 ). It seems clear that cellular accumulation of these substances is due, at least in part, to binding; but this does not rule out the possible participation of active transport in the overall accumulation in vivo. Levi et al. ( 1969 ) demonstrated that the liver cell contains two plasma protein fractions which they called Y-protein and Z-protein. These proteins play an important role in the selective uptake of organic anions by the liver cell. Solomon ( 1963 ) and Schanker ( 1965 ) described a study of the uptake of procain by rat liver slices. Although this compound is bound to some extent by tissue components, it appears to become concentrated in the slice mainly by a process of active transport.

Bilirubin is an example of an organic anion, actively secreted into bile. An immense body of literature has accumulated since Staedeler coined the name bilirubin in 1864. The first bilirubin determination for clinical use was developed by Ehrlich in 1883 and Hijmans van den Bergh ( 1916 ) distinguished the direct and indirect bilirubin reaction. In 1953 Cole et al. found the bilirubin conjugated with glucuronic-acid connected with the direct bilirubin reaction of Hijmans van den Bergh and the unconjugated bilirubin connected with the indirect reaction

of Hijmans van den Bergh.

Of the bilirubin produced daily, 80% originates from haemoglobin in the erythrocytes demolished in the reticulo-endothelial cells. In serum the unconjugated bilirubin is present in the albumin form ( Ostrow, 1963 ). Less than 1 per cent of the total amount of unconjugated bilirubin is present in the blood in its free form, i.e. not bound to albumin. Under pathological conditions the amount of free bilirubin can increase.

The liver cell plays a complex role in the bilirubin metabolism ( Brandt, 1972 ).

Dissociation of the bilirubin-albumin complex may occur on or along the liver cell membrane ( Brown, 1965 ). Intracellular proteins ( Levi, 1969 ) play a very important role in the selective uptake by the liver cell. In the endoplasmic reticulum the conjugation process of bilirubin takes place by means of the enzyme glucuronyl-transferase; the activated glucuronide is derived from glucose ( Butt, 1961 ).

The conjugating capacity of the liver cell is unlimited, but the excretory capacity for conjugated bilirubin has limits ( Fleischner, 1970 ). There is no precise knowledge concerning the mechanism by which the liver excretes the bilirubin.

The great majority of bilirubin is excreted by the liver in the form of water soluble diglucuronide ( Hoffman et al., 1960 ). Secretion of bile acids determines the excretion; also hormones such as secretine play an important role ( Wheeler, 1965 ).

As can be seen from the review in this chapter progress has been made in the past twenty years in the understanding of the mechanisms of bile formation.

However in the last ten years no essential supplement to the earlier statements are described.

This latter was confirmed in the reviews on mechanisms on bile formation in the theses from van Berge Henegouwen ( 1974 ) about bile acids and cholestase and Vonk ( 1978 ) about the influence of bile salts in hepatic transport mechanism.

## CHAPTER IV

### JAUNDICE AND CHOLESTASIS.

#### *4.1. Disease of liver and biliary tract.*

Although the liver has already attracted much attention and has been in the past a subject for detailed study by physicians in most areas of medicine, many problems concerning the liver have not yet been resolved. A worth while historical review concerning the liver and jaundice has been written by Moulin ( 1971 ).

Disorders of the liver and biliary system may occur in hepatic cells, the reticulo-endothelial system and the vascular system or bile ducts. In general disorders of liver and biliary system can be classified as jaundiced or non-jaundiced with or without pain. Each condition may be reflected in one or more typical patterns associated with diagnostic methods as biochemical tests, needle biopsy, radiological and radioisotopes investigations. However the case history, the clinical picture and the observations made during the physical examination may also play an important role in the differential diagnosis of liver and biliary tract disease.

#### *4.2. Jaundice.*

Jaundice is usually classified under three main headings ( Young, 1973 ):

1. Haemolytic jaundice, due to overloading of liver cells with bilirubin.
2. Hepatocellular jaundice, resulting from an inability of the liver cells to excrete bilirubin.

3. Surgical or obstructive jaundice, due to mechanical interference with the flow of bile down the ducts.

There may be a combination of obstructive and hepatocellular factors.

#### *4.3. The cholestasis syndrome.*

Cholestasis is a visible stagnation of bile pigment in bile canaliculi, hepatocytes and in Kupffer cells ( Popper, 1968, 1970 ). It can also be defined as a failure of normal amounts of bile to reach the duodenum ( Sherlock, 1975 ), or a disturbance of hepatocytic secretion of bile ( Popper, 1975 ). Cholestasis may be produced by a number of factors. Extra-hepatic cholestasis is caused by complete or incomplete obstruction of the extrahepatic biliary passage in an axis from the papilla of Vater to the bifurcation of the main hepatic duct at the hilus of the liver. Obstruction of only one part of the intrahepatic biliary duct system, even if including a main branch of the duct only exceptionally leads to jaundice. Biochemical alterations associated with obstruction are usually found.

Clinical and laboratory manifestations of cholestasis, without demonstrable obstruction on surgical exploration or cholangiography, is one of the main problems in the differential diagnosis of jaundice. This condition is termed intrahepatic cholestasis.

Whatever may be the cause of cholestasis, the hepatocyte changes may be the same. The characteristic picture of severe cholestasis may present in various forms with absence of portal inflammation or with a severe inflammatory reaction ( Popper, 1956 ).

Examination by electron microscopy demonstrated alterations not only in the bile canaliculi, but also in hepatocellular organelles

throughout the lobule ( Schaffner, 1959. ) in all forms of cholestasis. Even electron microscopy does not detect any difference between the lesions produced by mechanical obstruction and the primary form of cholestasis. Desmet ( 1972 ) suggested therefore that the differential diagnosis is not based on the functional or structural evaluation of the cholestasis, but rather on appreciation of the accompanying features such as inflammation or the type of cell damage, the etiology or the empiric knowledge of the course of development of the condition.

#### *4.3.1. Mechanism of cholestasis.*

The initial event in the development of extrahepatic cholestasis is obviously obstruction in the bile ducts. Secondary events within the liver cell are then initiated and a secondary intrahepatic cholestasis is produced which in its turns leads to the same symptoms ( Popper, 1975 ).

At its origin in the liver the biliary system is a closed system. Under normal circumstances the conjugated bilirubin excreted by the liver cell into this system, cannot escape and can only be transported to the intestinal tract. When an obstruction in the biliary system exists the permeability of the biliary tree may alter and bilirubin can then pass into the blood ( Schalm, 1971 ). The wall of the intercellular capillaries is formed by the liver cells themselves. When damage to the liver parenchyma occurs the integrity of the intrahepatic biliary tree is destroyed and bilirubin excreted in the bile capillaries, can also leak into the blood. In intrahepatic cholestasis the primary cause is generally obscure but again secondary changes follow within the liver cell itself. Up to now the mechanism whereby this occurs has not been established although there have been many hypotheses.

Schaffner and Popper ( 1969 ) described a dysfunction of smooth endoplasmatic reticulum whilst mitochondrial and canalicular membrane injury has been described by Schersten ( 1972 ) and Ozawa et al ( 1973 ). Recently Erlinger ( 1978 ) reported about the hypothesis that cholestasis may result either from a disturbance of the systems responsible for solute transport into the bile canaliculi ("solute pumps") or from an alteration of canalicular microvilli.

#### 4.3.2. *Pathology.*

All of changes observed are time dependent. In cholestasis conventional microscopy shows accumulation of bile in liver cells, Kupffer cells and the canaliculi ( Cameron, 1962 ). Biliary cirrhosis results from prolonged cholestasis. In extrahepatic cholestasis dilated intrahepatic ducts and a proliferation and dilatation of marginal bile ducts in the edematous portal zone can be observed ( Sherlock, 1975 ). In intrahepatic cholestasis multiplied bile ducts are not seen, but liver cell damage is always present.



## CHAPTER V

### INVESTIGATION IN LIVER AND BILIARY TRACT DISEASE.

#### *5.1. Biochemical liver function tests.*

Diseases of the liver are reflected in characteristic alterations in the composition of serum and urine. By determining the serum content of substances whose concentration is affected by injured liver cells or which are released by injured cells it is possible to prove the presence of active liver disease in suspect patients. Such measurements may help to characterize the type of liver disease and may assist in the assessment of extent of liver damage as an aid to prognosis and management.

Nevertheless, tests based on biochemical changes only give limited information; the difficulty being that most tests in clinical use do not measure functions of the liver, but indicate the rate of damage to liver cells. A coordinated use of several tests mostly lead to better interpretation. Unfortunately these tests may also indicate damage to other organs. Therefore it may be at times necessary to help define the cause of hyperbilirubinaemia in the jaundiced patient by a battery of tests. It has been suggested that in many of these cases the laboratory information will suffice if limited to the determination of serum bilirubin, serum alkaline phosphatase and serum transaminases ( Wroblewski, 1957, 1959; Latner, 1958; Goldstein, 1959 ). A combination of different enzyme tests and analysis of iso-enzyme patterns may be more useful.

In this context it is important to consider each test on its specificity to detect hepato-biliary dysfunction, its sensitivity to reflect liver injury in an early phase and selectivity for identifying the type of liver disease present ( Schenker, 1971 ).

#### 5.1.1. *Serum bilirubin.*

Estimation of bilirubin gives an accurate record of the intensity of any jaundice which may be present and may give some indication as to the type of jaundice.

The original observation of Hijmans van den Bergh ( 1916 ) with the Ehrlich diazo reagent and the distinction between the direct and indirect reactions has been followed by a multitude of varying technics ( Gray, 1953 ). Free pigments is responsible for the indirect reaction, while the glucuronides give a direct reaction. Total serum bilirubin determinations show a lack of sensitivity and selectivity. However the determination of the individual indirect and direct reacting bilirubin fractions can increase the sensitivity ( Schenker, 1971 ).

When the bilirubin test in urine is positive it indicates hepato-biliary disease; conjugated bilirubin is water soluble and therefore passes through the glomerulus of the kidney. An increase of urobilin in the urine is a sensitive indication of hepato-cellular dysfunction, often when other tests are still normal. Persistent absence of urobilin in urine strongly suggests complete biliary obstruction.

#### 5.1.2. *Serum alkaline phosphatase.*

As early as 1933 changes in blood phosphatase are reported in liver disease ( Roberts, 1933 ). Armstrong et al ( 1934 ) discussed the increase of phosphatase levels in experimental obstructive jaundice. Serum alkaline phosphatase has proved to be a very useful diagnostic tool for diseases that directly or indirectly involve the liver. The enzyme originates from bone, liver intestine and from the placenta. Many characteristics of the enzyme are given in an review article of King ( 1953 ).

Normal liver parenchymal cells are not particularly rich in alkaline phosphatase, 40-70% of the serum alkaline phosphatase originates from bone ( Kritzler, 1949 ). The major route of excretion of alkaline phosphatase is the biliary tract. Therefore the level rises in biliary obstruction and to a lesser extent when the liver cells are damaged ( Sherlock, 1975 ). Serum alkaline phosphatase is a rather sensitive and selective indicator in certain hepato-biliary diseases; however the major difficulty is its non-specificity. It is often impossible to distinguish between obstructive and hepato-cellular jaundice by the quantitative estimation of serum alkaline phosphatase. A variety of biochemical techniques are developed to identify the origin of the alkaline phosphatase in serum, none of them being completely reliable. Iso-enzyme studies have made it possible to differentiate between raised levels of serum alkaline phosphatase in bone and liver disease ( de Jong, 1970; Warnes, 1972 ). Recently Warnes ( 1977 ) reported on the intestinal alkaline phosphatase fraction to differentiate between intra- and extrahepatic cholestasis. Simultaneous measurement of the 5-nucleotidase also can help to differentiate between liver and bone alkaline phosphatase, because this latter enzyme is not derived from bone ( Schenker, 1971; v.d.Slik, 1975 ).

#### *5.1.3. Serum transaminases.*

The serum transaminases glutamic oxaloacetic transaminase ( S.G.O.T. ) and glutamic pyruvic transaminase ( S.G.P.T. ) provide a useful diagnostic aid in the detection of lesions involving the hepatocytes. However these enzymes are also present in heart and skeletal muscles. Since the report of the quantitative estimation of glutamic oxaloacetic transaminase activity in human serum by Karmen ( 1953 ), the changes

occurring in liver and biliary tract disease have been studied by many workers ( Wroblewski, 1957, 1955; Madsen, 1958; Latner, 1958; Goldstein, 1959 ). The main difference between the two enzymes is that raised S.G.P.T. is especially related to liver disease, the S.G.O.T. is also raised in other pathological conditions as myocardial infarction, pulmonary embolism and shock ( Wroblewski, 1959; MacLagan, 1963; Sherlock, 1975 ). The main value of the transaminases in assessing hepato-biliary disease is their large sensitivity for liver cell damage, especially in the early diagnosis of viral hepatitis. In addition they are valuable in the detection and follow up of active chronic hepatitis, cirrhosis, in toxic or drug induced liver injury and in infiltrative disease of the liver ( Wroblewski, 1959; MacLagan, 1963; Schenker, 1971; Sherlock, 1975 ).

Serum transaminases have less value in diagnosing obstructive jaundice. Madsen et al. ( 1958 ) found normal or only slightly elevated serum transaminases in the presence of biliary obstruction without signs of acute inflammation. If the obstructive jaundice was complicated by acute inflammation of the gallbladder and biliary tract, the transaminases were constantly elevated. Wroblewski ( 1959 ) reported moderate increments of transaminase activity in extrahepatic biliary obstructive jaundice, although both enzymes are altered in the same sense. However in acute extrahepatic biliary obstruction the S.G.P.T. activity usually exceeds the corresponding S.G.O.T. activity. The serum enzyme activity generally returns to normal within a week after relief of the biliary obstruction. Extra-hepatic biliary obstructive jaundice is readily differentiated from jaundice due to acute viral hepatitis; the serum alkaline phosphatase is usually higher in the former.

Transaminase values twenty times above the normal value and certainly when above fifty times the normal values indicate the presence of acute diffuse hepato-cellular disease and are strong evidence against extrahepatic obstruction. In addition the transaminase test has not proved to be of any assistance in distinguishing between the different types of chronic liver disease ( Madsen, 1958 ).

In 1972 the Commission on Biochemical Nomenclature on the Nomenclature and Classification of Enzymes advised to replace the name transaminase by the name aminotransferase ( Florkin, 1973 ).

There are some tests worth mentioning which can give assistance in the differential diagnosis of patients with disturbed liver function.

#### *5.1.4. Gamma-glutamyl transpeptidase.*

Gamma-glutamyl transpeptidase ( G.G.T.P. ) is an enzyme that can also indicate alterations in the liver ( Leevy, 1974; Dragosics, 1976 ). Serum G.G.T.P. is elevated in hepatitis, alcoholic liver disease and cholestasis of various origins, its level turns out to be a sensitive indicator, which remains high during the convalescent phases of liver disease. The increase of G.G.T.P. in cholestasis is not specific. Therefore it gives no additional diagnostic information in cholestasis. It is more helpful in combination with serum transaminases. An elevated G.G.T.P. can distinguish between an increase of alkaline phosphatase due to liver disease from an increase due to bone disease.

#### 5.1.5. *Lipoprotein-X.*

Disturbed liver function alters the composition of lipoproteins in the blood. In cholestasis an abnormal lipoprotein, called lipoprotein-X, can occur ( Seidel, 1969, 1973 ). Its estimation can be valuable in the detection of cholestasis ( Seidel, 1973; Mayr, 1975; Mordasini, 1975 ). Lipoprotein-X is detectable at an early stage and the specificity seems to be equal to or sometimes better than the usual tests for the differential diagnosis of cholestasis. However it does not help to differentiate between intra- and extrahepatic cholestasis.

#### 5.1.6. *The bromsulphalein test.*

This test was introduced by MacDonald in 1938 and is based on the uptake and excretion of an injected dye into the bile by the hepatocytes. The retention in the blood is a measure of the function of the hepatocyte. In the absence of jaundice the B.S.P. test is of particular value in assessing liver dysfunction ( MacLagan, 1963; Schenker, 1971; Sherlock, 1975 ). The B.S.P. test is of little value in the differential diagnosis of jaundice. Anaphylactoid reactions can occur, especially following serial tests ( Astin, 1965; Sherlock, 1975 ). The main value of the test is its great sensitivity in demonstrating early or mild hepato-biliary dysfunction. At present there is a less widespread use of this test because of the ease of the miscellaneous biochemical tests.

### 5.2. *Liver biopsy.*

The microscopic examination of liver tissue, obtained by biopsy, is an important tool in the diagnosis of liver disease.

Jaundice is a major indication for a liver biopsy, but the method carries an extra risk in this category of patients.

Paul Ehrlich ( 1883 ) was the first to employ liver biopsy to study the diabetic liver. Since Menghini ( 1958 ) introduced his "one second" needle biopsy, it has become a commonly used procedure in liver diagnosis. Whilst early methods involved much risk, the Menghini aspiration techniques has proved to be a relatively safe method: mortality of 0.015 to 0.017 per cent has been reported ( Thaler, 1964; Linder, 1967 ). Much care should be taken if haemostasis is abnormal, if there is local infection or prolonged obstructive jaundice. Ascites and lack of cooperation on the part of the patient may hamper the procedure ( Menghini, 1970; Sherlock, 1975 ). Complications which may occur are haemorrhage, biliary peritonitis and puncture of other viscera. Whatever the difficulties, an experienced histo-pathologist can distinguish the cause of cholestasis ( Scheuer, 1973; Sherlock, 1975 ).

By combining laparoscopy with needle biopsy, biopsy can be taken whilst the liver is directly visualised.

## CHAPTER VI. VISUALISATION OF LIVER AND BILIARY TRACT.

### *6.1. Radiology.*

In general radiology plays a major role in the diagnosis of diseases of the biliary tract. Attempts have been made to obtain an impression of the dynamics of the biliary system, the origin and localisation of an obstructing process. The most important techniques for the demonstration of clinical disorders of the gallbladder and ductal system are discussed.

#### *6.1.1. Abdominal plain film.*

Plain films are the simplest radiological examination. They may show enlargement of the liver and the spleen. A distended gallbladder may appear as a soft tissue mass, particularly if it impresses a gas filled hepatic flexure of the colon or the duodenum. The chief value of plain films, however, lies in the demonstration of calcified gall-stones, various types of calcification in the liver or gas in the bile ducts or gall-bladder. Less than 20 per cent of stones in the gallbladder and only some 5 per cent of stones in the bile duct are sufficiently calcified to show ( Young, 1973 ). Plain films alone do not suffice and additional information by other techniques is necessary.

#### *6.1.2. Oral cholecystography.*

Since the introduction of oral cholecystography by Graham and Cole ( 1924 ) this diagnostic procedure has become one of the



most widely employed x-ray examinations in the investigation of the biliary tract. All compounds currently used for gallbladder visualisation are chemically similar and all contain iodine. Visualisation of the intrahepatic ducts and common bile duct by this method is unusual. The diagnostic reliability of an oral cholecystographic medium is largely dependent on its chemical structure which determines the rate and degree of absorption of the medium by the small intestine and the ratio of hepato-biliary to renal elimination. Of equal importance is the functional capacity of those organs which play a role in the absorption, metabolism and excretion of the cholecystographic media. ( Teplick, 1965 ).

An accuracy of at least 98 per cent in the diagnosis of gallstones has been reported ( Baker, 1958; Alderson, 1960; Ocksner, 1970 ).

Non-visualisation of the gallbladder continues to be a problem in oral cholecystography. Wickbom and Rentzhog ( 1955 ) described 722 cases, where the gallbladder did not fill. In 93 per cent operation confirmed the presence of stones in these cases, with or without abnormalities of the gallbladder wall. In the remaining 7 per cent operation failed to disclose gallstones, but the lack of filling was due to moderate or distinct gallbladder wall abnormalities, impaired liver function and inability of the patient to accept the contrast material. Furthermore duodenal ulcer may be a source of error in cholecystography ( Orator, 1927; Leb, 1931 ).

Oral cholecystographic media are rarely responsible for significant side-effects. Serious complications from biliary contrast materials relate primarily to renal toxicity ( Rene, 1959; Teplick, 1965; Canals, 1969 ). Teplick ( 1965 ) discussed possible underlying mechanisms as impairment of liver function, dehydration, electrolyte imbalance, hypertension and multiple doses which contribute to serious side reactions.

A direct cytonephrotoxic effect of the contrast material appears to be unlikely. Another complication of oral administration of gallbladder dye may be coronary occlusion ( Littmann, 1958 ).

The prime indication for oral cholecystography is the clinical suspicion for gallbladder pathology. None of the contrast media at present available for cholecystography and cholangiography are reliable in the presence of hepatocellular or sustained obstructive jaundice, and in these cases the gallbladder and ducts cannot be visualised by conventional contrast methods.

#### *6.1.3. Intravenous cholangiography ( I.V.C. ).*

The common bile duct can be visualised by intravenous administration of iodinated contrast agents.

Berk ( 1976 ) described some cholangiographic agents with respect to concentration and rate of excretion in the bile. The intravenously administered agent is excreted rapidly by the liver without chemical change; 90 per cent of the administered agent is normally excreted in the bile systems and about 10 per cent by the kidneys ( Schoolmeesters, 1971 ). The clinical use of intravenous cholangiography includes visualisation of the common bile duct for stones, stricture evaluation and examination after cholecystectomy ( Wollam, 1967 ).

The reliability of properly performed oral cholecystography is so high that there is little additional information to be obtained about the gallbladder from intravenous cholangiography ( Amberg, 1973 ). In all patients where no visualisation is obtained with oral studies, I.V.C. has to be performed to exclude malabsorption of the oral contrast agent. I.V.C. may also be useful to demonstrate common bile duct stones in patients with a non-visualising gallbladder. Wollam ( 1967 ) reported

about the relatively high incidence for common bile duct stones in patients where the gallbladder can not be visualised. Superimposed intestinal gas can be a serious hindrance to diagnostic accuracy: therefore tomography is often absolutely necessary.

There are a number of interrelated factors which determine the degree of bile duct opacification during intravenous cholangiography ( Berk, 1976 ) such as:

- the rate of excretion and the concentration of the iodinated organic anion in bile.
- the presence and degree of hepatic dysfunction or bile duct obstruction.
- the diameter of the common bile duct.
- the rate of emptying of the biliary tree.
- the radiographic technical factors.

In the presence of impaired liver function or biliary obstruction prolonged drip-infusion cholangiography will increase the chances of biliary visualisation ( Fuchs, 1975 ).

Adverse reactions to intravenous cholangiography are more common than to oral cholecystography or even intravenous urography ( Ansell, 1970 ): they include nausea, vomiting and hypotension. Acute renal failure has also been described ( Craft, 1967 ).

Intravenous cholangiography is contraindicated in patients with known idiosyncrasies to the contrast material or simultaneous damage of liver and kidneys. The reported mortality rate for intravenous cholangiograms varies from 1 in 5.000 to 1 in 10.000 studies ( Ansell, 1970 ). Intravenous cholangiography is ineffective when the bilirubin level is above 4 mg per 100 ml. When the bilirubin level is between 3 and 4 mg per 100 ml only about one third of the studies are successful ( Amberg, 1973 ).

#### 6.1.4. *Operative cholangiography.*

The direct approach either into the cystic duct or directly into the common bile duct at laparotomy results in excellent visualisation of the duct system. Operative cholangiography can indicate the number of stones retained in the common bile duct and is useful to identify variations in biliary duct anatomy ( Burhenne, 1975; Zollinger, 1975 ).

#### 6.1.5. *Percutaneous transhepatic cholangiography.*

Percutaneous transhepatic cholangiography ( P.T.C. ) has been in use for many years. Where visualisation of biliary system is not possible by oral or intravenous cholangiography in jaundiced patients, direct administration of a contrast agent in the intrahepatic bile ducts by a liver puncture can provide information. Huard and Do-Xuan-Hop ( 1937 ) first used this method to visualise the bile ducts. Numerous extensive reports on P.T.C. have been published ( George, 1965; Zinberg, 1965; Zuheir, 1966; Miranda, 1967 ). The method may be of value to differentiate between hepatocellular and obstructive jaundice and can be of considerable assistance to the surgeon. However the frequent morbidity in earlier work and the necessity for surgical intervention immediately after the procedure have limited its use and applicability ( Thämmig, 1975; Pereiras, 1977 ).

Göthlin ( 1973 ) reported complications in about 12 per cent of the patients undergoing this examination, including those with bile leakage, bleeding, pain and liver abscess. Complications only occurred in patients with tumours obstructing the bile ducts. No correlation was found between the complications and the thrombotest or the depth and duration of jaundice.

A new interest in percutaneous puncture developed with the introduction of the flexible tube for puncture instead of the rigid needle. Using the fine Okuda needle, developed at the Chiba University ( 1974 ), P.T.C. can be performed without immediate surgery and gives less complications and therefore less discomfort for the patient. The risk was found to be low in the early series and continues to decrease as more experience is obtained.

In recent investigations the overall success rate varied from 90-100 per cent ( Elias, 1976; Jain, 1977; Pereiras, 1977; Yap, 1977 ). In these studies complications occurred in 3 to 7 per cent and varied from fever and shivering after the procedure, cholangitis, transient hypotension to right upper quadrant discomfort. No mortality was reported. In the presence of obstructive lesions of the common bile duct, elevated intraluminal pressure and increased viscosity of stagnant bile may cause poor distal flow of the opaque medium and prevent adequate mixing of injected contrast and bile. Resultant problems in interpretation include false proximal localisation of the site of obstruction and pseudodeflects due to bad mixing ( Ferruci, 1977 ). These sources of potential diagnostic errors were earlier also described by Kittredge and Baer ( 1975 ). In a study of the problems of interpretation of P.T.C. results, they reported that cases of complete block hampered the interpretation.

Percutaneous transhepatic cholangiography is not only used in jaundiced patients. George et al ( 1965 ) had already observed that the absence of clinical jaundice does not exclude the use of P.T.C. Frankel ( 1977 ) using a teflon canula, discussed the results of a diagnostic study in fifteen non-jaundiced patients. He found P.T.C. of particular value in the

investigation of those patients who continue to have problems related to the biliary system following biliary surgery.

#### 6.1.6. *Transjugular percutaneous cholangiography.*

Hanafee and Weiner ( 1967 ) introduced a method by which a catheter, passed percutaneously into the right internal jugular vein and which reaches the hepatic vein via the superior caval vein, right atrium and inferior caval vein. Through this catheter a needle may be inserted for cholangiography by puncturing the bile ducts from inside the liver. In this way liver biopsy is also possible ( Rösch, 1973; Thelen, 1977 ). This way of performing cholangiography has the advantage that it is possible to examine a patient with bleeding diathesis, ascites, or interposed colon or who has had hepatic lobectomy ( Hawkins, 1976 ). Further it offers an approach to percutaneous transhepatic cholangiography that may also alleviate the necessity for immediate surgery.

Hanafee ( 1967 ) obtained studies of excellent diagnostic quality in 64 per cent of the patients and reported no morbidity. In a later study Weiner and Hanafee ( 1970 ) reported one death from sepsis in their series of 56 examinations.

Possible complications may be sepsis, bilihaemie, injury to the caval vein, pericarditis, febrile reactions and intra-hepatic or intra-biliary duct hemorrhage ( Hanafee, 1967, 1970; Rösch, 1973; Günther, 1975 ). The complication rate seems lower than for P.T.C. with the rigid needle. The only contra-indication is cholangitis, but the anatomic condition of the venous system may be a limitation to the practicability of the examination. The success rate for transjugular cholangiography varies from 84 to 93 per cent; for the transjugular liver biopsy it is about 88 per cent ( Rösch, 1973; Thelen, 1977 ).

In these latter studies the patients tolerated the procedure without major discomfort and did not complain about passage of the catheter and needle through the veins. There were no major complications.

A modified technique, using a flexible needle, was introduced by Hawkins et al ( 1976 ). With the flexible needle it is possible to puncture the right antecubital vein. This antecubital venous approach appears to be a simpler method than the original method as reported by Hanafée and Röscher. The success rate was 100 per cent, there were no complications.

In conclusion it would appear that the transjugular route offers a feasible, safe and effective approach for cholangiography and liver biopsy. However there are both advantages and disadvantages in comparison with the standard transperitoneal techniques. Safety is the main advantage so that the technique can be performed in circumstances where other techniques are contra-indicated.

#### *6.1.7. Endoscopic retrograde cholangiography.*

The recent advances in fiber optics and the increasing availability of flexible endoscopes make direct vision of almost any part of the gastrointestinal tract possible. Using a special fiberscope, the ampulla of Vater can be readily visualised, a catheter can be introduced into the common bile duct or pancreatic duct and contrast material can be injected. The site, extent and cause of an obstruction can be seen, however the duct proximal to a complete obstruction cannot be demonstrated.

In 1965 Rabinov and Simon succeeded in cannulating the pancreatic duct in one patient and in 1968 McCune et al. reported the endoscopic cannulation and roentgenologic

visualisation of the pancreatic duct. The examination with flexible endoscopes has been effectively used in many centers throughout the world, since the introduction by the Japanese in 1970 ( Takagi, 1970 ).

The success rate is about 70%, whereby a successful visualisation of common duct and biliary system was obtained ( Cotton, 1972; Goodale, 1975; Sherlock, 1975; Sobbe, 1977 ). The success rate depends on the experience of the operator and the underlying disease. Unsuccessful attempts resulted from pyloric narrowing and abnormally located ampulla. Complications vary from transient febrile reactions to cholangitis. ( Cotton, 1972; Robbins, 1973 ). For the latter there is an overall incidence of 0.2% to 1.5% ( Goodale, 1975 ). bile leakage and hemorrhage have also been noted ( Sherlock, 1975 ).

Okuda et al ( 1973 ) reported on the diagnostic significance of the technique and noted no accidents, although in about half of the subjects, a transient rise in serum amylase occurred shortly after the procedure. Nevertheless this procedure may be of great significance in patients in whom a roentgenologic study of the biliary system is imperative, where transhepatic cholangiography has failed or has been contra-indicated. However in inexperienced hands it is a time consuming method which causes great discomfort to the patient.

#### *6.1.8. Angiography of the liver.*

Seldingers technique of arterial catheterization made it possible to demonstrate the vascular supply of the liver with a high degree of accuracy. Though Alfidi ( 1968 ) and Baum ( 1969 ) considered the diagnosis of primary and metastatic neoplasms as the main indication for hepatic arteriography, selective and superselective techniques permit a diagnosis of



various types of lesions ( Gürtler, 1977 ). To enhance the visualisation of the arteries, subtraction may be essential ( Young, 1973 ). According to Gürtler ( 1977 ) the same applies to the administration of vaso-dilating or vaso-constricting agents. Recently Jonsson et al ( 1977 ) reported the injection of a single bolus of prostaglandines into hepatic arteries to be a harmless and very useful pharmacoangiographic aid.

Some benign conditions will be found to be responsible for jaundice: aneurysms of the aorta have been known to compress the bile duct and to produce jaundice. Young ( 1973 ) demonstrated an aneurysm of the hepatic artery. Arteriography is reasonably safe and simple in experienced hands, although even then there is a definite morbidity rate. Further there is a limitation to the visualisation of altered arteries dependent on the extent of the space-occupying processes in the liver. It will be difficult to diagnose tumours or metastases with a diameter smaller than 2 to 3 cm. especially when they are not vascularized.

Besides arteriography, hepatic venography and spleno-portography can also give information about existence of liver abnormalities, but the major indication for these studies are diffuse liver diseases ( Graafland, 1960; Cavaluzzi, 1977 ).

#### *6.2. Computerised tomography.*

There are technical limitations to the amount of information which can be obtained by X-ray examination. Using the conventional film technique a large proportion of the available information is lost in attempting to portray the information from a three dimensional body in a two-dimensional form on a photographic film. In principle computerised transverse axial tomography will therefore achieve a better

utilisation of the available information ( Hounsfield, 1973 ). The aim of the procedure is to produce a series of tomographic images. A part of the body is scanned from various angles by a narrow beam of X-rays and the transmitted X-ray photons impinge on an arrangement of crystal detectors. The readings obtained are stored in a computer. A picture of the internal structure of the part of the body studied is reconstructed from the calculated absorption coefficients of the various tissues along the X-ray beam path. The constructed picture can be displayed on a cathode-ray tube or by a greyscale computer print out of the absorption coefficients, related to small previously defined volumes of tissue. The increased sensitivity of computerised tomography enables tissue of closely related density to be defined, and a picture of the soft tissue structure to be built up. Lesions are seen as changes from normal density and are interpreted in the light of pathological changes which are known to occur. Tissue density may be artificially enhanced by intravenous injection of contrast material.

Ambrose ( 1973 ) studied the clinical application of C.T.-scanning to the diagnosis of brain disease and reported some limitations of the technique such as artefacts in images due to movement and poor resolution of small structures.

In 1975 Schellinger et al reported about the ACTA-scanner, a total body scanner, which permits study of virtually all regions of the body. They described their clinical results with 193 patients. Since that time various publications have appeared in which the clinical role of C.T.-scanning has been described especially with reference to the study of the liver and biliary tract.

Some studies compared this technique with other diagnostic methods ( Alfidi, 1976; Mac Carty, 1977; Stephens, 1977; Harell, 1977; Havrilla, 1977; Kree1, 1977 ).

Computed tomography is highly accurate in detecting and defining

space-occupying lesions and in detecting fatty infiltration of the liver parenchyma ( Alfidi, 1976; Sagel, 1976; Stephens, 1976, 1977 ). The accuracy in diagnosing space-occupying processes has been reported to be over 90% but in diffuse liver disease C.T.-scanning has a limited value ( Stephens, 1977; Levitt, 1977 ).

The value of C.T.-scanning as a non-invasive method of detecting obstructive biliary disease has been well recognized ( Alfidi, 1976; Sagel, 1976; Stanley, 1976 ). Dilated ducts are easy to recognize because of the low density of bile but it can be difficult to differentiate between metastatic liver disease and dilated biliary ducts. In the diagnosis of obstruction an accuracy rate varying from 88 per cent to 97 per cent has been reported ( Levitt, 1977; Havrilla, 1977 ). In about 75 per cent the underlying cause of obstruction was determined ( Stephens, 1976 ). The use of contrast media can be used to accentuate the contrast between liver parenchyma and dilated ducts ( Stephens, 1977; Havrilla, 1977 ). Improved technology has also enhanced the image of the liver and reduced artefacts ( Sagel, 1976; Harell, 1977; Kreel, 1977 ).

Like any diagnostic radiological procedure C.T.-scanning provides information that must be visually interpreted and the diagnostic accuracy is dependent on the knowledge and experience of the interpreter ( Stephens, 1977 ).

### 6.3. *Ultrasound study of the liver and biliary tract.*

Ultrasound, as an aid to medicine, is derived from the sonar used for maritime and industrial purposes. Sound waves, with a frequency above the upper range of human hearing, can penetrate the body and are reflected from tissue interfaces in the path of the beam. In this way changes in tissue boundaries can be registered.

The first study on the use of reflected ultrasound for medical diagnosis was made in 1949 by Ludwig and Sthruthers; the first two-dimensional ultrasonic picture of the liver was published by Howry and Bliss in 1952. Since that time the use of ultrasound has significantly grown ( Leopold, 1975; Reid, 1976; Taylor, 1976; Frommhold, 1977 ).

Ultrasound is produced by means of the piezo-electric effect which consists of the transformation of electrical into mechanical energy ( Curie, 1881 ). Two methods are primarily used to register ultrasound: an A-mode ( linear and uni-directional ) and a B-mode scanning, the latter producing cross sectional images ( Sweet, 1975 ). Grey scale developments, a technique to distinguish echo intensities by the degree of blackening produced in the recording system, has improved the overall results in detecting abnormalities ( Taylor, 1973 ). The limitations of ultrasound techniques are caused by limited penetration of the beam, erroneous changes in registration caused by bone and reflections caused by intestinal gas ( Sweet, 1975 ).

Hill ( 1968 ) reported on possible hazards when applying ultrasound. When continuous high power beams are used thermal effects, cell disruption and cavitation may occur. However these should not be a problem with the currently available diagnostic apparatus, because the intensity used is low. Ultrasound has been recognized as a safe and non-invasive

procedure to evaluate the status of the biliary tract ( Leopold, 1973; 1976; Gosink, 1976 ). The major value of ultrasound in the diagnosis of gallbladder disease is to identify dilations, stones and other lesions ( Gosink, 1976 ). Normal bile ducts are difficult to indentify because of their small diameter. If the ducts become dilated it is easier to identify them. Focal or diffuse liver disease can be detected as well; however at the present time scintigraphy has a slight advantage over ultrasound ( Rasmussen, 1973; Leyton, 1973; Hawkins, 1975 ). Ultrasound can distinguish solid from cystic lesions.

There are several studies which compare the results of ultrasound with nuclear medicine procedures ( McCarty, 1970; Leyton, 1973; Taylor, 1974 ). Nuclear medicine studies appear to be more sensitive indicators to predict the presence of disease in the liver than ultrasound, but have a higher false positive rate ( Lomonaco, 1975 ). Ultrasound on the other hand is nearly as effective in detecting the type of disease, but is considerably less sensitive than nuclear medicinal techniques. Ultrasound has the benefit of being cheap and harmless; however there are limitations due to bone and bowel gas. It may prove to be one of the first choice imaging techniques in most cases of jaundice. Nuclear medicine and ultrasound complete each other in evaluating liver and biliary tract disorders. With respect to the computerised tomography ultrasound should also be seen as complementary screening study ( Meire, 1977 ).

#### *6.4. Miscellaneous.*

There are a number of other procedures which can be used to differentiate surgical from non-surgical jaundice but which have not found widespread acceptance.

Strack et al ( 1971 ) reported an integrated procedure to

diagnose hepato-biliary disease. By means of a mid-line incision, made under local infiltration anaesthesia, the liver and adjacent structures can be inspected. In addition open transhepatic cholangiography and open liver biopsy with eventually omento-portography can be performed; this procedure has also been called minilaparotomy.

A non-invasive technique reported by Morin et al ( 1976 ), is the demonstration of dilated bile ducts by total body opacification. Total body opacification is a procedure whereby intravenously injected contrast material becomes distributed throughout the vascular compartment of the entire body in proportion to the blood supply; avascular or hypovascular areas are then visualised as lucent areas. In this way dilated ducts can be demonstrated and a differentiation can be made between surgical and medical jaundice.

## CHAPTER VII.

### LIVER SCINTIGRAPHY, THE STUDY OF THE LIVER USING STATIC IMAGES.

#### 7.1. *Introduction.*

Since Stirett et al ( 1954 ) used colloidal radio-active gold to perform the first hepatic scan many publications about hepatic imaging have appeared. A variety of radiopharmaceuticals have been used for this purpose with various advantages and disadvantages ( Johnson, 1975 ).

In 1964 Harper et al reported the use of  $^{99m}\text{Tc}$  Technetium Sulfur colloid for hepatic imaging and this has remained to date the reagent of choice for routine liver examinations. Colloidal particles are removed from the blood by the phagocytic action of the Kupffer cells which form part of the reticulo-endothelial system and are uniformly distributed throughout the liver. By using this capacity a static image of the liver can be obtained using radio-active colloids which provides information about the localisation, shape and size of the liver together with information concerning focal and diffuse abnormalities. However a study of the vast literature on the subject clearly demonstrates a considerable overlap in the criteria differentiating between normal variations, artefacts and abnormality. A number of variations in the size and shape of the normal liver have been described which form a limitation to the accuracy of the interpretation of scintigrams ( McAfee, 1965; Mould, 1972 ). The imprint of extrahepatic structures can also alter the liver shape ( Johnson, 1975; Berghuis, 1976 ). Overlap by other organs can cause reduction of count rates and treatments such as radiotherapy reduce accumulation of radio-

activity in the absence of true pathology. Objective criteria for abnormality are therefore hard to define and the interpretation given to the images obtained is highly subjective. The overall erroneous interpretation rate has been shown to vary with the experience of the observer ( Ludbrook, 1972; Conn, 1972; Nishiyama, 1975 ).

#### *7.1.1. Liver scintigraphy and focal liver disease.*

A major indication for hepatic imaging is to distinguish between focal defects and diffuse parenchymal disease. Space occupying lesions produce focal defects; but on the other hand focal defects can occur in diffuse disease. The reliability of hepatic imaging in focal disease is dependent on the size of the lesion, its location in the liver and the sensitivity of the detector used ( Covington, 1970; Lunia, 1975; de Ruiter, 1977 ). Since focal defects may indicate a variety of pathological conditions the specific nature of a local lesion can seldom be established by a scintillation study alone. It has been suggested that more accurate information about the nature of colloid filling defects in the liver can be provided by multiple radionuclide studies ( Muroff, 1974; Johnson, 1975; Shtasel, 1976; Yeh, 1977 ) or using combined imaging techniques ( Taylor, 1976; Gooneratne, 1977 ). With these techniques an increase in diagnostic accuracy has been claimed.

#### *7.1.2. Liver scintigraphy and diffuse liver disease.*

Scintigraphic imaging is a diagnostic aid of limited value in diffuse parenchymal liver disease. The sensitivity of detection of diffuse involvement in mild disease states is less than observed with focal defects.



These non-specific findings vary from normal activity distribution, "patchy" or "mottled" distribution within the liver, to focal defects ( McAfee, 1965; Ephraïm, 1972; Johnson, 1975; Berghuis, 1976 ). In cases of advanced cirrhosis a so called colloid shift to the reticulo-endothelial system of spleen and bone marrow may occur. Antar ( 1977 ) speaks of reticulo-endothelial failure of the liver. The characteristic findings in such cases are decreased radio-activity in the often enlarged liver, increased activity in an enlarged spleen, accumulation of radio-activity in bone marrow and high radio-activity in the cardiac blood pool. All of this results from reduced hepatic blood flow ( Shaldon, 1961 ), a decrease in the hepatic clearance of the radiocolloid and injury of the liver cells. In other diffuse liver diseases as acute or chronic hepatitis some of these findings can also occur ( Luthra, 1968; Berghuis, 1976 ). DeNardo et al ( 1976 ) reported the measurement of radiocolloid clearance rates by liver and other reticulo-endothelial tissues as an aid to differentiation between a number of diffuse liver diseases.

#### *7.1.3. Accuracy of liver scintigraphy.*

The diagnostic value of liver scintigraphy is limited by the rate of occurrence of false positive and negative results. Several investigators have evaluated the accuracy of liver scans in focal disease in large series of patients ( McAfee, 1965; Covington, 1970; Lunia, 1975; de Ruiter, 1977; Marty, 1977; Cedermarck, 1977 ). In 1977 de Ruiter et al. found an overall agreement rate of 83 per cent when correlating scintigraphic to autopsy findings. This results is somewhat higher than the accuracy rate reported by other investigators which vary from 77-80 per cent. In de Ruiter's series false

positive reports occurred in 15 per cent and false negative reports in 18 per cent. In the other investigations false positive reports vary between 9 and 30 per cent and false negative reports between 12 to 15 per cent. The observation of de Ruiter that accuracy of liver scintigraphy increases in enlarged liver is worth mentioning. Covington ( 1970 ) discussed the errors and pitfalls which may cause false positive and false negative reports.

#### *7.1.4. Liver scintigraphy and jaundice.*

Colloid scintigraphy of the liver in jaundiced patients provides only non specific information and has therefore limited diagnostic value. As in diffuse liver disease patterns of "reticulo-endothelial liver failure" can occur. Findings of focal lesions can be due to space-occupying lesions but may also be caused by dilated bile ducts ( McAfee, 1965; Heck, 1971; Berghuis, 1976; Shtasel, 1976 ). A distinct defect or diminished isotope uptake in the region of the porta hepatis in jaundiced patients may be due to metastatic disease or anatomic variation but is also highly suspect for enlarged bile ducts ( Drum, 1972 ) and may indicate extrahepatic biliary obstruction. Heck ( 1971 ) established criteria for the determination of biliary duct enlargement and found an overall diagnostic reliability of 78 per cent.

In cases of obstructive jaundice in children caused by biliary atresia, choledochal cysts or the inspissated bile syndrom no distinguishing features could be observed ( DaCosta, 1977; Smith, 1977 ). However in some cases the presence of liver disease was confirmed, but no definitive information was provided as to the site of obstruction.

Several investigators compared the results obtained by nuclear liver imaging with those of ultrasound and C.T.-scanning ( Jääskeläinen, 1969; Leyton, 1973; Taylor, 1974, 1977; MacCarthy, 1977; Rasmussen, 1978; Scherer, 1978 ). A similar degree of overall accuracy in diagnosing focal disease has been found for ultrasound ( Rasmussen, 1978 ) but both ultrasound and C.T.-scanning can differentiate space-occupying lesions with a higher degree of accuracy than scintigraphy. In diffuse liver disease, such as cirrhosis, nuclear imaging is superior but in general colloid scans seem to produce more false positive results in comparison to ultrasound and C.T.-scanning ( MacCarthy, 1977; Taylor, 1977; Rasmussen, 1978 ). In obstructive jaundice C.T.-scanning and ultrasound are of more value due to the demonstration of dilated intrahepatic bile ducts. The combination of ultrasound and nuclear imaging more accurately assesses focal hepatic lesions than either modality alone ( Grossman, 1976; MacCarthy, 1977 ). C.T.-hepatic imaging appears only occasionally to give extra information.

## CHAPTER VIII.

### CHOLESCINTIGRAPHY, THE FUNCTIONAL STUDY OF LIVER AND BILIARY TRACT.

#### 8.1. *Introduction.*

The concept that the functional capacity of the liver might be assessed by measuring the ability of liver cells to remove and excrete an intravenously injected dye was first introduced in 1901 by Abel and Rowntree. In 1923 the first paper dealing with the use of Rose Bengal for the study of liver function was presented ( Delprat, 1923 ). The dye was administered intravenously in dogs and the rate of elimination from the blood stream and the influence of liver injury on the rate of elimination was estimated. The first results of the Rose Bengal test in human subjects was reported by the same investigator in 1924. The introduction of a radioactive Rose Bengal uptake-excretion test by Taplin et al in 1955 represented a further development of the earlier Rose Bengal test. A new era for studying liver function with radioactive substances was heralded by this development.

#### 8.2. $^{131}\text{I}$ -Rose Bengal.

Taplin et al ( 1955 ) reported on the results of a study of the turnover of radioactive dye in rabbits to prove the potential clinical applicability in liver and biliary tract disease. A gamma ray scintillation counter and recording equipment were used to make external measurements over the liver area. In the same publication they also demonstrated the preliminary clinical results in patients with some common diseases of liver.

These diseases seem to produce fairly typical uptake-excretion patterns, which are readily distinguishable from those recorded in normal individuals.

Rose Bengal is a fluorescein derivate and is labelled with  $^{131}\text{I}$ , which emits both gamma and beta rays of several energies and has a half life of 8.14 days. It is removed from the blood exclusively by the polygonal cells of the liver and excreted via the bile. Peak levels in the liver are reached within 30-40 minutes after injection of the substance; normally it appears in the duodenum in 15-20 minutes ( Neibling, 1972 ). Meurman ( 1960 ) studied the distribution and kinetics of  $^{131}\text{I}$ -Rose Bengal in animals.

Among other things he described autoradiographic findings, which show that  $^{131}\text{I}$ -Rose Bengal is mainly taken up centrilobularly in the liver of normal animals. In necrotic areas of damaged livers a very high uptake of the substance was also shown. A notable fact is that when retention of  $^{131}\text{I}$ -Rose Bengal occurs in the blood the radioactivity in different organs was usually increased, for example in the stomach wall. Therefore it is possible for the dye to be excreted in the gastro-intestinal tract, even when there is complete obstruction of the common bile duct. Nordyke ( 1972 ) also reviewed the metabolic and physiologic aspects of  $^{131}\text{I}$ -Rose Bengal in studying liver function and the patency of the biliary tract and confirmed earlier findings of Meurman ( 1960 ). Burke and Halko ( 1966 ) first reported the use of the scintillation camera with  $^{131}\text{I}$ -Rose Bengal for the continuous visualisation of the dynamics of liver uptake and excretion.

#### 8.2.1. *Clinical application of $^{131}\text{I}$ - Rose Bengal.*

Following the introduction of the test by Taplin ( 1955 ) various applications of the  $^{131}\text{I}$ - Rose Bengal test have been described.

##### 8.2.2.1. *Estimation of liver function.*

"Liver counting" to estimate liver function is a relatively insensitive method to distinguish between normal and abnormal function ( Rosenberg, 1956; Moertel, 1958 ). The estimation of blood clearance is a more sensitive and less complex alternative technique ( Sapirstein, 1955; Davies, 1976 ).

##### 8.2.2.2. *Differential diagnosis of jaundice.*

The first application of the test in relation to jaundice was reported by Eyler et al ( 1965 ). Since then several similar publications have appeared. Winston and Blahd ( 1972 ) reviewed the results of several investigators who used rectilinear scanners and scintillation cameras. They pointed out that with this tracer study several conclusions about the etiology of jaundice can be drawn, but that the differentiation of partial biliary tract obstruction and cholestasis is not reliable. Several modifications to the test and a detailed study of the results could not significantly increase the reliability of the test in relation to the differential diagnosis or the site of obstruction ( Whiting, 1968; Nordyke, 1960; Berk, 1963; Neibling, 1972; Gamlen, 1975 ).

#### 8.2.2.3. *Miscellaneous indications for the use of $^{131}\text{I}$ -Rose Bengal.*

The test has made a significant contribution to the difficult differential diagnosis of jaundice in childhood ( Sharp, 1967; Thaler, 1968; Rosenthal, 1969 ). For the diagnosis of choledochal cysts the test has also proved to be a most effective procedure ( Williams, 1970; Park, 1974; Oshiumi, 1977 ). Shoop ( 1969 ) reported a cirrhotic patient with hepatoma in whom the tumour concentrated the tracer as well or better than the remaining fibrotic liver tissue. Leakage of bile into the peritoneal cavity due to trauma or biopsy can also be detected ( Spencer, 1967; Rosenthal, 1969 ). Eikman ( 1975 ) used the test to study the patency of the cystic duct as an diagnostic aid in acute cholecystitis.

The disadvantages of the  $^{131}\text{I}$ - Rose Bengal limit its wide spread use as a radiopharmaceutical.  $^{131}\text{I}$ iodine has physical properties which are not optimal for imaging and which lead to relatively high radiation doses. The thyroid must be blocked before starting the study and there is a relative high rate of false positive reports ( Davies, 1976 ).

Other labelled agents have also been tested and used for clinical investigations. Reports have appeared about  $^{131}\text{I}$ -toluidine blue ( Chen-Stute, 1977 ),  $^{123}\text{I}$ -bromsulphalein ( Goris, 1973 ),  $^{123}\text{I}$ -indocyanine green ( Ansari, 1974 ),  $^{131}\text{I}$ -asialo-orosomucoid ( van Rijk, 1977 ) and  $^{111}\text{In}$ -phenolphthalein ( Lin, 1977 ).

#### 8.3. $^{99\text{m}}\text{Tc}$ -labelled hepato-biliary agents.

Scintigraphic imaging of the hepato-biliary system has significantly improved with development of  $^{99\text{m}}\text{Tc}$ -labelled reagents.

These radiopharmaceuticals do not have the disadvantages of the  $^{131}\text{I}$ -labelled agents and the excellent physical characteristics of  $^{99\text{m}}\text{Tc}$  make them preferable for organ imaging.

Many complexes labelled with Technetium have been proposed as hepato-biliary agents since the first report from Baker et al in 1974 about their findings with  $^{99\text{m}}\text{Tc}$ -pyridoxylideneglutamate (  $^{99\text{m}}\text{Tc}$ -PDG ) as cholescintigraphic agent ( Lin, 1974; Ronai, 1975; Jenner, 1976, Fritzberger, 1976; Noronka, 1977; Wistow, 1977 ). A number of  $^{99\text{m}}\text{Tc}$ -labelled amino acid complexes of pyridoxylidene showed excellent hepato-biliary excretion and found therefore a wide application in the clinical investigation of hepato-biliary disorders ( Baker, 1974, 1975; Ronai, 1975; Poulou, 1976; Fotopoulos, 1977; Papadimitriou, 1977; Verdegaaal, 1977; Clarke, 1978; Lubin, 1978 ).

Since 1976 hepato-biliary imaging with derivatives of imino-diacetic acid ( IDA ) have been performed and the first clinical reports seem again to indicate improvement ( Wistow, 1977; Tjen, 1977, 1978; Rosenthal, 1978; Chiotellis, 1978 ).

#### 8.3.1. $^{99\text{m}}\text{Tc}$ -pyridoxylideneglutamate.

In 1975 in an extensive investigation Baker reported the experimental aspects and clinical applicability of  $^{99\text{m}}\text{Tc}$ -PDG. The compound showed a high rapid concentration in the polygonal liver cells with a good visualisation of the liver 3-5 minutes post injection and of the gallbladder about 10 minutes after injection.

Good experimental work on this subject was also done by Fotopoulos ( 1977 ) and Jenner ( 1976 ). They confirmed earlier statements that pyridoxal complexes are valuable in the diagnosis of disturbances of the hepatobiliary tract, and that the study is a useful supplement to radiocontrast studies.



Ronai et al ( 1975 ) reported on the clinical findings with  $^{99m}\text{Tc}$ -PDG in 70 patients; they described the distribution patterns in normal subjects, patients suffering from right upper quadrant abdominal pain and jaundiced patients. The normal findings included a visualisation of the biliary tract and the gallbladder within 10-15 minutes and accumulation in the gastro-intestinal tract within 20 minutes.

*8.3.1.1.  $^{99m}\text{Tc}$ -PDG test in gallbladder disease.*

In the investigation of abdominal pain, Ronai ( 1975 ) found the cholescintigram a reliable investigation to detect acute inflammatory disease of gallbladder. However in most cases of chronic cholecystitis a normal cholescintigram was found. In all patients there was a similarity with X-ray investigation. Poulou ( 1976 ) found no visualisation of the gallbladder in patients with chronic cholecystitis, but used the  $^{99m}\text{Tc}$ -PDG scan in patients when focal defects in or near the usual gallbladder bed were found on the colloid scan. When the defects fill in on the  $^{99m}\text{Tc}$ -PDG scan it confirms that they were secondary to the gallbladder impression or to a partial intrahepatic gallbladder and were not due to metastases. Stadalnik et al ( 1977 ) reported a 100 per cent accuracy of the  $^{99m}\text{Tc}$ -PDG scan in cholecystitis and compared the results with cholecystography and ultra sonography. A normal gallbladder can fail to accumulate radioactivity ( Eikman, 1973; Ronai, 1975, 1977 ).

#### 8.3.1.2. $^{99m}\text{Tc}$ -PDG test in jaundice.

The problem of finding reliable parameters to determine whether the cause of jaundice is intra or extra-hepatic has also constituted a challenge for cholescintigraphy. Several attempts were made to modify or extend the original  $^{99m}\text{Tc}$ -PDG test for more accuracy in differentiating between medical and surgical jaundice ( Ronai, 1975; Poullose, 1976; Verdegaal, 1977; Papadimitriou, 1977; Lubin, 1978 ).

The complete obstruction pattern generally posed no great problem, on the contrary the patterns of partial obstruction or delayed excretion on the sequential scintigrams potentiated difficulties of differential diagnosis. In the study of Ronai ( 1975 ) in 36 jaundiced patients, the absence of gastro-intestinal activity at 18 hr. after injection of the radio-pharmakon allowed a reliable diagnosis of complete extra-biliary obstruction. Further evidence supporting this diagnosis was provided by presence of a defect in the liver or background activity due to the presence of the distended gallbladder. Ronai distinguishes a negative gallbladder image, a so called Courvoisier sign from a non-visualised gallbladder. He found this typical phenomenon in 80 per cent in patients with biliary obstruction.

In patient with incomplete biliary obstruction there is delayed excretion of the reagent into the gastro-intestinal tract. Hepatocellular disease may also give this pattern.

Ronai stated that an incomplete biliary obstruction is difficult to differentiate from a liver parenchyma disturbance unless a scintigraphic Courvoisier sign or distended common bile duct is seen in the scintigram. Verdegaal ( 1977 ) also used the Courvoisier sign in the differentiation between intra and extra-hepatic jaundice, combined with the results of ultrasound.

Lubin ( 1978 ) approached the problem of distinguishing between hepatocellular disease and obstructive jaundice by estimating the time of appearance in the intestine and by using the 20 min/ 5 min ratio as a measure of clearance efficiency of the polygonal cell. He also related this appearance time to bilirubin values and found a delayed excretion of the agent ( 30-180 minutes after injection ) at a bilirubin level of 2.8 mg%, a very delayed ( 24 hours ) excretion by a bilirubin value of 11 mg% and no visualisation at a bilirubin of 12.2 mg%. However his overall accuracy in this series patients was reported as 72.4 per cent. Poulou ( 1976 ) showed less optimism in his report and regarded the  $^{99m}\text{Tc}$ -PDG test as less helpful to distinguish intrahepatic and extrahepatic jaundice. Some other indications for the use of  $^{99m}\text{Tc}$ -labelled components are assessing the patency of a biliary-intestinal anastomosis, assessing functional disturbances of the sphincter of Oddi ( Papadimitriou, 1977 ) and demonstrating intra-peritoneal bile leakage ( Fotopoulos, 1977 ).

#### *8.4. Iminodiacetic - acid derivatives.*

There is a continuously growing interest in the use of N-substituted iminodiacetic acid for hepato-biliary studies.

Wistow ( 1977 ) stated:

"An ideal hepatobiliary agent for scintigraphy should have the following characteristics:

- rapid extraction from the plasma by the polygonal cells of the liver
- rapid transit through these cells
- high biliary concentration
- little or no absorption from the intestine
- minimal concentration in the urinary tract

- high labeling yield with  $^{99m}\text{Tc}$  Technetium  
 - availability as a sterile, non-toxic instant kit."

The molecular size and weight of a compound, its polarity ( lipid solubility ) and molecular structure and possible protein-binding influence the excretion of a compound into bile ( Millburn, 1970 ). Substances with a molecular weight between 300 and 1000 are preferentially excreted in the bile. Increasing the molecular weight of a compound within this range may favourably affect its biliary excretion ( Wistow, 1977 ).

Loberg et al ( 1976 ) first reported investigations with radio-pharmaceuticals based on N-substituted iminodiacetic acid. Iminodiacetic acid ( IDA ) is a small molecule, capable of chelating ( radioactive ) metals. It can easily be synthetically incorporated into bifunctional analogs. Several IDA-derivates have been characterized ( Wistow, 1977 ):

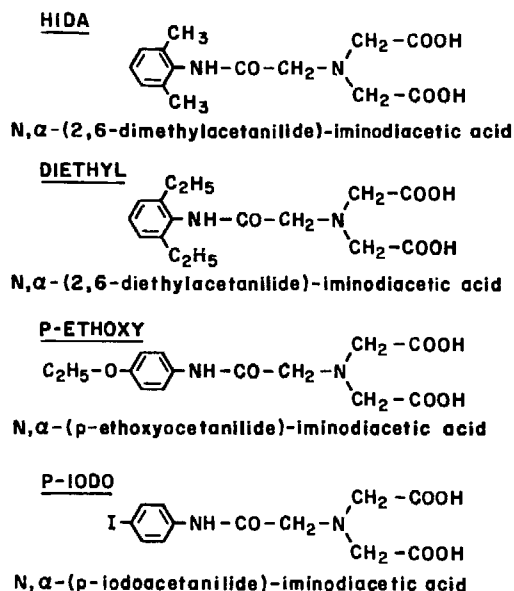


Fig.8-1 Structural formulae of a number of IDA-derivatives  
 ( Wistow et al, 1977 ).

#### 8.4.1. Chemistry and structure.

IDA derivatives are extracted and excreted through the hepatocyte with an extremely fast blood clearance, a short hepatocyte transit time and prompt appearance in the bile. Chemically, they have many of the features listed earlier as necessary for significant bile excretion. The molecular weight of dimethyl-IDA is 294.30. This compound has hydrophilic and lipophilic ends separated by a substantial distance. Chelation with  $^{99m}\text{Tc}$  likely creates a dimer, thus decreasing the hydrophilic nature of the carboxyl groups and increasing the effective molecular weight of the compound. It has been shown that replacing the methyl groups by ethyl groups at the 2,6 positions of the benzene ring slightly increases the molecular weight and substantially increases the lipid solubility. This implies a faster blood clearance of the compound and increases the biliary concentration with reduced renal excretion ( Wistow et al, 1977 ).

Fonda and Pedersen ( 1978 ) studied the structure of  $^{99m}\text{Tc}$ -diethyl-IDA and showed by Sephadex column chromatography that  $^{99m}\text{Tc}$ -diethyl-IDA consists of two clearly identifiable components which are interchangeable forms. These two components may be the mono- and bicomplex of N-(2,6-diethyl-acetanilido) iminodiacetic acid with one atom of technetium. It seems of no clinical importance but supports the theory of Loberg ( 1976 ), who investigated the radiochemical properties of IDA-derivates. His results were later confirmed by several other authors ( Wistow, 1977; Ryan, 1977; Rosenthall, 1978; Chiotellis, 1978; Fonda, 1978 ). Using paper chromatography he found a labeling yield of dimethyl-IDA with  $^{99m}\text{Tc}$

greater than 99%; no detectable pertechnetate or colloid was found. The results of the radiochemical purity studies using Sephadex gel permeation chromatography showed that 98% of the  $^{99m}\text{Tc}$ -dimethyl-IDA was eluted from the column in its chelate form, indicating the in-vitro stability of the compound, i.e. the bond strength between technetium and IDA.

#### 8.4.2. Biodistribution.

The tissue distribution of IDA derivatives was expected to be intermediate between those of the anti-arrhythmic agents lidocaine and methylidocaine (Kniffen, 1974). The distribution studies of Loberg (1976) in both mice and dogs showed that approximately 82-87% of  $^{99m}\text{Tc}$ -dimethyl-IDA was cleared through the hepatobiliary system. He explained the hepatobiliary clearance of the agent by the fact that certain lipophilic chelating groups are eliminated through the bile. The blood clearance of  $^{99m}\text{Tc}$ -dimethyl-IDA is very rapid: at 5 min. post injection only 3% of the injected dose remained in the blood and at 30 min. the level is less than 1%. Blood clearance in dog was slower; 3% of the injected dose remained in circulation at 30 min. Similar in-vivo kinetics were found by Ryan (1977) and Chiotellis (1978).

Loberg (1976) tested the in-vivo stability of the  $^{99m}\text{Tc}$ -diethyl-IDA by reinjecting the contents of urinary bladder and gallbladder. In comparison with the findings in the original study the results of the reinjections suggest that  $^{99m}\text{Tc}$ -diethyl-IDA is excreted in its original radiochemical form. Wistow (1977) tested several IDA analogues and compared the results with  $^{131}\text{I}$ -Rose Bengal and pyridoxal compounds in baboon studies.  $^{99m}\text{Tc}$ -diethyl-IDA showed the lowest blood level during the whole study, and the highest level of biliary concentration

during the first 30 min. This is four times the Rose-Bengal concentration and 1.6 times that of  $^{99m}\text{Tc}$ -dimethyl-IDA. After 30 min.  $^{99m}\text{Tc}$ -diethyl-IDA shows somewhat higher value of biliary concentration 14.1% compared to 11.9% for  $^{99m}\text{Tc}$ -dimethyl-IDA, but the whole cumulative dose in bile for  $^{99m}\text{Tc}$ -diethyl-IDA is 80% and for  $^{99m}\text{Tc}$ -dimethyl-IDA 75%.

Chiotellis ( 1978 ) also made a comparative study in rabbits with  $^{99m}\text{Tc}$ -dimethyl-IDA and  $^{131}\text{I}$ - Rose Bengal and found the  $^{99m}\text{Tc}$ -agent more suitable for rapid serial imaging. Both Wistow and Chiotellis found a greater urinary excretion for the IDA-derivates in comparison with Rose Bengal. In this study  $^{99m}\text{Tc}$ -diethyl-IDA has the lowest renal excretion. This does not seem to be a real disadvantage.

Subramanian ( 1977 ) reported about the influence of structural changes on biodistribution of  $^{99m}\text{Tc}$ -labelled IDA derivates. The studies were performed in rabbits and confirmed earlier statements that the relative concentrations and rates of clearance by the liver and kidney can be markedly altered by selecting different substituents for coupling IDA.

#### *8.4.3. Clinical application of IDA derivates.*

Since the first experimental work of Loberg et al ( 1976 ) with IDA derivates several investigators reported about application of these radiopharmaceuticals in diagnosing hepatobiliary disease ( Ryan, 1976, 1977; Biersack, 1977; Cox, 1977; Sauer, 1977; Nielsen, 1977; Tjen, 1977, 1978; Welcke, 1977; Sialer, 1977; Maquire, 1978; Rosenthal, 1978 ).

The normally administered dose is 0.07-0.10 mCi/Kg body weight  $^{99m}\text{Tc}$ -labelled derivate.

The normal scintigram demonstrates the bile duct system, the gallbladder and excretion of the radiopharmaceutical in the intestine, all within 40-60 minutes after i.v. administration of the IDA derivate. In normal subjects gallbladder visualisation takes place between 10 and 40 minutes post injection. Gallbladder visualisation was demonstrated in all normal subjects; however in previous reports with other agents ( Eikman, 1973; Ronai, 1975) in some subjects free of gallbladder disease, the gallbladder showed no accumulation of radioactivity. Ronai ( 1977 ) stated that gallbladder filling with  $^{99m}\text{Tc}$ -dimethyl-IDA was achieved in all normal subjects whether they fasted or not. Renal activity was frequently seen within the first 5-10 minutes, but disappeared within 20-30 minutes.

#### *8.4.3.1. IDA derivatives in gallbladder disease.*

In all investigations of patients with acute cholecystitis or chronic cholecystitis with cystic duct obstruction, none demonstrated gallbladder filling. Rosenthal ( 1978 ) reported this failure to demonstrate the gallbladder in patients with chronic cholecystitis without cystic duct obstruction using  $^{99m}\text{Tc}$ -dimethyl-IDA. Patients with proven stone in the cystic duct did not show any filling of the gallbladder ( Nielsen, 1977 ). Several authors studied gallbladder function after stimulation by fatty meal or cholecystokinin ( following the example of Eikman et al in 1975 ) to empty the gallbladder before the radiopharmaceutical is administered ( Sialer, 1977; Rosenthal, 1978 ). Rosenthal ( 1978 ) found in one patient with chronic cholecystitis and a patent cystic duct filling of the gallbladder only with a second study after stimulation with cholecystokinin. However he did not find any further difference in patients with no-visualisation of the gallbladder in whom



a repeat study was performed after stimulation. Nielsen ( 1977 ) reported studies with  $^{99m}\text{Tc}$ -diethyl-IDA and recommended the procedure as a screening for patients with possible gallbladder disease.

#### *8.4.3.2. IDA derivatives in jaundice.*

In all studies the diagnostic accuracy proved to be strongly dependent on the severity of the jaundice. Rosenthal ( 1978 ) using  $^{99m}\text{Tc}$ -dimethyl-IDA in his investigations studied the visualisation of the biliary ducts in relation to serum bilirubin level. If serum bilirubin level is 5 mg% or less a reliable diagnosis can be made; an accurate visualisation of the ductal system is possible. Under these circumstances the pattern of partial obstruction are described as dilated bile ducts and slow excretion of radioactivity in the gut. When the biliary ducts were not dilated Rosenthal diagnosed hepatobiliary disease, and when there was no gut activity 24 hours after administration of the agent it was suspect for complete extrahepatic obstruction. When bilirubin levels were between 5 and 12 mg% biliary ducts could not accurately be identified, however a visualisation of the gallbladder was possible. In these cases hepatocellular disease and extrahepatic obstruction could be distinguished by the presence or absence of intestinal activity and the visualisation of the gallbladder.

Rosenthal stated that when serum bilirubin levels are higher than 12 mg% the hepatic uptake of  $^{99m}\text{Tc}$ -dimethyl-IDA is almost negligible regardless of the cause of jaundice. Therefore poor uptake and no excretion into the gut after 24 hours cannot distinguish between hepatocellular disease and extrahepatic obstruction. This agrees with the findings of Lubin ( 1977 ) who investigated his patients with  $^{99m}\text{Tc}$ -pyridoxylidene glutamate

Broadly outlined the findings of Ryan ( 1977 ) are similar to the results stated above. In addition he modified the dose of the administered radiopharmaceutical in severely jaundiced patients; by increasing the dose of  $^{99m}\text{Tc}$ -dimethyl-IDA he achieved adequate images up to 18 hours after injection. With bilirubin levels in the range of 15 mg% or higher, a dose of 10-15 mCi prove more satisfactory for imaging on the second day. However in spite of these measure he concluded that  $^{99m}\text{Tc}$ -dimethyl-IDA did not distinguish hepatocellular disease from partial obstruction.

#### *8.4.3.3. IDA derivatives in miscellaneous investigations of liver and biliary tract.*

To assess the patency of surgical pathways, i.e. bilio-digestive anastomoses especially in case of jaundice an IDA study provides useful information ( Biersack, 1977; Reichelt, 1977; Rosenthal, 1978 ). Reichelt ( 1977 ) reported about the typical patterns of sequential scans with  $^{99m}\text{Tc}$ -diethyl-IDA in polycystic liver disease. There is only limited experience with IDA studies in childhood disease as biliary atresia and choledochal cysts ( Reichelt, 1978 ).

#### *8.4.3.4. Combined studies.*

A few investigations have reported the use of IDA-derivates combined with other diagnostic investigations. Ryan ( 1976 ) reported the combined use of  $^{99m}\text{Tc}$ -dimethyl-IDA and ultrasound in the differential diagnosis of jaundice. He concluded that combined use of both investigations provided a high degree of accuracy in the differential diagnosis of jaundice.

In analogy to earlier investigations such as hepatography, a functional kinetic investigation of the whole liver ( van Bochove, 1970; Gamlen, 1975 ), there are several reports about the extension of the original, sequential IDA-studies with supporting qualitative assessment of liver function. Time-activity curves, generated from regions of interest over the liver, gallbladder and other areas, can give additive information ( Sauer, 1977; Biersack, 1977; Welcke, 1977 ). Cox ( 1977 ) reported the use of functional imaging techniques developed by de Graaf ( 1975 ) to depict the spatial distribution of the rate of change of IDA activity in multiple liver areas. In this study functional images of the liver for both the uptake and excretion phase of the IDA turnover are generated, and diffuse disturbances in liver function can be diagnosed as well as small foci which are missed when only time-activity curves are generated.

CHAPTER IX.  
THE RADIOPHARMACEUTICAL,  
N ( 2,6-DIETHYL ACETANILIDO )-IMINODIACETIC ACID.

9.1. *Synthesis.*

N ( 2,6-diethyl acetanilido ) - iminodiacetic acid has been evaluated in this clinical study. This derivate of iminodiacetic acid is commercially available in the form of a sterile, pyrogen-free lyophilized tin complex as an instant kit ( Solco-Hida<sup>R</sup> ).

Diethyl-IDA has a molecular weight of 322.36 and is synthesized by reacting alpha - chloro 2,6 diethyl acetanilid with iminodiacetic acid in refluxing ethanol water. Chemical synthesis is shown in fig. 9-1.

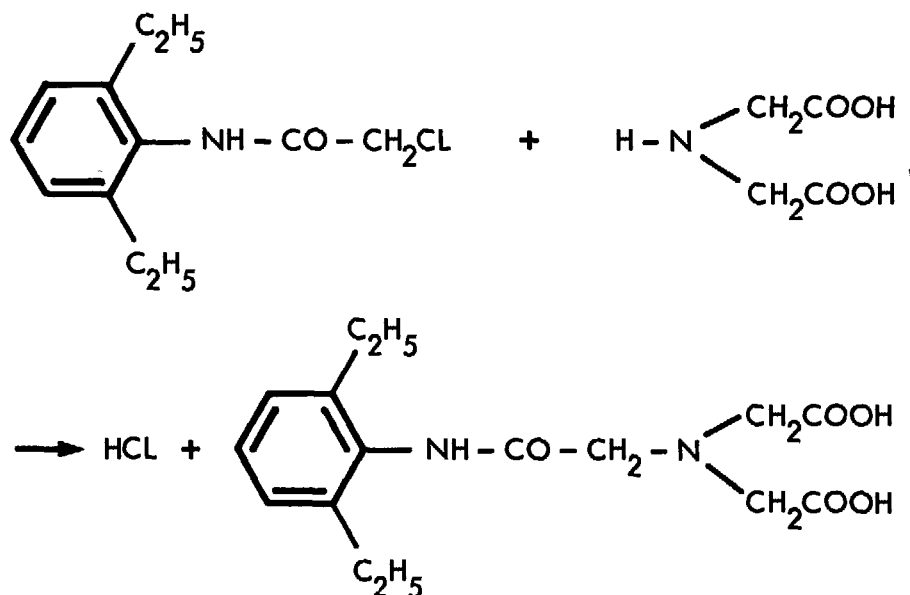


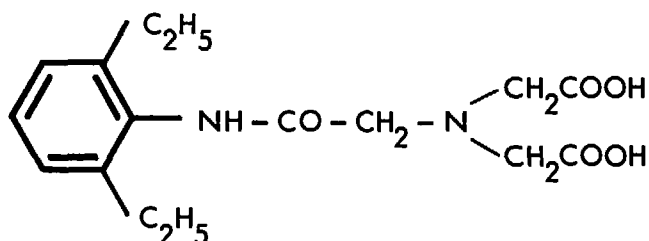
fig. 9-1 Synthesis of N ( 2,6-diethyl acetanilido ) - iminodiacetic acid.

### 9.2. Preparation of the clinical reagent.

1-4 ml. sterile, pyrogen free  $^{99m}\text{Tc}$ -pertechnetate solution, as eluted from the generator, is transferred aseptically to the labelling vial. A clear colourless solution with a pH value of 5.5 ( +0.4 ) is obtained, which is ready for administration ( see fig. 9-2 ). Further purification of the labelled compound is not necessary and the labelled product remains stable for two hours.

### DI - ETHYL - IDA

#### DIETHYL ACETANILIDO-IMINODIACETIC ACID



#### $^{99m}\text{Tc-Sn-N-DIETHYL ACETANILIDO-IMINODIACETIC ACID}$

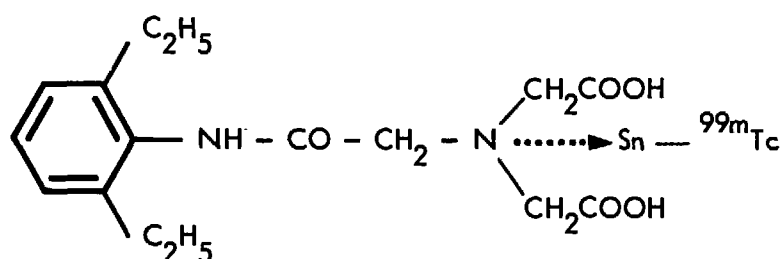


fig. 9-2 The reagent before and after labelling with  $^{99m}\text{Tc}$ -pertechnetate.

*9.3. The quality control of radiopharmaceuticals used for biological evaluations.*

To control the radiopharmaceutical used for biological studies for the presence of free  $^{99m}\text{Tc}$ -pertechnetate, thin layer chromatography was used. For routine quality control of the reagents for in-vivo studies ascending thin layer chromatography, using silica gel as the stationary phase and normal saline as continuous phase, was used.  $R_f$  values were recorded using a radiochromatogram scanner ( Berthold ).



fig. 9-3 Autoradiogram of  $^{99m}\text{Tc}$ -diethyl-IDA in comparing with  $^{99m}\text{TcO}_4$ .

The values obtained were compared with  $^{99m}\text{TcO}_4^-$  and  $^{99m}\text{Tc-Sn-colloid}$  controls. With normal saline as solvent  $^{99m}\text{Tc-diethyl-IDA}$  has an  $R_f$  value of 0.61 whilst  $^{99m}\text{TcO}_4^-$  has an  $R_f$  of 0.83 and  $^{99m}\text{Tc-colloid}$  of 0.0.

Diethyl-IDA shows a labelling yield on average of 93.4% and in an analysis of a number of kits no pertechnetate ion was detected.

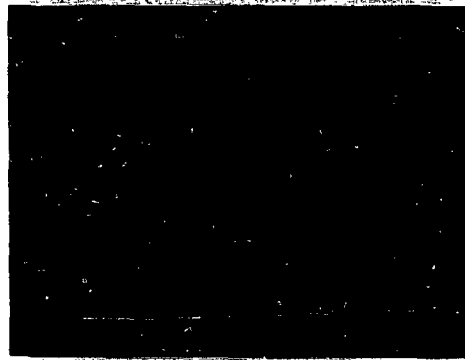
The radiochromatogram of  $^{99m}\text{Tc-diethyl-IDA}$  compared with  $^{99m}\text{TcO}_4^-$  is shown in figure 9-3 as an autoradiogram.

Typical profile scans of radiochromatograms are shown in figure 9-4. The first image shows  $^{99m}\text{Tc-Sn-colloid}$  at the origin, the second image the  $^{99m}\text{TcO}_4^-$  which migrates to give a peak with an  $R_f$  value of 0.83. The third scan depicts the  $^{99m}\text{Tc-diethyl-IDA}$  peak.

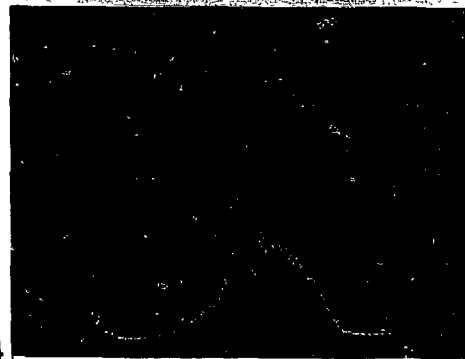
1



2



3



4

fig. 9-4 Profile scans of  $^{99m}\text{Tc-Sn-colloid}$  (1),  $^{99m}\text{TcO}_4$  (2) and  $^{99m}\text{Tc-diethyl-IDA}$  (3).



#### 9.4. *The radiopharmaceutical in animal studies.*

##### 9.4.1. *Kinetic studies in the rat.*

The biodistribution of diethyl-IDA following intravenous injection was studied in adult wistar rats ( weight 200 gm ) by injecting 0.1 ml ( 25 uCi ) of the radiopharmaceutical. Groups of five rats were sacrificed at 2, 15, 60, 120, 180, 210, 240 and 270 minutes post injection. Samples of blood ( 1 ml ), the liver, the stomach, intestine and kidneys were removed, weighed to determine the wet weight and counted in a gamma well counter. The organ concentration, expressed as a percentage of the injected dose per gram of wet tissue was studied as function of time following injection. Figure 9-5 shows the curves obtained from blood, liver, intestines, stomach and kidneys.

It can be seen from these curves that a regression in the blood and liver curves can already be observed 2 minutes post injection. This suggests that the turn-over in rats is very rapid and that already 2 minutes p.i. activity can be found in the intestine. The time-activity curves obtained from stomach and kidneys show an atypical course.

On comparison it is possible to draw the conclusion from these curves that the diethyl-IDA, excreted into the intestine, is not reabsorbed by the intestinal mucosa in concentrations that are detectable in blood. To prove this statement 0.2 ml  $^{99m}\text{TcO}_4^-$  and 0.2 ml  $^{99m}\text{Tc}$ -diethyl-IDA were operativey introduced into the duodenum of anaesthetized rats.

One hour after the operation the animals were sacrificed and liver and blood concentrations were counted. The results, expressed as percentage of the administered dose per gram tissue and per ml blood, are shown in table 9-1.

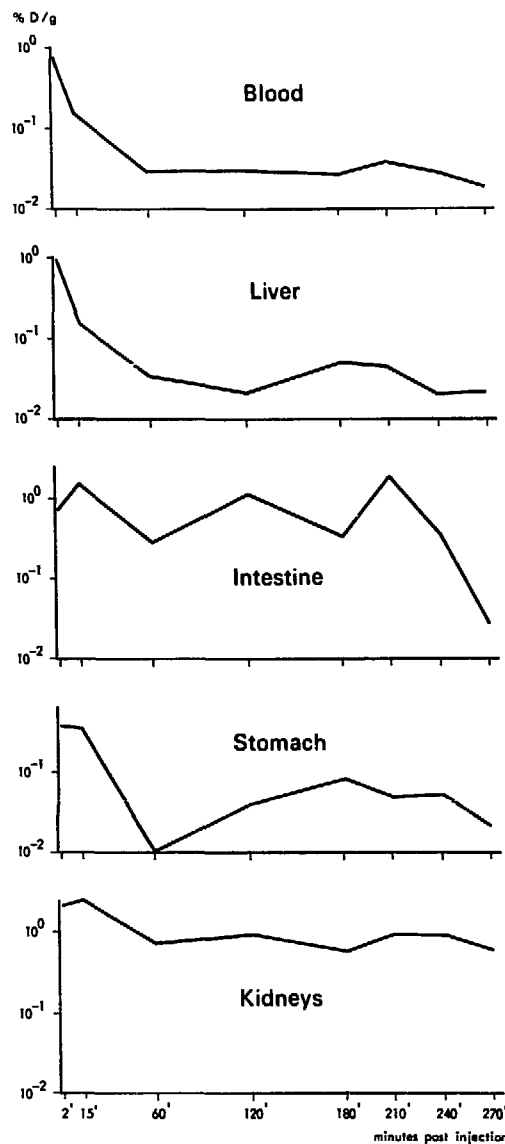


Fig. 9-5 Time-activity curves obtained from blood, liver, intestine, stomach and kidneys in rat after injection of 25 uCi  $^{99m}\text{Tc}$ -diethyl-IDA.

	$^{99m}\text{TcO}_4$	$^{99m}\text{Tc}$ -diethyl-IDA
blood % / ml	0.14	0.01
lever % / mg	0.32	0.01

Table 9-1 Blood and liver concentrations of  $^{99m}\text{Tc}$ -pertechnetate and  $^{99m}\text{Tc}$ -diethyl-IDA, 1 hr. after administration of these reagents into the duodenum of rats.

It can seen from this table that  $^{99m}\text{Tc}$ -pertechnetate is reabsorbed from the intestinal mucosa into the blood and taken up by the liver, confirming the findings of van Bochove ( 1970 ), whereas no reabsorption of  $^{99m}\text{Tc}$ -diethyl-IDA was observed in our study.

To test the possibility that perhaps  $^{99m}\text{Tc}$ -diethyl-IDA that has already passed the liver and has been excreted into intestine could be reabsorbed the intestinal contents of a rat injected intravenously with  $^{99m}\text{Tc}$ -diethyl-IDA was transferred into the duodenum of another rat. One hour after administration the liver and blood concentration of this rat were estimated. No significant amount of activity was observed in these samples. In confirmation of the observations of Stöffler et al ( 1978 ) in patients, no reabsorption of  $^{99m}\text{Tc}$ -diethyl-IDA from the intestinal mucosa could be demonstrated in the rat.

The kinetics of the radiopharmaceutical was studied in vivo in rats after intravenous injection of the reagent while the rat was positioned under the gamma camera. Time-activity curves were generated by the computer with the whole liver as region of interest ( See figure 9-6 ).



fig. 9-6 Time-activity curve of the liver from a wistar rat after intravenous administration of 25 uCi  $^{99m}\text{Tc}$ -diethyl-IDA.

In this way 8 rats were investigated; the results of the maximum uptake time of the radiopharmaceutical is shown in table 9-2.

Rat. no.	Maximum uptake time of the liver in seconds	
1.	90	
2.	100	
3.	60	
4.	80	
5.	160	
6.	80	
7.	80	$\bar{x} = 94$
8.	100	SD = 29

Table 9-2 Maximum uptake time of  $^{99m}\text{Tc}$ -diethyl-IDA by the liver of rat.

The average maximum uptake time was 94 seconds with a standard deviation of 29 seconds.

The studies discussed earlier concerning the biodistribution in rats show a rapid turnover of the radiopharmaceutical; only the descending part of the liver curves could be seen.

The results of these studies confirm the rapid uptake of the radiopharmaceutical by the liver within two minutes of administration.

#### *9.4.2. Biodistribution in animals; whole body autoradiography.*

To study the overall distribution patterns of  $^{99m}\text{Tc}$ -diethyl-IDA whole body autoradiography was performed.

$^{99m}\text{Tc}$ -diethyl-IDA was administered to an adult wistar rat and one hour post injection the animal was anaesthetized using aether. It was then frozen in hexane cooled to  $-70^{\circ}\text{C}$  by carbon-dioxide ice and bedded in a gel of carboxymethyl cellulose ( 3% solution in water ). When frozen it forms a firm support around the animal. The frozen block was mounted on a large microtome stage ( Jung cryo microtome ), which was placed in a deep-freeze. Sagittal or transversal sections through the whole body of the frozen animal were made with a section thickness of 20  $\mu\text{m}$ . Interesting sections were obtained for further study by applying a piece of adhesive tape to the surface of the block before a section was cut, the cut section then adhered to the tape ( figure 9-7 ). The section were freeze-dried and pressed against a photographic film for exposure. In this way images could be obtained to study the macroscopic distribution of radioactivity.

Figure 9-8 shows the autoradiogram of a sagittal section of a rat. The distribution of the reagent can be seen on the film as black spots associated with the liver and intestines.



Fig. 9-7 Sagittal section of a frozen rat.



Fig. 9-8 Autoradiogram of a sagittal section of a rat one hour after administration of  $^{99m}\text{Tc}$ -diethyl-IDA.

## CHAPTER X.

### CHOLESCINTIGRAPHY IN NORMAL INDIVIDUALS.

#### *10.1. Method.*

One hundred and fifty one consecutive patients presenting with suspected liver and biliary tract disease and twenty normal individuals were referred for cholescintigraphy. All patients included in this study were adults from the Rotterdam area. No special premedication or other precautions were taken. In all investigations the patients were fasting from at least six hours before the study.

Scintigraphy was performed with the aid of a Searle High Performance gamma camera using a 140 keV diverging collimator or a Searle Large Field of View gamma camera using a 140 keV parallel hole collimator. An on line computer ( Med.II, General Electric ) accumulated one minute frames for 45 minutes post injection.

The patient was placed in the supine position with the camera over the heart, liver and upper abdomen. 5mCi of the reagent was administered intravenously with the patient positioned under the gamma camera and the data storage system was started simultaneously.

Serial scintigrams were recorded on polaroid and X-ray film 2, 5, 10, 20, 30 and 45 minutes after injection. When the gallbladder was visualised but no intestinal activity was observed in the image after 45 minutes, an oral gallbladder stimulating agent ( Sorbitract<sup>R</sup> ) was administered. When no intestinal activity after stimulation was observed an additional scintigram was performed 18-24 hours post injection to demonstrate delayed intestinal excretion or complete obstruction.

The same procedure was followed when no gallbladder or common bile duct could be observed within 45 minutes post injection.

## *10.2. Data processing.*

### *10.2.1. Time-activity curves.*

The digital information stored in the computer was analyzed and time-activity curves were generated by selecting regions of interest for heart, right and left liver lobe, gallbladder, common bile duct and duodenum. The regions above the liver area were chosen so that no great intrahepatic bile duct was included. From these curves the "maximum uptake time" ( $T_{\max}$ ) and half value time of excretion ( $T_{\frac{1}{2}}$ ) were calculated. In this study only the  $T_{\max}$  and  $T_{\frac{1}{2}}$  for right and left liver lobe were used on the interpretation of the results of the study of the patient. In figure 10-1 the regions of interest and the generated curves are shown. The generated curves belong to an individual without liver disease or biliary tract disturbance.

### *10.2.2. Functional imaging.*

The functional imaging technique, developed by de Graaf ( 1975 ) was first utilized for the evaluation of liver function by van Rijk ( 1977 ) and has proved to be very promising when combined with diethyl-IDA ( Cox et al, 1977 ). With the functional imaging program the rate of change of diethyl-IDA concentration at each point in the 64x64 computer matrix covering the field of view of the gamma camera is measured. A time-activity curve is generated for each point and the slopes of the accumulation and excretory phases are calculated. For any given phase the rate of change is assessed and incorporated in a grey scale which is then reproduced as an image in which the brightness of each picture element ( pixel ) reflects the rate of change of activity: the greater the rate of change the brighter the pixel.



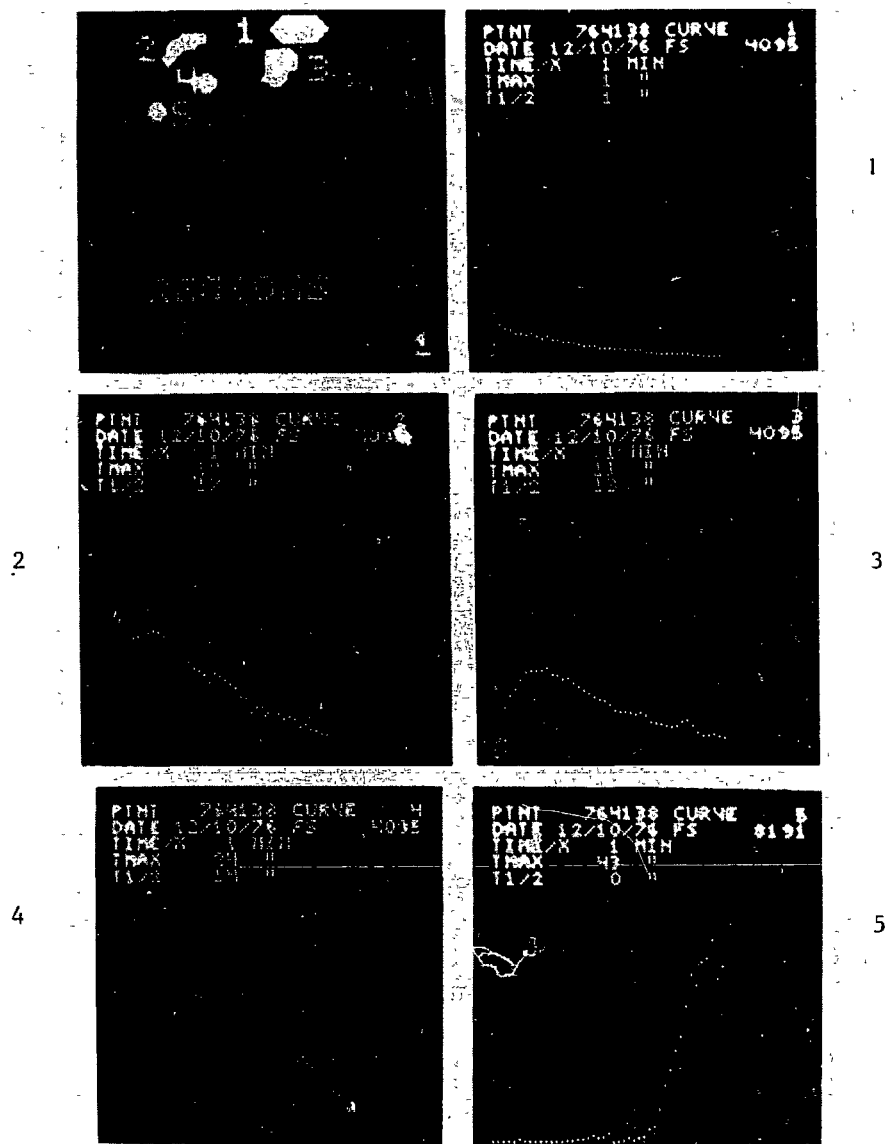


Fig. 10-1 Regions of interest and corresponding time-activity curves of a normal individual.

1. blood pool
2. right liver lobe
3. left liver lobe
4. common bile duct
5. gallbladder

For each study two functional images are generated i.e. accumulatory phase ( upslope ) and excretory phase ( downslope ) for the diethyl-IDA turnover ( see figure 10-2 ). By means of this technique diffusely disseminated disease is more readily detectable than with time-activity curves from regions of interest, partly because the amount of normally functioning liver tissue which may mask the presence of small foci of disease is greatly reduced. In a normal subject a homogeneous image is obtained whilst in the diseased state a focal defect in either uptake or excretory phase may be observed and in cases of disseminated disease a diffusely inhomogenous image will results.

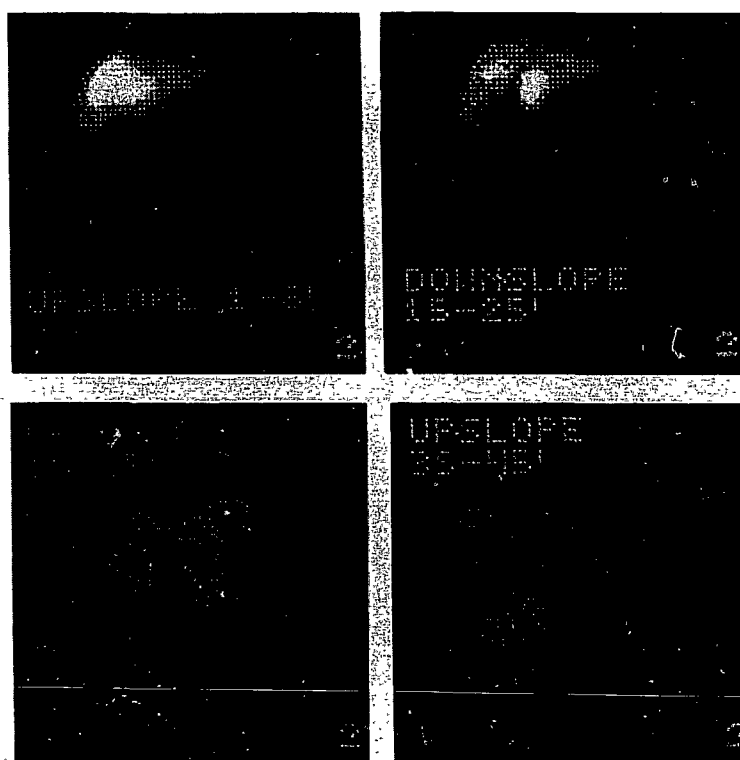


Fig. 10-2 Functional images of a normal individual.

### 10.3. *Clinical results in normal individuals.*

In twenty patients without disturbances of liver or gallbladder function, cholescintigraphy was performed.

#### 10.3.1. *Serial scintigram of a normal individual.*

After intravenous injection of 5 mCi diethyl-IDA the liver is visualised within 2 minutes post injection, while the blood pool activity disappeared within 5 minutes post injection. In agreement with the time during which blood pool remains visible the kidneys can be seen until 5 minutes post injection. Activity in the intrahepatic bile ducts is visible between 5 and 20 minutes post injection, the gallbladder between 10 and 40 minutes p.i. with an average time of 20 minutes p.i. Intestinal activity can be observed between 10 and 45 minutes post injection. A serial scintigram is therefore interpreted as normal when within 45 minutes p.i. gallbladder and intestinal activity are visible and when there is an indication of intra-hepatic bile ducts including the common bile duct. ( table 10-1 ).

Organ	Time of visualisation
Liver	0 - 2
Bile ducts	5 - 20
Gallbladder	10 - 40
Intestine	10 - 45

Table 10-1 Serial scintigram of normal individual: Time of visualisation in minutes after injection.

Blood pool activity and kidneys should not be visible after 5 minutes p.i. In normal circumstances a clear visualisation of the intrahepatic bile ducts may not be obtained because activity in other parts of the liver can obscure bile duct activity. Figure 10-3 shows the serial scintigram of an individual without liver disease or biliary tract disturbance.

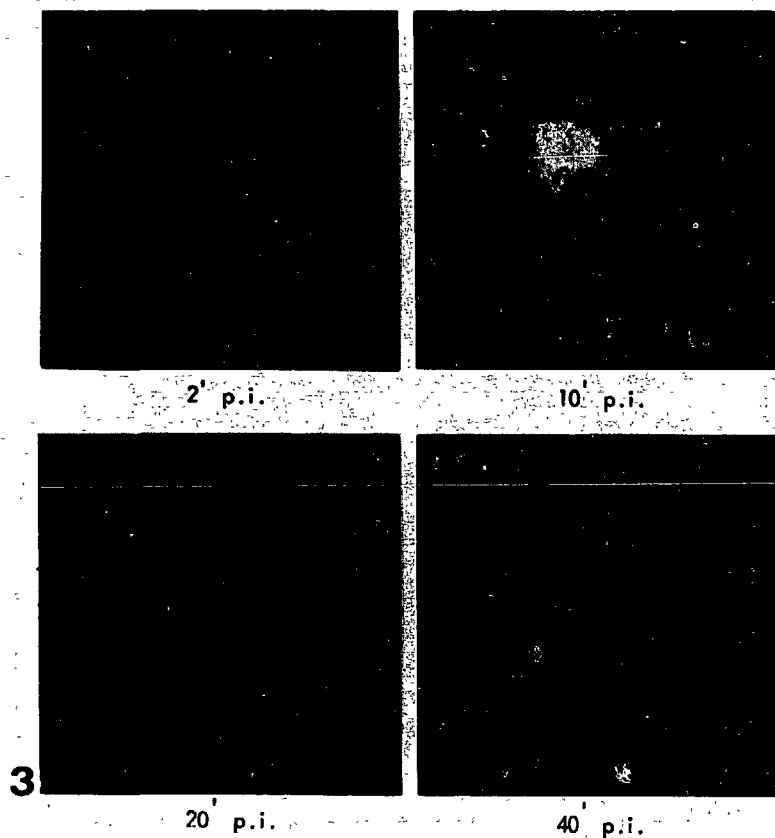


Fig. 10-3 Serial scintigram of a normal individual.

### 10.3.2. Time-activity curves and functional images in normal individuals.

From a series of twenty normal individuals the average  $T_{\max}$  for right and left liver lobes and the average  $T_{\frac{1}{2}}$  for the excretion were calculated. Table 10-2 shows the mean values for the calculated  $T_{\max}$  and  $T_{\frac{1}{2}}$  in minutes with their standard deviations.

No individuals	serial scintigram	$T_{\max}$ in minutes		$T_{\frac{1}{2}}$ in minutes	
		right lobe	left lobe	right lobe	left lobe
20	normal uptake and excretion patterns	10.4 (3.17)	13.11 (4.54)	25.0 (5.23)	27.14 (5.27)

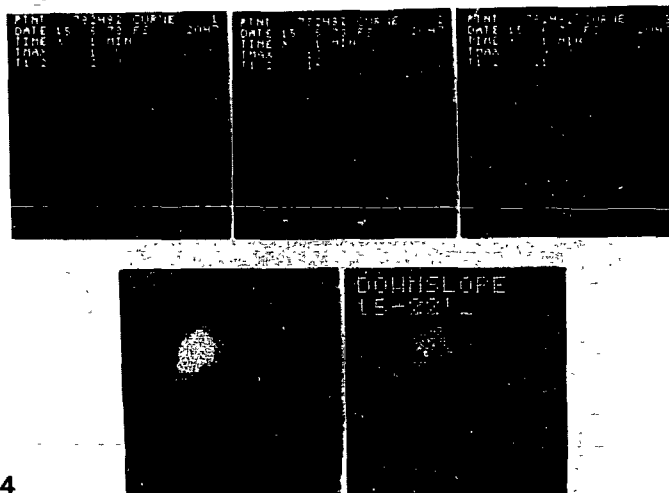
Table 10-2 Time-activity curves in normal individuals; maximum uptake time and half value time for each liver lobe with standard deviation ( between brackets ).

Figure 10-4 shows the time-activity curves obtained from the individual whose normal serial scintigram was shown in figure 10-3. Maximum uptake time for both right and left liver lobe is 10 minutes. The  $T_{\frac{1}{2}}$  for the right liver lobe is 15 minutes and for the left liver lobe 20 minutes.

Functional images for upslope and downslope of right and left liver lobe were also evaluated. A homogenous distribution of the brightness of the pixels is interpreted as normal.

In all the normal individuals the functional images were interpreted as normal.

Figure 10-4 shows the functional images, respectively upslope and downslope of the individual with normal serial scintigram and time-activity curves.



4

Fig. 10-4 Time-activity curves and functional images of the individual whose serial scintigram is shown in fig. 10-3.

## CHAPTER XI.

### CHOLESCINTIGRAPHY IN PATIENTS WITH LIVER AND/OR BILIARY TRACT DISEASE.

#### *11.1. Introduction.*

In a retrospective investigation the results of 160 examinations in 151 patients with different pathology were studied.

Ninety-nine patients were jaundiced, meaning that in each patient total serum bilirubin level was above 17  $\mu\text{mol/l}$ .

Fifty-two patients were not jaundiced but suffered from various kinds of liver or biliary tract disorders. These disorders were reflected in disturbed biochemical blood patterns.

#### *11.2. Serum bilirubin level and serial scintigram.*

In this study the elevation of the total serum bilirubin value and some serial scintigram parameters were evaluated in a group of 99 jaundiced patients. They were divided in nine groups of various bilirubin levels. The bilirubin values used were determined at the time of cholestiscintigraphy. In figure 11-1 for each bilirubin level the number of patients with a given type of diethyl-IDA excretion into the intestines has been shown.

Three types of excretion are distinguished:

- normal excretion signified by visibility of intestinal activity within 45 minutes post injection,
- delayed excretion when intestinal activity is visible between 45 and 24 hours post injection,
- complete obstruction when there is no intestinal activity after 24 hours post injection.

It can be seen that 44 patients ( 44.4% ) show a normal intestinal excretion, 25 patients ( 25.2% ) delayed intestinal excretion and

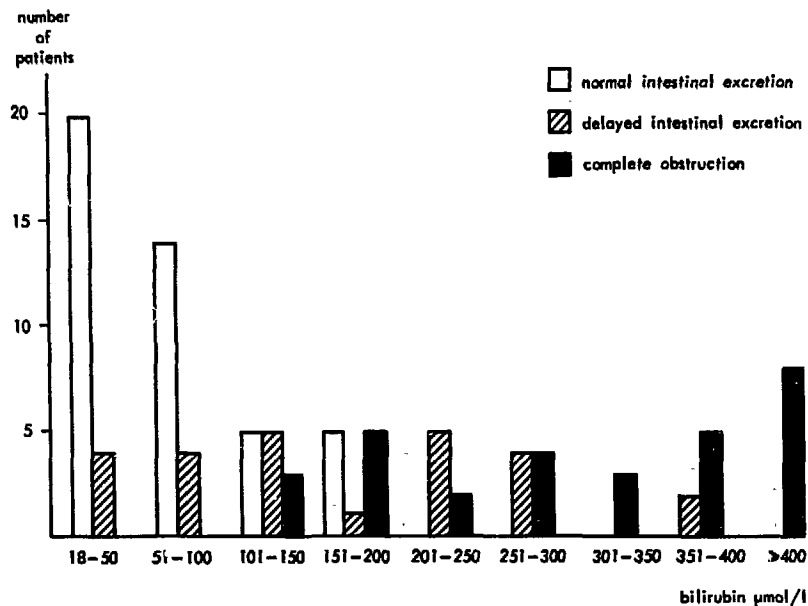


fig. 11-1 Relation between total serum bilirubin and intestinal excretion of diethyl-IDA.

30 patients ( 30.3% ) a complete obstruction. Above a bilirubin value of 200  $\mu\text{mol/l}$  only delayed excretion or complete obstruction is observed. These findings suggest that normal excretion may be observed upto levels of 200  $\mu\text{mol/l}$ . However when we make a comparative study of patients suffering from parenchymal and obstructive disease it is clear that the delayed intestinal excretion in only twelve patients ( 46.1% ) of the total studied jaundiced patients is caused by an obstructive disease and in all other cases by parenchymal or various disease ( figure 11-2, 11-3, 11-4 ). Complete obstruction was not observed in parenchymal disease. In 28 patients complete obstruction was caused by a block in liver hilus or in common bile duct; in two patients it was caused by diffuse metastases in liver.



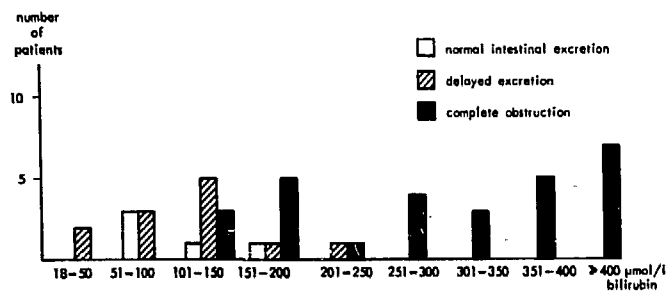


fig. 11-2

Relation between the total serum bilirubin level and the intestinal excretion of  $^{99\text{m}}$ Tc-diethyl-IDA in patients with obstructive disorder of the bile ducts.

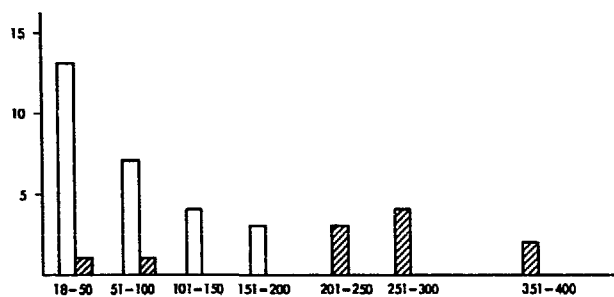


fig. 11-3

Relation between the total serum bilirubin level and the intestinal excretion of  $^{99\text{m}}$ Tc-diethyl-IDA in patients with liver parenchyma disturbance.

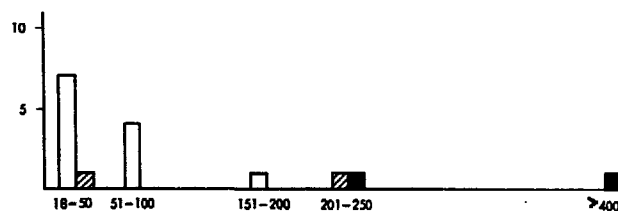


fig. 11-4

Relation between the total serum bilirubin level and the intestinal excretion of  $^{99\text{m}}$ Tc-diethyl-IDA in patients with various diseases.

The rate of clearance of the radiopharmaceutical from the blood by the hepatocytes is a measure of liver function. In the serial scintigram this is represented by the degree of persistence of blood pool activity. In individuals with normal liver function blood pool activity disappeared within 5 minutes of injection. With the rise of total bilirubin in blood, the percentage of patients with persistent blood-background activity increases. Above bilirubin values of 200  $\mu\text{mol/l}$  all patients with parenchymal and obstructive disease show persistent blood-background activity.

In figure 11-5 this relation is reproduced.

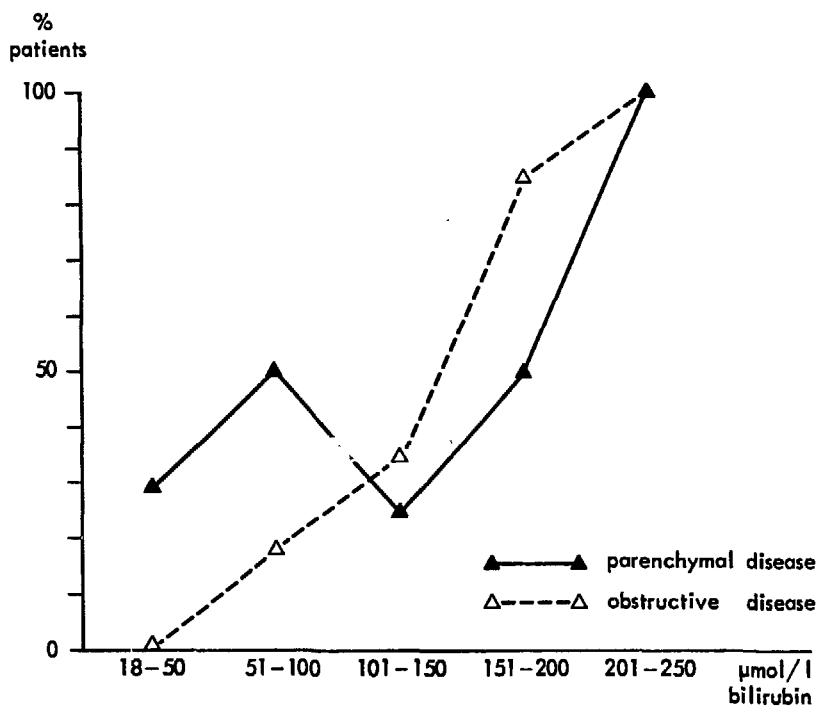


fig. 11-5 The relation between bilirubin value and persistence of blood-pool activity.

In figure 11-6 the relation of bilirubin level to visibility of the bile ducts, including the common bile duct is shown. The bile ducts were neither in parenchymal nor in obstructive disease visible at bilirubin levels above 150  $\mu\text{mol/l}$ . However non-visibility of bile ducts does not imply obstruction and detectable intestinal activity is possible up to levels of 350-400  $\mu\text{mol/l}$ .

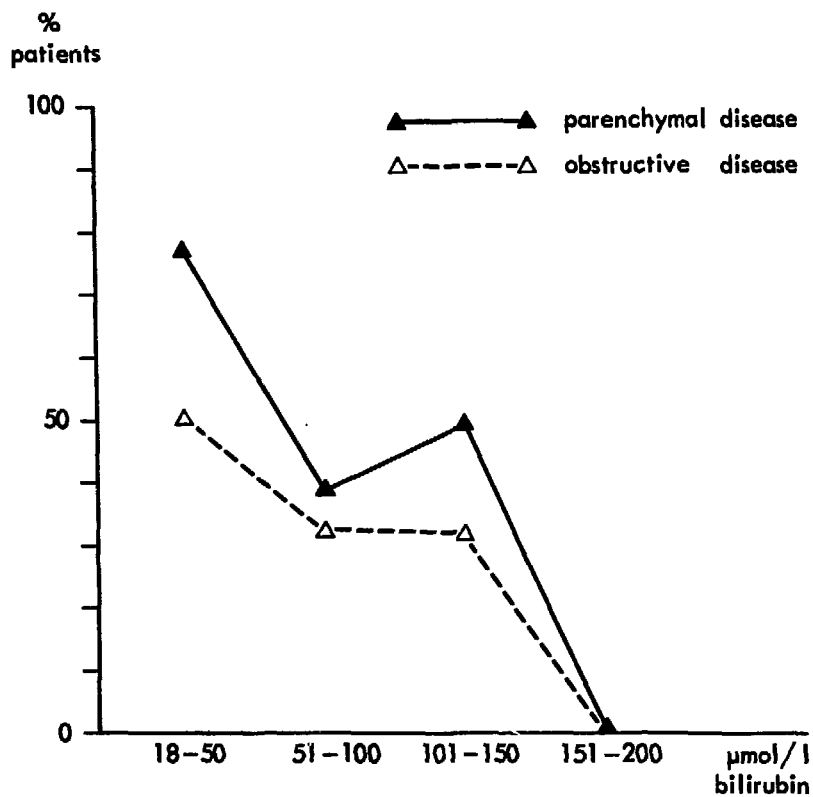


fig. 11-6 Relation between bilirubin value and visibility of bile ducts.

#### 11.2.1. Discussion.

With increasing total bilirubin in serum fewer parameters of the serial scintigram can be used to interpret the results for clinical investigation. The non-visibility of the bile ducts above bilirubin levels of 150  $\mu\text{mol/l}$  is probably due to the fact that the amount of radiopharmaceutical excreted in the bile ducts under these circumstances is decreased to such a level that the radioactivity cannot surpass the activity in the surrounding liver tissue. The observation of persistent blood-pool activity suggests that in parenchymal disease the hepatocytes are less able to clear the blood from the radiopharmaceutical as blood bilirubin levels increase. Combined with the fact that none of the patients with parenchymal disease showed complete obstruction, it is supposed that in parenchymal disease the reagent can always be excreted to some extent. In our series delayed excretion of diethyl-IDA seems possible until levels of 350-400  $\mu\text{mol/l}$  bilirubin are reached. Therefore the most important disturbance in parenchymal disease is observed in the uptake phase of the reagent by the hepatocytes.

In parenchymal disease without bile duct obstruction, delayed excretion patterns suggesting partial obstruction on the serial scintigram are possible. These delayed excretion patterns also form the bottle neck in the differentiation between parenchymal and obstructive disease in the serial scintigram.

All cases with complete obstruction patterns on the serial scintigram were associated with genuinely obstructed patients. Together with the finding that blood-pool activity persists in obstructed patients with bilirubin values above 200  $\mu\text{mol/l}$  it supports the idea that in obstructed disease with blood bilirubin values above 250  $\mu\text{mol/l}$  no reagent can enter the bile ducts.

In agreement with the bilirubin pathway in obstructive disease it is possible that the radiopharmaceutical will be taken up by the hepatocytes but re-enters the blood from the hepatocytes because of raised pressure in the bile ducts.

CHAPTER XII.  
CHOLESCINTIGRAPHY IN JAUNDICED PATIENTS WITH LIVER AND/OR  
BILIARY TRACT DISEASE.

*12.1. Introduction.*

In this study the results in 99 jaundiced patients are discussed.  
The classification of the patients is presented in table 12-1.

No. patients	Group of diseases
45	obstructive diseases
38	parenchymal diseases
16	various other diseases

Table 12-1 Classification of jaundiced patients.

*12.2. Cholescintigraphy in obstructive disease.*

In this study 45 patients with obstructive disease of the biliary tract were observed. They could be differentiated in 22 patients with obstruction from a tumour in the head of the pancreas, 7 patients with an obstructing tumour in liverhilus and 16 patients with an obstruction in the common bile duct due to stones and/or inflammation.

All diagnoses were confirmed by operation or post mortem investigation.

In table 12-2 the findings on the serial scintigram are shown.

Diagnosis	Number of patients	Visualisation of			
		liver	gallbladder	bile ducts	intestine
pancreas head tumour	22	10	0	0	2
liver hilus tumour	7	4	0	0	2
stones in common bile duct	7	6	0	4	6
cholangitis	2	2	0	0	2
stones in common bile duct and gallbladder	7	7	0	4	5

Table 12-2 Frequency of organ visualisation in 45 obstructive patients.

#### 12.2.1. Results in patients with pancreas head tumour.

Twenty-two patients with a proven tumour in pancreas head were investigated in this study. All showed progressive jaundice, raised alkaline phosphatase and slight to moderate elevation of serum transaminases. The distribution patterns of these biochemical parameters are reproduced in figure 12-1.

Cholescintigraphy using serial scintigrams showed complete obstruction in 20 patients ( 91.3% ). In two patients there was delayed intestinal excretion, due to partial obstruction. These two patients had relatively low bilirubin values: 103 and 114  $\mu\text{mol/l}$  whilst the alkaline phosphatase activity was 1500 and 177  $\text{mU/ml}$  respectively.

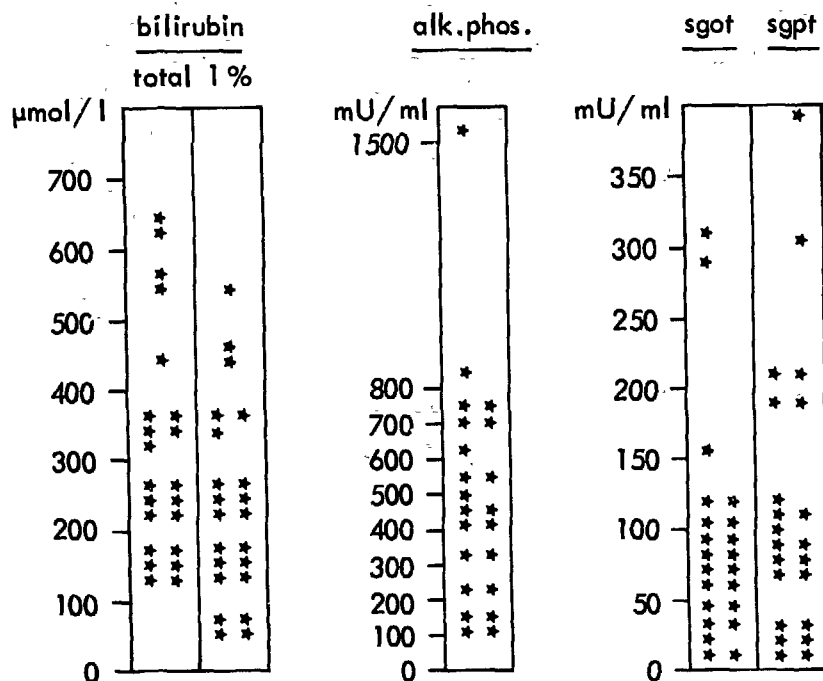


fig. 12-1 Range of biochemical blood parameters in 22 patients with pancreas head tumour.

The serial scintigrams of patients with complete obstruction showed two types of pattern. In 10 patients there was a moderate persistence of blood-pool activity and a relative good visualisation of the liver. Neither bile duct nor intestinal activity could be observed 24 hours post injection. In the other 10 patients with complete obstruction there was a poor visualisation of the liver associated with persistent high blood-pool activity. In some cases the liver could hardly be distinguished from blood pool.



In 16 patients of the twenty patients with complete obstruction, excretion of the reagent by the kidneys was observed. There was no correlation between bilirubin values and the observed scintigraphic patterns in these patients. In the first mentioned type of serial scintigrams bilirubin ranges varying from 110 to 360  $\mu\text{mol/l}$ ; in the latter the range varied from 198-624  $\mu\text{mol/l}$ .

Time-activity curves and functional images were generated from the data stored in the computer. As routine the one minute frames during the first 8 to 10 minutes of the study were compressed to produce a cumulative image. In this way a clearer image of both the liver and intrahepatic structures was obtained. In this series it was only possible to generate the curves and functional images from 8 patients in whom a relative good visualisation of the liver on the serial scintigram was obtained.

In all other cases the uptake of the radiopharmaceutical in the liver was so poor that only curves and functional images of blood pool were obtained. In table 12-3 the values for maximum uptake time (  $T_{\text{max}}$  ) and half value time for excretion (  $T_{\frac{1}{2}}$  ) are shown in comparison with the functional images, bilirubin values and serial scintigrams.

The maximum uptakes times for right and left liver lobes are prolonged whilst the half value time for the excretion phase was not calculated because it exceeded the total time of the examination.

The excretion phase shows three characteristic curves:

1. half value time is prolonged ( L ),
2. the curve develops into a plateau after a maximum uptake value is reached ( P ),
3. there is a continuously ascending curve during the whole period of the study ( AC ).

The two patients whose curves show a plateau for both liver lobes were confirmed as patients with complete obstruction due to a pancreas head tumour with liver metastases. The patient with continuously ascending curve proved to have a complete obstruction due to a pancreas head tumour. Both patients with a prolonged half value time for both liver lobes, showed complete obstruction in the serial scintigram, however in one of these patients this could not be confirmed by surgery.

The functional images in all the 8 patients show a normal upslope, demonstrating that the hepatocyte uptake of the radio-pharmaceutical is normal although uptake was somewhat delayed in some cases, as can be seen on the time-activity curves. In six patients the downslope was considered to be abnormal demonstrating that the hepatocyte is able to excrete although the excretion phase is disturbed.

Total bilirubin umol/l	Intestinal excretion serial scintigram	T-max		T-½		Upslope		Downslope	
		right	left	right	left	right	left	right	left
198	C	10	19	L	L	N	N	A	A
110	C	20	30	L	P	N	N	A	A
103	D	10	14	L	P	N	N	A	A
114	D	30	26	P	L	N	N	A	A
372	C	17	23	P	P	N	N	BPA	BPA
200	C	10	14	L	L	N	N	A	A
280	C	14	21	P	P	N	N	A	A
173	C	AC	AC	AC	AC	N	N	BPA	BPA

Table 12-3 Maximum uptake time and half value time of the time-activity curves of 8 patients with pancreas head tumour in comparison with functional imaging, bilirubin values and intestinal excretion on serial scintigram.

C=complete obstruction, D=delayed excretion, L=lengthened, P=plateau, AC=ascending curve, N=normal, A=abnormal, BPA=blood pool activity, T-max and T-½ are in minutes.

Right=right liver lobe. Left=left liver lobe.

In the investigation of the patients with a finally confirmed extrahepatic obstruction due to pancreas head tumour the following examinations were initially performed to determine whether the jaundice had an extrahepatic or an intrahepatic cause. See table 12-4.

Diagnostic investigation	no. patients	visualisation of liver and/or bile duct.	
		success	failure
abdominal plain film	9	-	-
oral cholecystography	1	0	1
arteriography	1	1	0
percutaneous trans-hepatic cholangiography	10	9	1
ultra sound study	12	12	0
colloid liver scintigraphy	11	11	0

Table 12-4 Clinical investigation in 22 patients with bile duct obstruction by tumour in pancreas head.  
Frequency of visualisation of liver and/or bile ducts.

In 3 patients abdominal plain film showed calcifications in the right upper abdomen; in none of these patients stones were found in gallbladder or bile ducts. In the other 6 patients no further information could be obtained with this examination.

The oral cholecystography was performed in a patient with a total bilirubin of 200  $\mu\text{mol/l}$ . Arteriography of coeliac trunk and superior mesenteric artery did not demonstrate pathology.

In 3 patients the colloid scintigram of the liver indicated the presence of space occupying lesion, which was confirmed in all cases by surgery, 1 patient showed a normal liver scintigram, 1 patient diminished activity in liver hilus and 6 patients an atypical diffuse inhomogeneous distribution of radio-activity in the liver.

The success rate in diagnosing extrahepatic obstruction of percutaneous transhepatic cholangiography ( P.T.C. ) and ultra sound study is given in table 12-5 and compared with the results of cholescintigraphy.

	no. patients	dilated bile ducts	dilated gallbladder	intestinal excretion	correct diagnosis
percutaneous transhepatic cholangiography	9	8	3	1	8
ultra sound study	12	9	6		9
cholescintigraphy	22			2	22

Table 12-5 Frequency of visualisation of obstruction patterns in P.T.C. ultra sound and cholescintigraphy.

Criteria for the diagnosis extrahepatic obstruction are the dilated bile ducts on the image obtained by P.T.C. and ultra sound and for cholescintigraphy the delay or absence of excretion on the serial scintigram, eventually combined with typical patterns obtained from the computer.

One patient showed a slight flow of contrast to the duodenum in the P.T.C. study though the serial scintigram showed a complete obstruction. Time-activity curves from this patient show a normal uptake and delayed excretion of the radio-pharmaceutical by the liver; the functional images show a normal upslope and slightly disturbed downslope. With regard to these findings there is also an agreement with the findings on the P.T.C. and the condition observed at operation.

The delayed excretion on the serial scintigrams in two patients was interpreted as due to partial obstruction, because the time-activity curves showed a plateau after the maximum uptake time was reached in at least one of the liver lobes.

P.T.C. was performed in one of these patients; no contrast flow into duodenum was seen. Similary the findings of the ultra sound did not agree with the findings by operation.

It should be mentioned that only in three patients the ultra sound study was suspect for the pathology of the pancreas; in three patients there was a suspicion of stones in the gallbladder, though in none of these patients gallbladder stones were found. In one patient with multiple stones in the gallbladder, no stones were found with ultra sound.

#### *12.2.1.1. Discussion.*

The results of this study revealed the following patterns of cholescintigraphy in patients with an obstructive jaundice due to pancreas head tumour.

##### **Serial scintigraphy:**

- abnormal intestinal excretion was always observed.
- delayed intestinal excretion was observed in 8.7% of the patients studied.
- complete obstruction was observed in 91.3% of the patients studied.

##### **Patients with a complete obstruction showed:**

- good liver visualisation with persistence of a slight blood pool activity in 50% of the cases studied.
- poor liver visualisation with persistence of a high level of blood pool activity in the other 50%.

##### **Patients with delayed intestinal excretion all showed:**

- good liver visualisation with a slight persistence of blood pool activity.

Computer data:

No additional information could be obtained with the computer  
in 54% of the patients studied.

Time-activity curves obtained from the patients with a complete obstruction showed the following patterns:

- normal T-max for both liver lobes in 17% of the patients studied.
- delayed T-max for both liver lobes in 66%.
- a lengthened T- $\frac{1}{2}$  for both liver lobes was observed in 33% of the patients studied.
- in both liver lobes the curve showed a plateau after T-max had been reached in 33% of the patients studied while in a further 17% only the left lobe was so affected.
- continuously ascending curve for both liver lobes in 17% of the patients studied.

Time-activity curves for the patients with a delayed excretion showed the following patterns:

- normal T-max for both liver lobes in 50%.
- delayed T-max for both liver lobes in 50%.
- the time-activity curve showed a plateau in 50% for the right lobe and in 50% for the left lobe.

Functional images obtained from all patients studied showed the following patterns:

- upslope images revealed a normal uptake phase in 100% of the patients studied.
- downslope images revealed a disturbed phase in 100% of the patients studied.

Clinical reliability:

Extrahepatic obstruction could be surmised if there was a complete obstruction on the serial scintigram.

In this series of patients extrahepatic obstruction was indicated on the serial scintigram in 91.3% of the cases.

Extrahepatic obstruction was indicated by the computer data when the time-activity curves of one or both liver lobes either developed a plateau after the maximum uptake was reached or showed a continuous increase during the whole study.

When serial scintigram patterns were combined with the results of the computer analysis the overall success rate for cholescintigraphy in diagnosing extrahepatic obstruction in these patients was 100%.

In this group percutaneous transhepatic cholangiography showed a success rate of 88% in diagnosing extrahepatic obstruction, whilst the success rate for ultra sound study was 75%.

#### 12.2.1.2. CASE HISTORIES



Case history no. 1

A 75-years-old male was admitted because of persistent pain in the right upper abdomen of more than six weeks duration and associated with persistent jaundice. On physical examination a slightly jaundiced man with an enlarged liver was presented.

Laboratory findings:	Total bilirubin 110 $\mu\text{mol/l}$ , direct reacting bilirubin 83 $\mu\text{mol/l}$ , alkaline phosphatase 410 $\text{mU/ml}$ , S.G.O.T. 320 $\text{mU/ml}$ , S.G.P.T. 700 $\text{mU/ml}$ .
Colloid liver scintigraphy:	Diminished activity in liver hilus.
Ultra sound:	Enlarged bile ducts in liver hilus.
Percutaneous transhepatic cholangiography:	Distended common bile duct, no entrance of contrast in duodenum.
Cholescintigraphy	
serial scintigraphy: ( figure 12-2 )	Good visualisation of the liver, no visible bile ducts or gall-bladder. No intestinal activity 24 hours post injection.
cumulative picture: ( figure 12-3 )	"Cold" area in liver hilus.
time-activity curves: ( figure 12-4 )	Maximum uptake time for both right and left lobes is delayed. The curve from right liver lobe shows a very prolonged excretion, the curve from left liver lobe shows a plateau.
functional images: ( figure 12-5 )	Upslope shows no aberration, the downslope functional image is diffusely disturbed.
conclusion:	Suspected bile duct obstruction.

Operative findings: Distended common bile duct; peroperative cholangiography showed no passage of contrast material into duodenum. Stenosis of common bile duct by adenocarcinoma of the head of the pancreas.

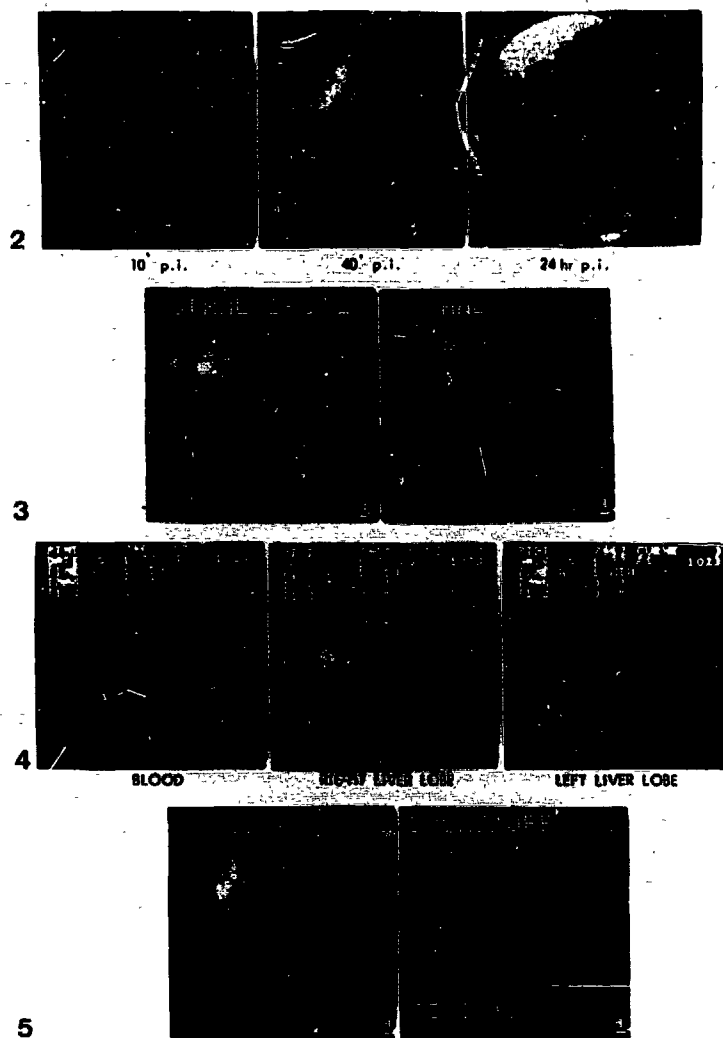


Fig.12: 2-5 Cholescintigraphy in a patient with bile duct obstruction due to pancreas head tumour.

Case history no. 2.

A 77-year-old female with known carcinoma of the uterus was admitted because of progressive jaundice.

Laboratory findings: Total bilirubin 211  $\mu\text{mol/l}$ , direct reacting bilirubin 157  $\mu\text{mol/l}$ , alkaline phosphatase 153  $\text{mU/ml}$ , S.G.O.T. 33  $\text{mU/ml}$ , S.G.P.T. 26  $\text{mU/ml}$ .

Colloid liver scintigraphy: Inhomogeneous distribution of activity, no suspicion of liver metastases.

Ultra sound: Distended gallbladder.

Cholescintigraphy

serial scintigraphy:  
( figure 12-6 ) Poor visualisation of the liver, persistent blood pool activity and excretion of the radio-pharmaceutical by the kidneys. 24 hours p.i. only visualisation of the kidneys, no intestinal activity.

time-activity curves:  
( figure 12-7 ) No uptake or excretion; curves similar to blood curve.

functional images:  
( figure 12-8 ) The upslope image represents only the accumulation in the kidneys; neither upslope, nor downslope provide information about the liver.

conclusion: Suspected bile duct obstruction.

Surgery: Enormously distended gallbladder, no metastases in liver.

Liver biopsy: Extrahepatic cholestasis.

Peroperative cholangiography: No flow down into the duodenum.

Operative conclusion:

Stenosis distal in duodenum  
caused by pancreas head tumour.

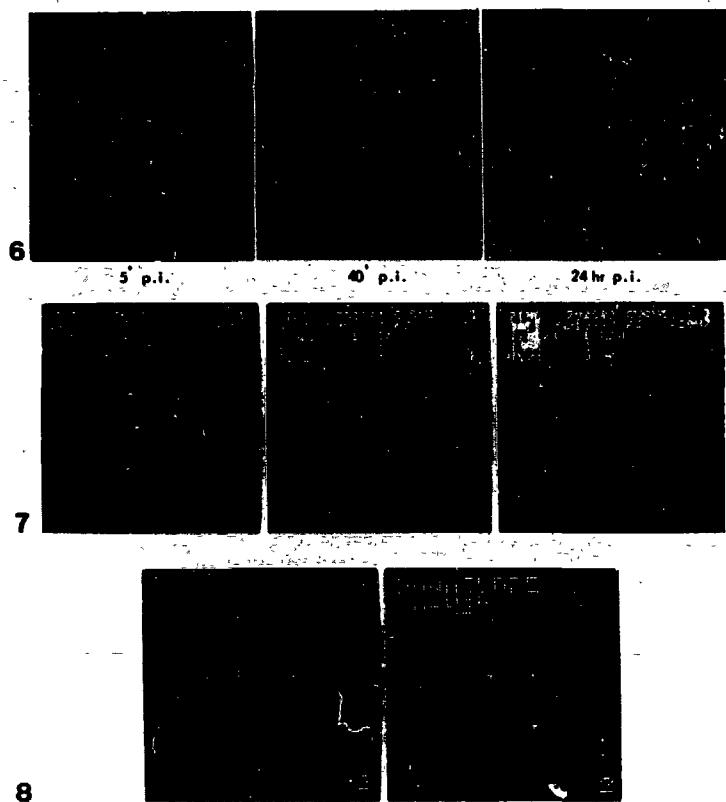


Fig. 12:6-8 Cholescintigraphy in a patient with bile duct obstruction due to pancreas head tumour.

### 12.2.2. Results in patients with tumour in liver hilus.

Seven patients with progressive jaundice due to an obstruction of the bile ducts in liver hilus were investigated. The biochemical blood parameters are shown in figure 12-9.

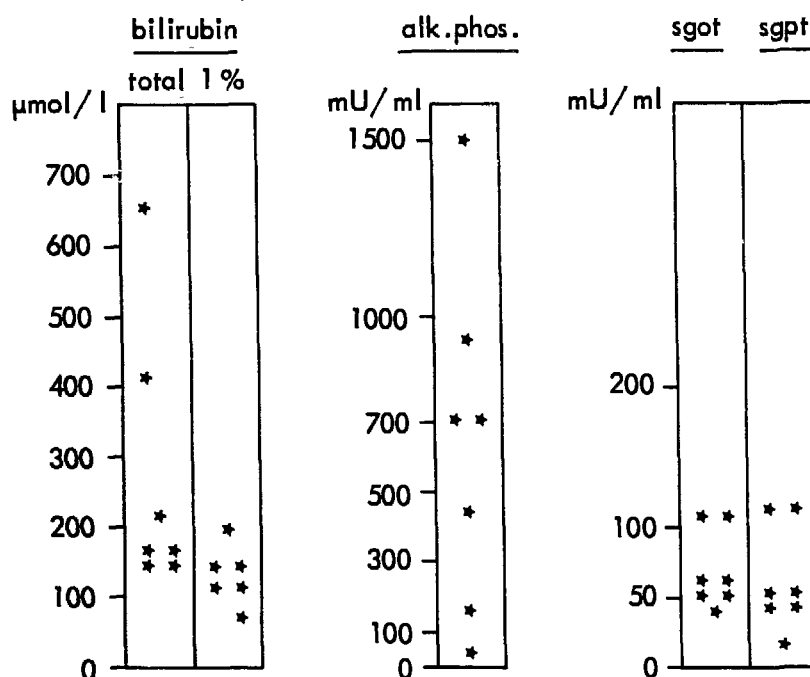


fig. 12-9 Range of biochemical blood parameters in 7 patients with obstruction of bile ducts in liver hilus.

The cholescintigraphic investigation showed in 5 patients ( 71% ) a complete obstruction on the serial scintigram and in 2 patients ( 29% ) a delayed intestinal excretion due to partial obstruction of the bile ducts. In these latter patients the bilirubin values were 170  $\mu\text{mol/l}$  and 210  $\mu\text{mol/l}$ , and the alkaline phosphatase values were respectively 928  $\text{mU/ml}$  and 55  $\text{mU/ml}$ . As in the case of patients with a pancreas head tumour the patterns of the serial scintigrams in the completely

obstructed patients are similar and are distinguished in "good" liver visualisation and "bad" liver visualisation. Also no relation between the type of pattern observed and bilirubin value was seen. In all of these patients cumulative images, time-activity curves and functional images were generated from the computer data. The cumulative images more clearly demonstrated a pathological process in liver hilus in 4 patients where this was suspected from the images of the serial scintigram. In table 12-6 the values for maximum uptake time and half value time for the excretory phase are shown, in comparison with the functional images, bilirubin values and intestinal excretion.

Total bilirubin umol/l	Intestinal excretion	T-max		T- $\frac{1}{2}$		Upslope		Downslope	
		right	left	right	left	right	left	right	left
400	C	BPA		BPA		BPA		BPA	
173	C	20	18	L	L	N	N	A	A
150	C	18	30	P	P	N	N	A	A
655	C	BPA		BPA		BPA		BPA	
170	D	16	16	L	L	N	N	A	A
150	C	BPA		BPA		BPA		BPA	
210	D	18	19	L	P	N	N	A	A

Table 12-6 Maximum uptake time and half value time of the time-activity curves of 7 patients with bile duct obstruction in liver hilus in comparison with functional images, bilirubin values and excretion on serial scintigram.

C=complete obstruction, D=delayed excretion, L=lengthened, P=plateau, BPA=blood pool activity, N=normal, A=abnormal.

In three patients the time-activity curves and functional images could not be generated because no uptake of the radiopharmaceutical by the liver was observed. In two patients there were diffuse metastases in the liver; in one patient there was a massive space occupying lesion in the left liver lobe originating from the hilus of a much congested liver.

In one patient, showing a delayed excretion, there was an almost normal maximum uptake time and prolonged half value time. In the three other patients the maximum uptake time was slightly delayed. Of these three patients, two showed lengthened half value time for the excretion phase instead of a plateau, though complete obstruction was proven.

Table 12-7 shows the other clinical investigations in these patients compared with the frequency of visualisation of liver and/or bile ducts.

Diagnostic investigation	no.patients	visualisation of liver and/or bile ducts	
		success	failure
abdominal plain film	2	-	-
oral cholecystography	1	0	1
intravenous cholangiography	2	0	2
percutaneous trans-hepatic cholangiography	3	3	0
ultra sound study	4	4	0
colloid liver scintigraphy	5	5	0

Table 12-7 Clinical investigation in 7 patients with bile duct obstruction by tumour in liver hilus.  
Frequency of visualisation of liver and/or bile ducts.

One patient who underwent a P.T.C. developed complications due to bile leakage and peritonitis. The patients in whom oral and intravenous cholangiography failed, had bilirubin values of 150-173  $\mu\text{mol/l}$ .

In table 12-8 the frequency of occurrence of obstruction patterns as dilated bile ducts and/or stenosis in liver hilus and the success rate of diagnosing extrahepatic obstruction by these investigations is shown.

diagnostic investigation	no. patients	dilated bile ducts	stenosis liver hilus	intestinal excretion	correct diagnosis
percutaneous transhepatic cholangiography	3	2	3		3
ultra sound study	4	2			2
cholescintigraphy	7			2	7

Table 12-8 Frequency of visualisation of obstruction patterns and success rate in diagnosing extrahepatic obstruction in P.T.C., ultra sound and cholescintigraphy.

The findings on the serial scintigram in regard to intestinal excretion could not be confirmed in these patients by other investigations. All operated patients showed an obstructing, malignant tumour in the liver hilus; in none of these patients however an attempt was made to check whether the obstruction was total or sub-total. In the two patients with delayed excretion no confirmation of partial bile duct obstruction could be obtained from P.T.C.

A correct diagnosis for P.T.C. was recorded if this investigation was able to show dilated intrahepatic bile ducts and the site of obstruction. Ultra sound showed dilated bile ducts in only two patients but gave no information as to the site and extension of the obstruction.



Liver scintigraphy was performed in 5 patients; in three patients there was a suspicion of a process in the liver hilus. A correct diagnosis for cholescintigraphy was recorded if this investigation was able to show extrahepatic obstruction. In 5 patients extrahepatic obstruction was suspected because a complete obstruction on the serial scintigram could be seen. In one patient extrahepatic obstruction was suspected because of delayed excretion on the serial scintigram and a time-activity curve from the left liver lobe which showed a plateau for the excreting phase. In the other patient with delayed intestinal excretion and lengthened half value time of the time-activity curves from both liver lobes, which signs could be also suspect for a diffuse liver parenchyma disturbance, the serial scintigram and cumulative images showed a persistent cold area in liver hilus ( see case history no.3 ). This finding was therefore suspect for an obstructing proces in liver hilus.

#### 12.2.2.1. Discussion.

The results of the study in patients with obstructive jaundice due to a malignant tumour in liver hilus showed the following patterns of cholescintigraphy.

##### Serial scintigram:

- no cases with normal intestinal excretion patterns were observed.
- delayed excretion was observed in 29% of the patients studied.
- suspicion of a pathological process in liver hilus was observed in 67%.

##### Patients with a complete obstruction showed:

- good liver visualisation with persistence of a slight blood pool activity in 40% of the cases.
- poor liver visualisation with persistence of a high blood pool acitivity in 60%.

Patients with delayed intestinal excretion all showed:

- a good liver visualisation with persistence of a slight blood pool activity.

Computer data:

No additional information from the computer analysis was obtained in 43% of the patients studied.

Time-activity curves obtained from patients with a complete obstruction showed the following patterns:

- delayed T-max for both liver lobes in all cases.
- lengthened T- $\frac{1}{2}$  for both liver lobes in 50%.
- a plateau following the T-max for both liver lobes in 50%.

Time-activity curves obtained from the patients with a delayed intestinal excretion showed the following patterns:

- normal T-max for both liver lobes in one of the patients.
- delayed T-max for both liver lobes in the other patient.
- lengthened T- $\frac{1}{2}$  for both liver lobes in one patient.
- the curve revealed a plateau for the left liver lobe in the other patient.

Functional images obtained from all the patients studied showed the following patterns:

- upslope image revealed a normal uptake phase in 100% of the patients studied.
- downslope image revealed a disturbed excretion phase in 100% of the patients studied.

Clinical reliability:

Extrahepatic obstruction could be diagnosed on the serial scintigram when there was a complete obstruction. In this series of patients extrahepatic obstruction could be diagnosed on the basis of the serial scintigram alone in 71%. The possibility of extrahepatic obstruction was also present if a persistent cold

area in the liver hilus could be observed on the serial scintigram without complete obstruction being present. In relation to this latter pattern when combined with the results where complete obstruction was observed on the serial scintigram extrahepatic obstruction was diagnosed in 86% of the cases studied.

The computer results indicated extrahepatic obstruction when there was a clear cold area in the liver hilus on the cumulative image, when time-activity curves showed a plateau after reaching maximum uptake time for one or both liver lobes or when the curve continued ascending during the whole study.

When serial scintigram patterns were combined with computer data the overall success rate for cholescintigraphy in diagnosing extrahepatic obstruction in patients with obstructive jaundice due to a liver hilus tumour was 100%.

The success rate in this study for percutaneous transhepatic cholangiography was 100% and for ultra sound study 50% in diagnosing extrahepatic obstruction.

#### 12.2.2.2. CASE HISTORY

Case history no. 3.

A 63-years-old female was admitted with progressive jaundice without abdominal pain. Physical examination showed an enlarged liver.

Laboratory findings:	Total bilirubin 170 $\mu\text{mol/l}$ , direct reacting bilirubin 88.2 $\mu\text{mol/l}$ , alkaline phosphatase 928 $\text{mU/ml}$ , S.G.O.T. 57 $\text{mU/ml}$ , S.G.P.T. 54 $\text{mU/ml}$ .
Colloid liver scintigraphy:	Enlarged left liver lobe, pathology right liver lobe, accumulation of colloid in bone marrow.
Mini-laparotomy:	Normal common bile duct, normal gallbladder.
Liver biopsy:	Suspect for biliary congestion; liver fibrosis.
Cholescintigraphy serial scintigraphy: ( see figure 12-10 )	Enlarged liver, diminished activity in the liver hilus, delayed intestinal excretion.
cumulative images: ( see figure 12-10 <sup>1</sup> )	Suspicion of space occupying process in liver hilus.
time-activity curves: ( see figure 12-11 )	Normal clearance from blood, normal uptake in right and left liver lobe, very delayed excretion.
functional images: ( see figure 12-12 )	Disturbed uptake liver hilus, disturbed excretion liver hilus and right liver lobe.
conclusion:	Suspected bile duct obstruction by tumour in liver hilus.

Surgery:

Malignant obstructive process in  
liver hilus, originating from  
right liver lobe.

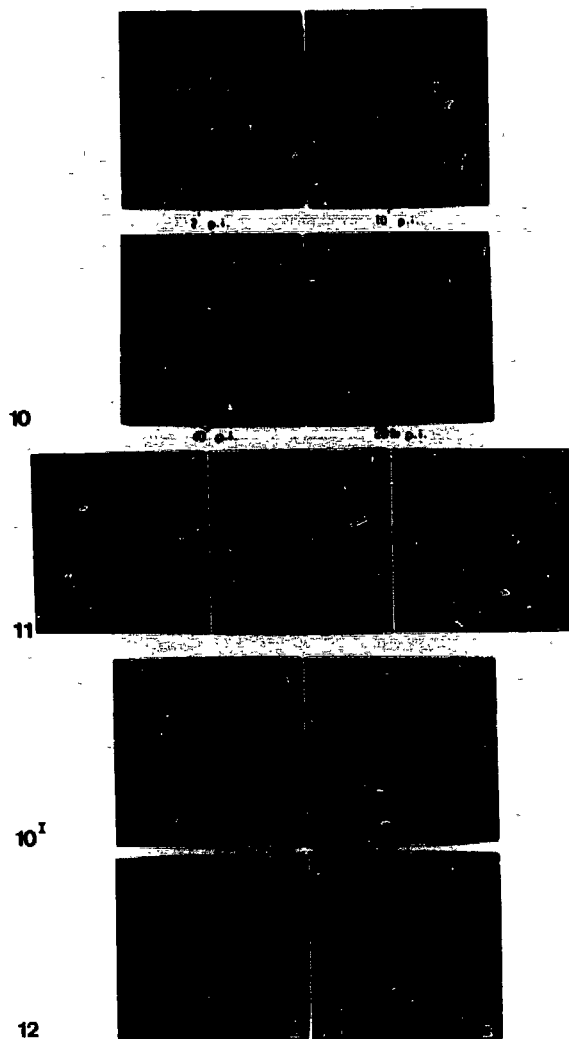


Fig. 12:10-12 Cholescintigraphy in a patient with a malignant obstructive process in liver hilus.

*12.2.3. Results in patients with non-malignant obstruction of the common bile duct.*

Sixteen jaundiced patients with a non-malignant obstruction of the common bile duct were investigated. The classification of these patients according to the diagnosis is shown in table 12-9.

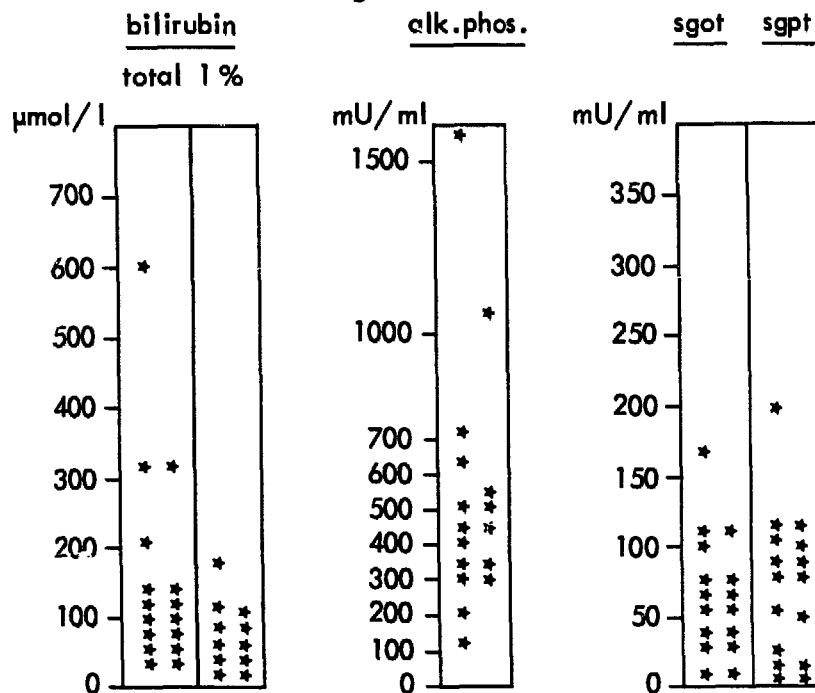
No. patients	disease
10	stones
3	stones and stricture of duodenal papilla
1	stones and biliary cirrhosis of the liver
1	stones and active cholangitis
1	active cholangitis and perforation of the gallbladder

Table 12-9 Classification of patients with non-malignant obstruction of the common bile duct.

Of the patients with common bile duct stones in six cases gallbladder stones were also found at operation; two patients had a cholecystectomy at an earlier date. The diagnosis of the patient with the perforation of the gallbladder was obtained during operation; stricture of the duodenal papilla was also found during operation and in one patient it had been previously demonstrated by endoscopic cholangiography.

The biochemical blood parameters of these patients are shown in figure 12-13. The range of alkaline phosphatase and transaminases is much the same as in common bile duct obstruction from pancreas head tumour, although total bilirubin values are significantly lower.

fig. 12-13 Range of biochemical blood parameters in 16 patients  
with a non-malignant obstruction of the common bile duct.



The serial scintigram showed normal excretion patterns in 5 patients, a delayed excretion in 8 patients and a complete obstruction in 3 patients. From these latter patients, two showed a stricture in the duodenal papilla with an impacted stone; the third patient was a thirteen-year-old girl with multiple stones in the biliary system and a biliary cirrhosis. Liver visualisation in completely obstructed patients was good in one case ( total bilirubin 325  $\mu\text{mol/l}$  ) and very poor in the other two ( total bilirubin respectively 306 and 600  $\mu\text{mol/l}$  ). Two patients with a clinically active cholangitis showed a delayed excretion. No significant differences were observed in the remaining patients, neither in the clinical symptoms nor at operation, which explained the delayed or normal intestinal excretion.



No visualisation of the gallbladder occurred in the patients with stones in the gallbladder. In 4 patients dilated bile ducts were observed on the serial images.

Time-activity curves and functional images could be generated from 14 patients. In two patients with complete obstruction only blood pool activity could be seen. In table 12-10 the computer data are shown in comparison with bilirubin values and excretion patterns as observed on the serial scintigrams. It can be seen from this table that only two patients show normal T-maximum for the right liver lobe; three patients show a normal T-maximum for the left liver lobe and only one patient shows normal T-maximum for both lobes. In all other patients the uptake of the radio-pharmaceutical by the liver is delayed; in 5 patients the curve for the left liver lobe is ascending throughout the whole study. In spite of the disturbed time-activity curves for the uptake by the liver, the upslope functional image was found to be normal for both liver lobes, except in two patients.

One of these latter patients was also suffering from hyperlipaemia and liver parenchyma involvement was possible; the other patient showed no other indication of liver parenchyma disturbance.

With the exception of two patients in all patients the time-activity curves show a disturbed excretion for both right and left liver lobes: the curve show a plateau for one or both liver lobes or show a continuous ascent for one of the liver lobes. The downslope functional image was in agreement for the left liver lobe; one patient with an abnormal curve for the right liver lobe showed normal functional images.

For two patients with a normal excretion curve for the left liver lobe the downslope functional image was described as normal. From this latter patients one patient showed an enlargement of the left liver lobe, the other was known to have a slight liver

function disturbance probably due to medication with psychopharmaca.

Total bilirubin umol/l	intestinal excretion	T-max		T- $\frac{1}{2}$		Upslope		Downslope	
		right	left	right	left	right	left	right	left
46	D	18	23	P	P	N	N	A	A
23	D	26	AC	P	AC	N	A	N	A
119	D	32	AC	L	AC	N	A	A	A
70	D	30	16	L	P	N	N	A	A
306	C	BPA		BPA		BPA		BPA	
129	D	29	AC	P	AC	A	A	A	A
143	D	17	AC	L	AC	N	N	A	A
78	D	21	AC	L	AC	N	A	A	A
80	N	12	19	23	26	N	N	N	A
140	N	21	17	L	21	N	N	A	A
200	N	24	24	L	P	N	A	A	A
325	C	25	16	L	P	A	A	A	A
74	N	9	12	16	33	N	N	A	A
81	N	20	28	P	L	N	N	A	A
600	C	BPA		BPA		BPA		BPA	
100	D	28	36	L	P	A	A	A	A

Table 12-10 Maximum uptake time and half value time of the time-activity curves of 16 patients with obstruction in common bile duct in comparison with functional imaging, bilirubin values and intestinal excretion observed on serial scintigram.

C=complete obstruction, D=delayed excretion, N=normal excretion, L=lengthened, P=plateau, AC=ascending curve, N=normal, A=abnormal, BPA=blood pool activity.

In this group of patients 32 other investigations were performed. The distribution of patients according to these parameters and success rate of visualisation of liver and/or bile ducts is shown in table 12-11.

In three of these patients a liver biopsy was also carried out. One patient showed peritoneal irritation after the biopsy. In two patients the biopsy indicated extrahepatic obstruction. Oral cholecystography was performed when bilirubin values of 70 and 74 umol/l were obtained; intravenous cholangiography was

carried out in cases with bilirubin values lower than 30  $\mu\text{mol/l}$ . Abdominal plain film in 4 patients showed calcifications in the right upper abdomen, in all cases stones were confirmed. The colloid liver scintigraphy was normal in four patients, two patients showed inhomogeneous distribution of the radioactivity and one patient showed intrahepatic lesions due to ( confirmed ) liver cirrhosis.

Diagnostic investigations	no.patients	visualisation of liver and/or bile ducts	
		success	failure
abdominal plain film	11	-	-
oral cholecystography	2	0	2
intravenous cholangiography	8	8	0
ultra sound study	4	4	0
colloid liver scintigraphy	7	7	0

Table 12-11 Clinical investigation in 16 patients with non-malignant obstruction in bile duct. Frequency of visualisation of liver and/or bile ducts.

The indication for a diagnosis of extrahepatic obstruction in intravenous cholangiography is the visualisation of dilated bile ducts or stones in the common bile duct; with ultra sound study also dilated bile duct should be shown. In 8 patients I.V.C. was performed; 6 showed patterns of extrahepatic obstruction. In 5 cases common bile duct stones were suspected. In three patients without stones on the radiographic image - although a good visualisation of the common bile duct was obtained - stones were found at operation.

In only one case ultra sound was suspect for extrahepatic obstruction. In none of these patients investigated stones in common bile duct and gallbladder could be demonstrate by ultra sound. In two cases the ultra sound study was suspect for a space occupying lesion in the right liver lobe; these findings could not be confirmed.

The results of the investigations are shown in table 12-12.

diagnostic investigation	no. patients	dilated bile ducts	stones in common bile duct	intestinal excretion	correct diagnosis
intravenous cholangiography	8	6	5	-	5
ultra sound study	4	1	-		1
cholescintigraphy	16	4		14	16

Table 12-12 Frequency of obstruction patterns in intravenous cholangiography, ultra sound and cholescintigraphy; success rate in diagnosing extrahepatic obstruction.

Suspicion of extrahepatic obstruction on the cholescintigram, in the case of normal intestinal excretion, exists when bile ducts appear dilated and time-activity curves show a delayed excretion phase. In one patient none of these parameters were present and the findings by cholescintigraphy were indicative of delayed intestinal excretion due to parenchymal disease. However extrahepatic obstruction by a process in the common bile duct remained a possibility because there seemed to be an interruption in the common bile duct on the serial scintigram ( see case history no.4 ).

As can be seen from table 12-10, in all patients with delayed intestinal excretion, time-activity curves from one or both liver lobes show a plateau after maximum uptake time has been reached or the curve continued to ascend during the whole study.

#### 12.2.3.1. Discussion.

The results of the study of patients with obstructive jaundice due to a non-malignant obstruction of the common bile duct showed the following patterns of cholescintigraphy.

##### Serial scintigram:

- normal intestinal excretion was observed in 31% of the patients studied.
- delayed intestinal excretion was observed in 50%.
- complete obstruction was observed in 19%.

In patients with a normal intestinal excretion dilated bile ducts were observed in 80% and interruption in the common bile duct in 20%.

In 20% of the patients with a normal intestinal excretion a persistent slight blood pool activity was observed.

Patients with a complete obstruction showed:

- good liver visualisation with persistence of slight blood pool activity in 33% of the cases.
- poor liver visualisation with persistence of high blood pool activity was observed in 67%.

In patients with a delayed intestinal excretion no persistent blood pool activity was observed.

Computer data:

No additional information could be obtained from the computer in 13% of the cases.

Time-activity curves obtained from patients with a normal intestinal excretion showed the following patterns:

- normal T-max for both liver lobes in 20%.
- delayed T-max for both liver lobes in 20%
- normal T-max for right lobe and delayed T-max for left lobe 20%.
- delayed T-max for right lobe and normal T-max for left lobe 40%.
- normal  $T_{\frac{1}{2}}$  for both lobes in 40%.
- lengthened  $T_{\frac{1}{2}}$  right lobe and normal  $T_{\frac{1}{2}}$  for left lobe 20%.
- lengthened  $T_{\frac{1}{2}}$  for right lobe and plateau curve for left lobe 20%.
- plateau curve for right lobe and lengthened  $T_{\frac{1}{2}}$  for left lobe 20%.

Time-activity curves obtained from patients with delayed intestinal excretion showed the following patterns:

- delayed T-max for right liver lobe in 100%.
- delayed T-max for left liver lobe in 38%.
- lengthened  $T_{\frac{1}{2}}$  for right liver lobe in 62%.
- the curve showed a plateau for right liver lobe in 38%.
- the curve showed a plateau for left liver lobe in 38%.
- continuously ascending curve for left liver lobe in 62%.

Time-activity curves obtained from the patient with a complete obstruction showed the following patterns:

- delayed T-max for the right liver lobe and normal for the left liver lobe.
- lengthened  $T_{\frac{1}{2}}$  for right liver lobe while the curve showed a plateau for the left lobe.

Functional images obtained in all the patients studied revealed the following patterns:

- upslope images were normal for both liver lobes in 50% and normal for the right liver lobe alone in 29%; abnormal for both liver lobes in 21% and abnormal for the left liver lobe alone in 29%.
- downslope images were disturbed for both liver lobes in 86% and disturbed for the left liver lobe only in 14%.

Clinical reliability:

Extrahepatic obstruction could be diagnosed if there was a complete obstruction on the serial scintigram, or if there was a visualisation of dilated bile ducts, or if there was a clear interruption in the common bile duct.

On the basis of this parameters extrahepatic obstruction was diagnosed on the serial scintigram alone in 50%.

Extrahepatic obstruction could be found by the analysis of the computer data if time-activity curves for one or both of the liver lobes showed a plateau or continued ascending during the whole study.

When serial scintigraphy patterns were combined with the results of the computer data the overall success rate for cholescintigraphy in diagnosing extrahepatic obstruction in this group of patients was 100%.

Identification of dilated bile ducts on the serial scintigram is a finding that may be dependent on the experience of the investigator; the computer study is therefore necessary in these cases to diagnose extrahepatic obstruction. In this group of patients the success rate for intravenous cholangiography in diagnosing extrahepatic obstruction was 63% and for ultra sound 25%.

#### 12.2.3.2. CASE HISTORIES



Case history no. 4.

A 76-years-old female was admitted because of slight jaundice associated with pain in right upper abdomen radiating to the back and coupled with nausea and vomiting. A cholecystectomy had been performed some time before. On physical examination the patient had slight jaundice and an enlarged liver lobe palpable in the middle abdomen.

Laboratory findings: Total bilirubin 50  $\mu\text{mol/l}$ , direct reacting bilirubin 15.2  $\mu\text{mol/l}$ , alkaline phosphatase 500  $\text{mU/ml}$ , S.G.O.T. 13  $\text{mU/ml}$ , S.G.P.T. 26  $\text{mU/ml}$ .

Intravenous cholangiography: Visualised a dilated common bile duct with large aberrations in diameter. There were no distinct indications for concretions.

Cholescintigraphy

serial scintigraphy:  
( figure 12-14 )

An enlarged liver, especially the left lobe which also showed reduced uptake of activity. Distended intrahepatic bile ducts with interruption in common bile duct; normal excretion into the intestine. The gallbladder was not visualised.

time-activity curves:  
( figure 12-15 )

Normal uptake and excretion in right liver lobe, a normal uptake in left liver lobe, but a delayed excretion.

cumulative image:  
( figure 12-16 )

Dilated intrahepatic bile ducts and interruption of common bile duct.

functional images:  
( figure 12-16 )

Upslope image shows disturbed uptake in left liver lobe and in the caudal part of the right liver lobe. Downslope image shows disturbed excretion in left liver lobe and in the caudal part of the right liver lobe.

conclusion:

Suspected of obstruction in common bile duct; liver parenchyma is slightly disturbed.

Surgery:

A congested liver was found ( caused by decompensated heart ) with slight dilated bile ducts and a stone in the common bile duct.

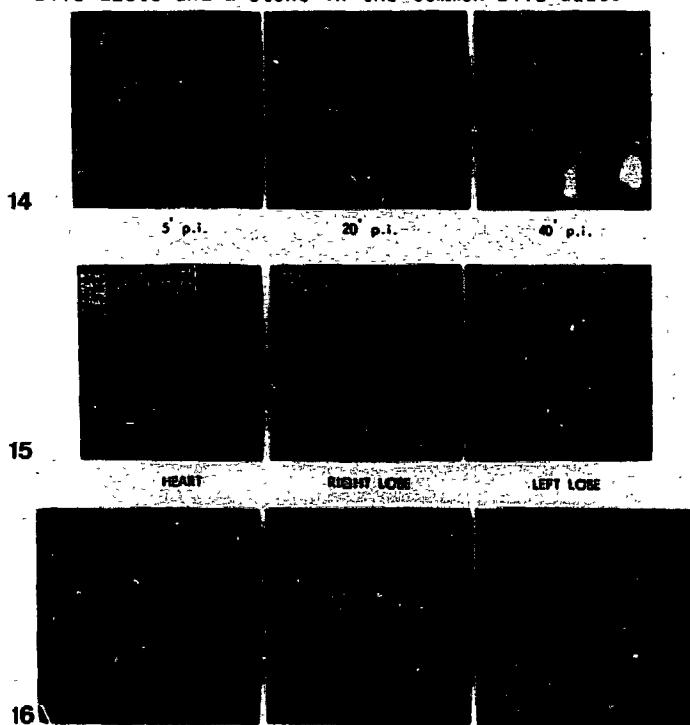


Fig. 12:14-16 Cholescintigraphy in a patient with a stone in the common bile duct.

Case history no. 5.

A 73-year- old female was admitted with pain in the right upper abdomen and jaundice.

Laboratory findings:

Total bilirubin 78  $\mu\text{mol/l}$ , direct reacting bilirubin 42  $\mu\text{mol/l}$ , alkaline phosphatase 410  $\text{mU/ml}$ , S.G.O.T. 70  $\text{mU/ml}$ , S.G.P.T. 134  $\text{mU/ml}$ .

Abdominal plain film:

Calcification in the gallbladder region.

Ultra sound:

Distended bile ducts and gallbladder.

Colloid liver scintigraphy:

Slightly enlarged liver without further abnormality.

Cholescintigraphy

serial scintigraphy:  
( figure 12-17 )

Good visualisation of the liver no intrahepatic bile ducts, gallbladder or common bile duct visible, delayed excretion of the reagent in the intestine.

time-activity curves:  
( figure 12-18 )

The right liver lobe shows delayed uptake and delayed excretion; left liver lobe: a continuously ascending curve.

functional images:  
( figure 12-19 )

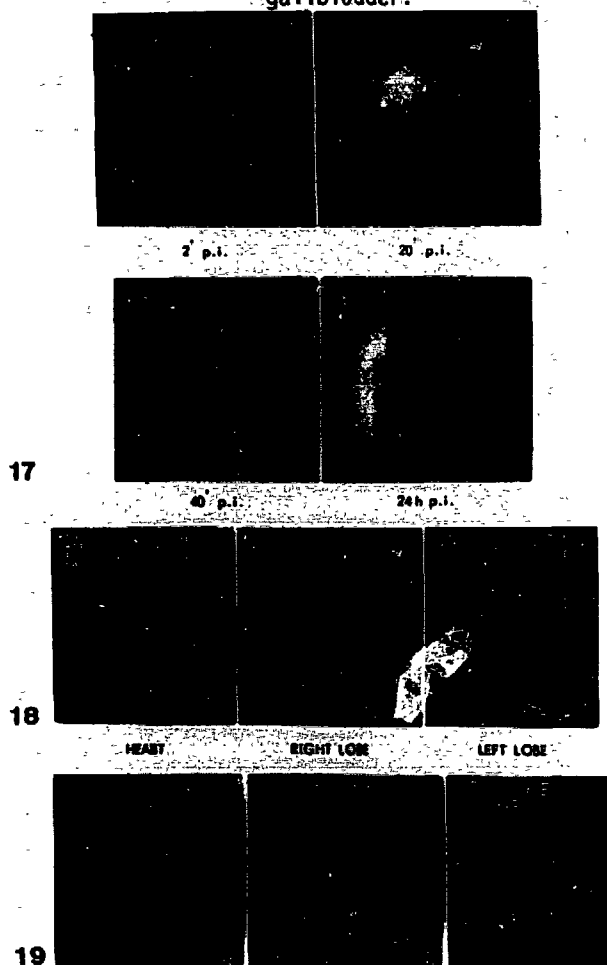
On the upslope image from 1-10' normal uptake in right and left liver lobe; on an upslope image generated from 30-45' the common bile duct is visible.

conclusion:

Suspected bile duct obstruction and slight disturbance of liver parenchyma.

**Surgery:**

A dilated common bile duct was found. No stones were visualised on peroperative cholangiography but further surgical exploration demonstrated stones in the distal common bile duct and in the gallbladder.



**Fig.12:17-19 Cholescintigraphy in a patient with multiple stones in common bile duct and in the gallbladder.**

Case history no. 6.

A 84-year-old female was admitted with jaundice and pain in right upper abdomen.

Laboratory findings:

Total bilirubin 140  $\mu\text{mol/l}$ , direct reacting bilirubin 99  $\mu\text{mol/l}$ , alkaline phosphatase 440  $\text{mU/ml}$ , S.G.O.T. 33  $\text{mU/ml}$ , S.G.P.T. 47  $\text{mU/ml}$ .

Abdominal plain film:

Calcification in the right upper abdomen.

Intravenous cholangiography:  
( performed when total bilirubin level fall to 26  $\mu\text{mol/l}$  )

A grossly dilated common bile duct with poor definition and no gallbladder.

Cholescintigraphy

serial scintigraphy:  
( figure 12-20 )

Good visualisation of the liver with dilatation of intrahepatic bile ducts and common bile duct; no visualisation of gallbladder but normal intestinal excretion. Delayed uptake by the right liver lobe with a delayed excretion. The uptake in the left liver lobe was normal but the excretion was delayed.

time-activity curves:  
( figure 12-21 )

functional images:  
( figure 12-22 )

Normal uptake by right and left lobe with a good image of the common bile duct on the image from 26-35'. The downslope functional image is diffusely inhomogeneous, confirming that the excretion phase of the whole liver is disturbed.

conclusion: Suspected bile duct obstruction;  
liver parenchyma disturbance.

Surgery: Multiple stones in gallbladder  
and common bile duct were  
demonstrated. Passage to the  
duodenum was poor.

Peroperative cholangiography: Grossly dilated common bile duct  
with multiple stones.

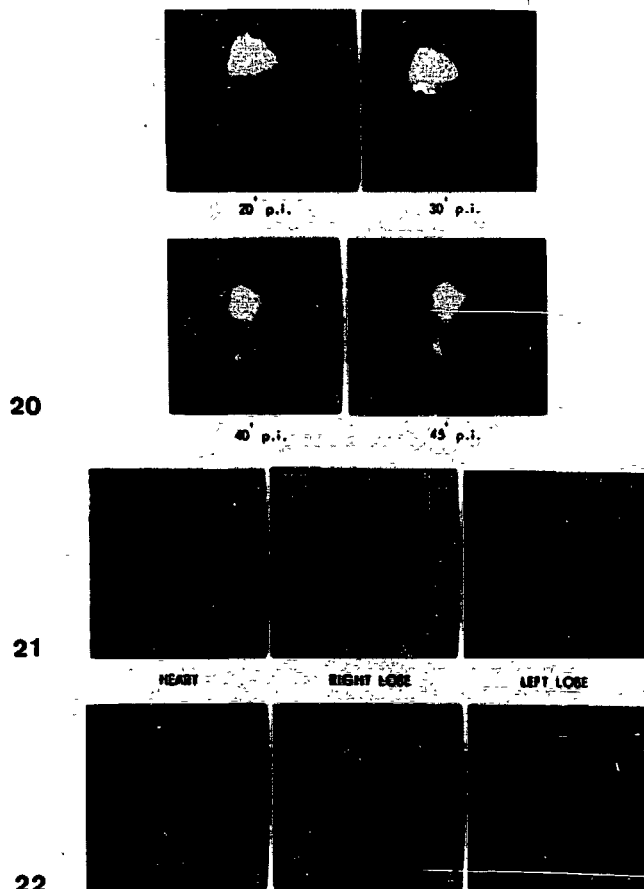


Fig.12:20-22 Cholescintigraphy in a patient with multiple stones  
in the common bile duct.

### *12.3. Cholescintigraphy in non-obstructive disease.*

In this series 54 patients with hyperbilirubinaemia were investigated; bile duct obstruction could not be demonstrated by clinical investigations.

These group was subdivided in patients who were suffering from parenchymal liver disease and in those who were suffering from various other disease states. The latter group included malignant involvement of the liver, different gallbladder diseases and patients with jaundice not due to liver or biliary tract disease.

#### *12.3.1. Results in patients with parenchymal liver disease.*

38 patients with jaundice due to parenchymal disease were studied. In 28 patients the diagnosis was confirmed by transcutaneous liver biopsy; in all other patients the diagnosis was confirmed by laparoscopy, operation or post mortem investigation. The classification of these patients is shown in table 12-13.

No.patients	disease
11	acute viral hepatitis
8	drug induced hepatitis
6	alcoholic hepatitis
5	aspecific, reactive hepatitis
3	chronic persistent hepatitis
3	chronic active hepatitis
2	cirrhosis

Table 12-13 Classification of patients with jaundice due to parenchymal disease.

In the serial scintigrams of 27 patients cholescintigraphy showed a normal intestinal excretion. In the other 11 patients there was delayed excretion. All but two patients with delayed intestinal excretion showed bilirubin values between 217 and 365  $\mu\text{mol/l}$ . Two patients with delayed intestinal excretion had relative low bilirubin values, respectively 32 and 86  $\mu\text{mol/l}$ . Both were shown to suffer from a serious alcoholic hepatitis; in these patients the colloid liver scintigram also showed poor accumulation of colloid in the liver and enhanced accumulation in the R.E.S. of spleen and bone marrow. Table 12-14 shows the biochemical parameters for each group of patients as related to the excretion pattern on the serial scintigram. In some patients the cholescintigraphic investigation was not performed in an early stage of the illness, because these patients were admitted at a later stage.



	total bilirubin umol/l	direct bilirubin umol/l	alkaline phosphatase mU/ml	S.G.D.T. mU/ml	S.G.P.T. mU/ml	intestinal excretion
	259	165	262	2100	2170	D
	28	-	56	27	96	N
acute	154	86	157	360	1040	N
	77	48	119	76	124	N
viral	32	10	181	60	310	N
	217	119	369	1250	1902	D
hepatitis	50	21	115	62	325	N
	359	232	260	600	756	D
	214	146	238	720	1230	D
	74	42	185	37	170	N
	140	65	169	149	142	N
	36	13	94	93	228	N
drug	222	110	185	215	330	D
induced	117	59	178	650	1390	N
	139	67	147	138	149	N
hepatitis	34	20	797	43	63	N
	26	11	317	203	430	N
	260	168	242	690	1140	D
	365	304	220	629	630	D
	18	5	76	21	13	N
alcoholic	108	21	82	24	17	N
hepatitis	86	52	147	155	93	D
	30	12	121	30	14	N
	32	20	228	112	17	D
	93	40	125	74	20	N
	42	16	263	31	60	N
aspecific	66	27	294	13	16	N
hepatitis	24	5	164	42	122	N
	18	8	134	83	130	N
	167	77	466	129	536	N
	78	-	78	650	519	N
chronic	55	16	222	158	207	N
persistent	69	28	600	54	215	N
hepatitis						
	264	128	302	1020	900	D
chronic	108	32	96	276	207	N
active	21	4	116	146	35	N
hepatitis						
	19	2	65	34	29	N
cirrhosis	289	126	195	239	100	D

Table 12-14 Biochemical parameters of 36 jaundiced patients with various parenchymal liver diseases in comparison to intestinal excretion of diethyl-IDA.

N = normal, D = delayed.

Time-activity curves and functional images for the right and left liver lobes of the patients investigated are shown in table 12-15 and compared with total bilirubin values and intestinal excretion patterns on the serial scintigrams.

In 9 patients no time-activity curves and functional images could be obtained; during the 45 minutes in which the investigation was performed only blood pool activity was observed.

In all of these patients intestinal activity was visible 24 hours after administration of the reagent.

The average maximum uptake time was 13.6 minutes for the right liver lobe and 15.6 minutes for the left liver lobe. Eight patients showed abnormal upslope images in spite of normal time-activity curves for the related liver lobes ( no. 4, 5, 13, 16, 24, 30, 31 and 32 ). In 8 patients there was a slight delay in the maximum uptake time, for the left and/or the right liver lobe ( no. 3, 14, 15, 28, 29, 32, 36 and 37 ); however the upslope image was described as normal.

In 7 patients the time-activity curves show a normal excretion for both liver lobes. In two patients there was a normal excretion time for one lobe ( no. 35 and 37 ). Abnormal downslope images were found in spite of normal curves in 8 patients ( no. 2, 5, 7, 17, 24, 26, 29 and 35 ).

All remaining pathological excretion curves showed delayed patterns: continuously ascending curves or curves that reach a plateau were not seen.

	patients no.	total bilirubin umol/l	intestinal excretion	T-max		T- $\frac{1}{2}$		Upslope		Downslope	
				right	left	right	left	right	left	right	left
acute viral hepatitis	1.	259	D	BPA		BPA		BPA		BPA	
	2.	28	N	12	13	23	27	N	N	A	A
	3.	154	N	15	25	L	L	N	N	A	A
	4.	77	N	12	12	L	L	N	N	A	A
	5.	32	N	10	11	26	22	N	A	A	A
	6.	217	D	BPA		BPA		BPA		BPA	
	7.	50	N	8	12	20	18	N	N	N	A
	8.	359	D	BPA		BPA		BPA		BPA	
	9.	214	D	BPA		BPA		BPA		BPA	
	10.	74	N	13	14	L	L	N	N	A	A
	11.	140	N	17	19	L	L	N	N	A	A
drug induced hepatitis	12.	36	N	12	9	9	25	N	N	N	A
	13.	222	D	9	15	L	L	A	A	A	A
	14.	117	N	15	21	L	L	N	N	N	A
	15.	139	N	14	14	L	L	N	N	A	A
	16.	34	N	14	16	L	L	A	A	A	A
	17.	26	N	7	12	30	31	N	N	A	A
	18.	260	D	BPA		BPA		BPA		BPA	
	19.	365	D	BPA		BPA		BPA		BPA	
alcoholic hepatitis	20.	19	N	12	9	L	L	N	N	A	N
	21.	103	N	25	25	L	L	A	A	A	A
	22.	96	D	BPA		BPA		A	A	A	A
	23.	30	N	12	14	L	L	N	N	A	A
	24.	32	D	14	17	21	27	A	A	A	A
	25.	93	N	10	9	L	L	A	A	A	A
aspecific hepatitis	26.	42	N	10	14	30	25	N	N	A	A
	27.	66	N	14	19	L	L	A	A	A	A
	28.	24	N	20	21	L	L	N	N	A	A
	29.	19	N	25	12	30	29	N	N	A	A
	30.	167	N	12	15	L	L	A	A	A	A
chronic persistent hepatitis	31.	78	N	18	11	L	L	A	A	A	A
	32.	55	N	15	11	L	L	N	A	A	A
	33.	69	N	11	14	30	27	N	N	A	A
chronic active hepatitis	34.	264	D	BPA		BPA		BPA		BPA	
	35.	109	N	15	19	L	27	A	A	A	A
	36.	21	N	20	26	L	L	N	N	A	A
cirrhosis	37.	19	N	11	19	29	L	N	N	N	A
	38.	289	D	BPA		BPA		BPA		BPA	

Table 12-15 Computer data of 38 jaundiced patients with parenchymal liver disease in comparison to total bilirubin values and intestinal excretion in serial scintigrams.

N=normal, D=delayed, L=lengthened, BPA=blood pool activity, A=abnormal, N=normal. Right=right liver lobe. Left=left liver lobe. T-max and T- $\frac{1}{2}$  are in minutes.

In addition to biochemical blood analyses in these patients 82 other investigations, encompassing 9 different diagnostic procedures, were performed to establish whether jaundice was caused by obstruction or parenchymal disease. ( see table 12-16 )

diagnostic investigation	no.patients	visualisation of liver and biliary tract.	
		success	failure
abdominal plain film	15	-	-
oral cholecystography	8	3	5
intravenous cholangiography	11	10	1
percutaneous transhepatic cholangiography	1	0	1
endoscopic cholangiography	1	1	
colloid liver scintigraphy	13	13	0
ultra sound study	5	5	-
laparoscopy	1	1	-
transcutaneous liver biopsy	28	28	-

Table 12-16 Investigations in 38 patients with jaundice due to parenchymal disease: frequency of visualisation of liver and biliary tract.

In two patients abdominal plain film showed concrements in the right upper abdomen. In the other patients no abnormalities were found. In patients where oral cholecystography failed, bilirubin values varied from 18-108  $\mu\text{mol/l}$ . I.V.C. failed in a patient with a bilirubin value of 108  $\mu\text{mol/l}$ . In one patient intravenous cholangiography could not be performed because of allergy to the contrast agent. Percutaneous transhepatic cholangiography "failed" because no bile ducts could be visualised.

The contribution which most investigations make to the diagnosis of jaundice caused by parenchymal disease is that they help to exclude obstruction. In 10 patients oral cholecystography and intravenous cholangiography showed no abnormality. In three patients there was clearly excretion of the contrast material by the kidneys when intravenous cholangiography was performed: no obstruction in the common bile duct could be demonstrated so that under these conditions the diagnosis of parenchymal disease was suspected. In 4 patients colloid liver scintigraphy showed uptake of the radiopharmaceutical by the R.E.S. of bone marrow and spleen and in 3 patients a scintigram with a mottled aspect was obtained. Both patterns were suspect for parenchymal disease of the liver. Table 12-17 shows the findings of the various investigations together with the frequency of correct diagnosing parenchymal disease.

diagnostic investigation	no. patients	normal	obstruction	parenchymal disease	correct diagnosis
oral cholecystography	9	3			-
intravenous cholangiography	11	7		3	3
percutaneous transhepatic cholangiography	1			1	1
endoscopic cholangiography	1	1			-
colloid liver scintigraphy	13	6		7	7
ultra sound study	5	3	2		-
laparoscopy	1	1			-
transcutaneous liver biopsy	28		1		27
cholescintigraphy	38	0	0	38	38

Table 12-17 Investigation in 38 jaundiced patients; frequency of findings and frequency of agreement in diagnosis.

Ultra sound investigation demonstrated dilated bile ducts in two patients ( table 12-15 no. 18 and 34 ) but liver biopsy could not confirm these findings. Percutaneous transhepatic cholangiography did not visualise bile ducts. This may be due to non-dilated bile ducts. The final diagnosis in this patient was drug induced hepatitis ( table 12-15 no. 19 ). In one patient liver biopsy showed patterns that were suspect for extrahepatic obstruction ( table 12-15 no.27 ). However this could not be confirmed by laparoscopy or endoscopic cholangiography.

Laparotomy was performed in two patients with suspicion of bile duct obstruction. No obstruction could be demonstrated but during operation parenchymal involvement was confirmed. In both patients cholescintigraphic patterns were suspect for parenchymal disease.

#### *12.3.1.1. Discussion.*

The results of the study revealed the following patterns of cholescintigraphy in patients with jaundice due to parenchymal liver disease.

#### *Serial scintigraphy:*

- intestinal excretion of the radiopharmaceutical was observed in all patients suffering from parenchymal liver disease.
- normal intestinal excretion was observed in 71% of the patients studied.
- delayed intestinal excretion was observed in 29%.

Patients with a normal intestinal excretion showed a slight persistence of blood pool activity in 33% of the total. Intrahepatic bile ducts were visible in 63% of this group of patients.

Patients with a delayed intestinal excretion showed a relatively good liver visualisation with persistence of a slight blood pool activity in 18% and a poor liver visualisation with persistence of high blood pool activity was observed in 82%.

#### Computer data

No additional information could be obtained with the computer in 24% of the patients studied.

Time-activity curves obtained from the two patients with a delayed intestinal excretion and persistence of slight blood pool activity showed:

- marginally normal T-max for both liver lobes.
- normal T- $\frac{1}{2}$  for both liver lobes in one of the patients studied.
- lengthened T- $\frac{1}{2}$  for both liver lobes in one of the patients studied.

Functional images generated in patients with delayed intestinal excretion show that in all cases there was a disturbed uptake and excretion phase for both liver lobes.

Time-activity curves obtained from patients with a normal intestinal excretion of the radiopharmaceutical showed:

- normal T-max for both liver lobes in 44% of the patients studied.
- delayed T-max for both liver lobes in 30%.
- delayed T-max for only the right lobe in 22%.
- delayed T-max for only the left liver lobe in 4%.
- normal T- $\frac{1}{2}$  for both liver lobes in 31% of the patients studied.
- lengthened T- $\frac{1}{2}$  for both liver lobes in 63%.
- lengthened T- $\frac{1}{2}$  for only the left liver lobe in 3%.
- lengthened T- $\frac{1}{2}$  for only the right liver lobe in 3%.

Functional images generated in all the patients studied with normal intestinal excretion, revealed the following patterns:

- disturbed uptake and excretion phase for both liver lobes was observed in 30%.
- disturbed uptake phase for one of the lobes and disturbed excretion phase for both liver lobes was observed in 15%.
- normal uptake phase for both liver lobes and disturbed excretion phase for both liver lobes was observed in 37%.
- disturbed excretion phase for only the left liver lobe was observed in 18%.

In 26% of the patients studied a normal intestinal excretion with normal patterns on the time-activity curves were observed. All these patients showed abnormal functional images.

In 28% of the patients with normal or delayed intestinal excretion there were normal functional images in spite of abnormal patterns in the corresponding time-activity curve.

#### Clinical reliability

Parenchymal disturbance could be suspected on the serial scintigram if there was a delayed intestinal excretion of the radiopharmaceutical with poor liver visualisation and persistent high blood pool activity. In this series of patients studied intrahepatic cholestasis as the causative agent for the jaundice could be diagnosed on the serial scintigram only in 24%.

A slight persistent blood pool activity in patients with normal intestinal excretion and in patients with delayed intestinal excretion was also indicative of parenchymal disease, although these patterns can also appear in patients with obstructive disease.

Computer data in all patients with parenchymal disease of the liver and jaundice showed normal or abnormal patterns of time-activity curves but all had abnormal functional images.



Parenchymal disease could be concluded in this group from the computer data when the typical patterns of time-activity curves of obstructed patients were absent, when both time-activity curves and functional images were disturbed and especially in patients with normal time-activity curves and disturbed functional images.

When serial scintigram patterns and computer data were combined the success rate in diagnosing intrahepatic cholestasis as the cause for jaundice was 100%.

In comparison the success rate in diagnosing parenchymal disease was for intravenous cholangiography 27%, for liverscintigraphy 54% and for liver biopsy 96%. Ultra sound could not diagnose parenchymal disease in the patients studied.

#### 12.3.1.2. CASE HISTORIES

Case history no. 7

A 86-year-old female was admitted because of biochemical liver function disturbances and a tumour in the abdomen.

Laboratory findings: Total bilirubin 19  $\mu\text{mol/l}$ , direct reacting bilirubin 2  $\mu\text{mol/l}$ , alkaline phosphatase 65  $\text{mU/ml}$ , S.G.O.T. 34  $\text{mU/ml}$ , S.G.P.T. 28  $\text{mU/ml}$ .

Colloid liver scintigraphy: Normal findings.

Cholescintigraphy

serial scintigraphy:  
( figure 12-23 )

Good visualisation of the liver, no persistent blood pool activity, normal bile ducts and gallbladder visibility. There was also a normal intestinal excretion of the radiopharmaceutical.

time-activity curves:  
( figure 12-24 )

Normal uptake and excretion patterns for the right liver lobe and a delayed uptake and excretion for the left liver lobe.

functional images:  
( figure 12-25 )

Normal uptake and excretion phase for the right liver lobe and a disturbed uptake and excretion phase for the left liver lobe.

conclusion:

No bile duct obstruction, disturbance of liver parenchyma from the left liver lobe.

Liver biopsy:

during operation from both right and left liver lobes, showed no abnormality in the right lobe and cirrhosis in the left lobe.

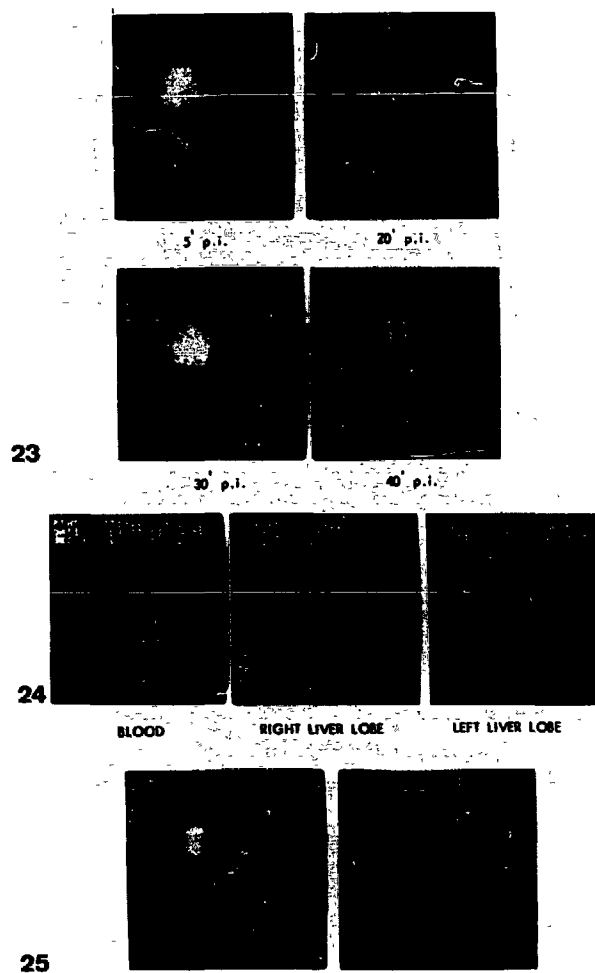


Fig.12:23-25 Cholescintigraphy in a patient with cirrhosis in the left liver lobe.

Case history no. 8

A 73-year-old man was admitted because of jaundice which developed after taking nitrofurantoin.

Laboratory findings:	Total bilirubin 260 $\mu\text{mol/l}$ , direct reacting bilirubin 168 $\mu\text{mol/l}$ , alkaline phosphatase 242 $\text{mU/ml}$ , S.G.O.T. 690 $\text{mU/ml}$ , S.G.P.T. 1140 $\text{mU/ml}$ .
Ultra sound:	Dilated bile ducts in the liver hilus and an enlarged pancreas head.
Cholescintigraphy I serial scintigraphy: ( figure 12-26 )	Poor visualisation of the liver with persistent blood pool activity and excretion of the radiopharmaceutical by the kidneys. There was delayed excretion of the radiopharmaceutical into the intestine.
time-activity curves: ( figure 12-27 )	Curves from both liver lobes did not rise above the level of the blood pool curve.
functional images: ( figure 12-28 )	Only visualisation of blood pool activity and kidneys.
conclusion:	Suspected generally disturbed liver parenchyma.
Liver biopsy:	Patterns that were characteristic of drug induced hepatitis.

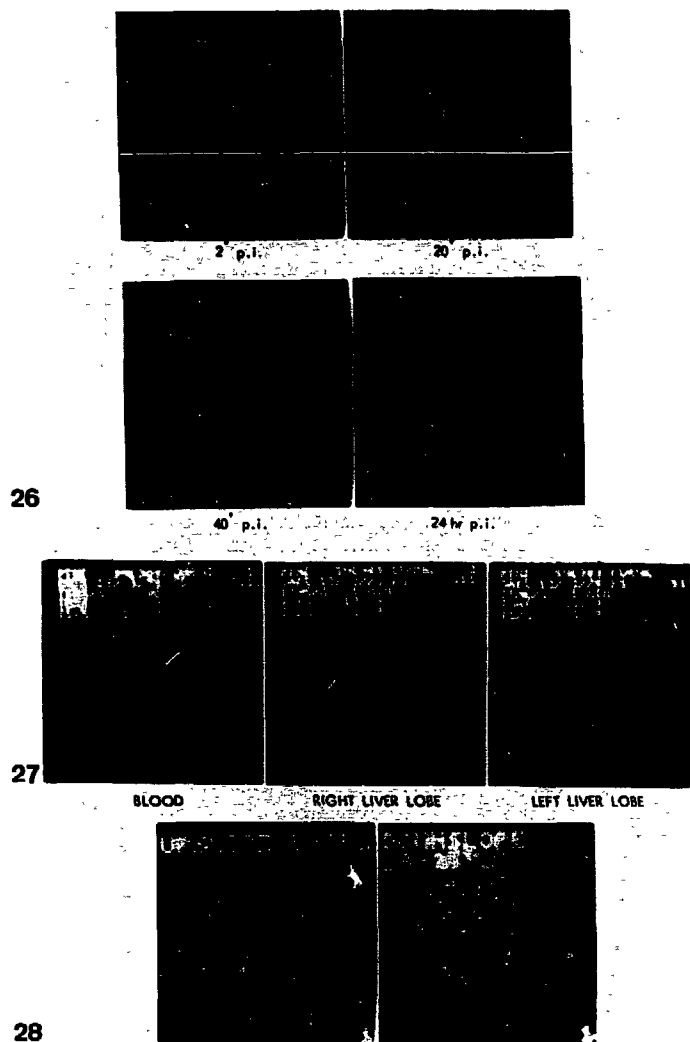


Fig. 12:26-28 Cholescintigraphy in a patient with drug induced hepatitis.

Cholescintigraphy was repeated after clinical improvement had set in, but before the biochemical liver functions were fully normalized.

Cholescintigraphy II

serial scintigraphy:  
( figure 12-29 )

Good visualisation of the liver without persisting blood pool activity; visibility of bile ducts and gallbladder; normal intestinal excretion of the radiopharmaceutical.

time-activity curves:  
( figure 12-30 )

Normal uptake patterns of both liver lobes, but a still slightly delayed excretion.

functional images:  
( figure 12-31 )

Normal uptake phase and slightly disturbed excretion phase.

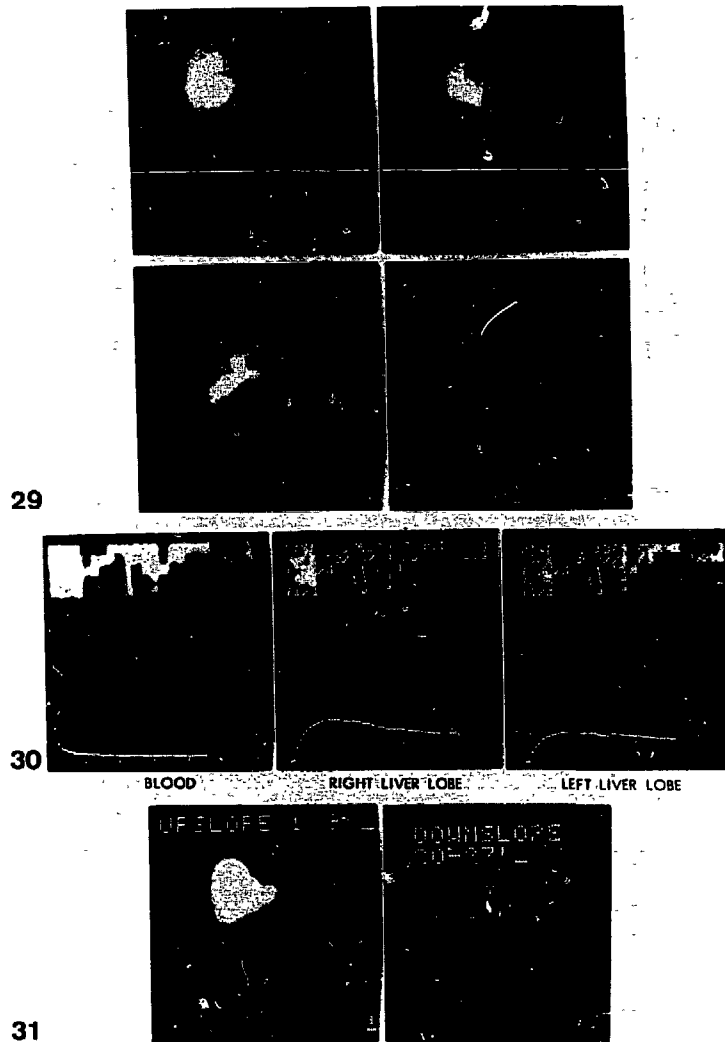


Fig. 12:29-31 Cholescintigraphy in a patient with drug induced hepatitis; after clinical improvement.



Case history no. 9

A 73-year-old male was admitted because of jaundice and gastrointestinal symptoms probably due to alcohol abuse.

Laboratory findings: Total bilirubin 86  $\mu\text{mol/l}$ , direct reacting bilirubin 52  $\mu\text{mol/l}$ , alkaline phosphatase 147  $\text{mU/ml}$ , S.G.O.T. 155  $\text{mU/ml}$ , S.G.P.T. 83  $\text{mU/ml}$ .

Colloid liver scintigraphy: Enlarged liver and spleen and increased accumulation of radio-colloid in bone marrow and spleen.

Cholescintigraphy I

serial scintigraphy:  
( figure 12-32 )

Poor visualisation of the liver difficult to distinguish from the persistent blood pool activity. Intestinal excretion of the radiopharmaceutical was seen 24 hours post injection ( to get better contrast computer images were generated from the gamma camera images ).

functional images:  
( figure 12-33 )

Strongly disturbed uptake and excretion phases for both liver lobes.

conclusion:

Suspected of diffuse liver parenchymal disturbance.

Liver biopsy:

Patterns of alcoholic hepatitis.

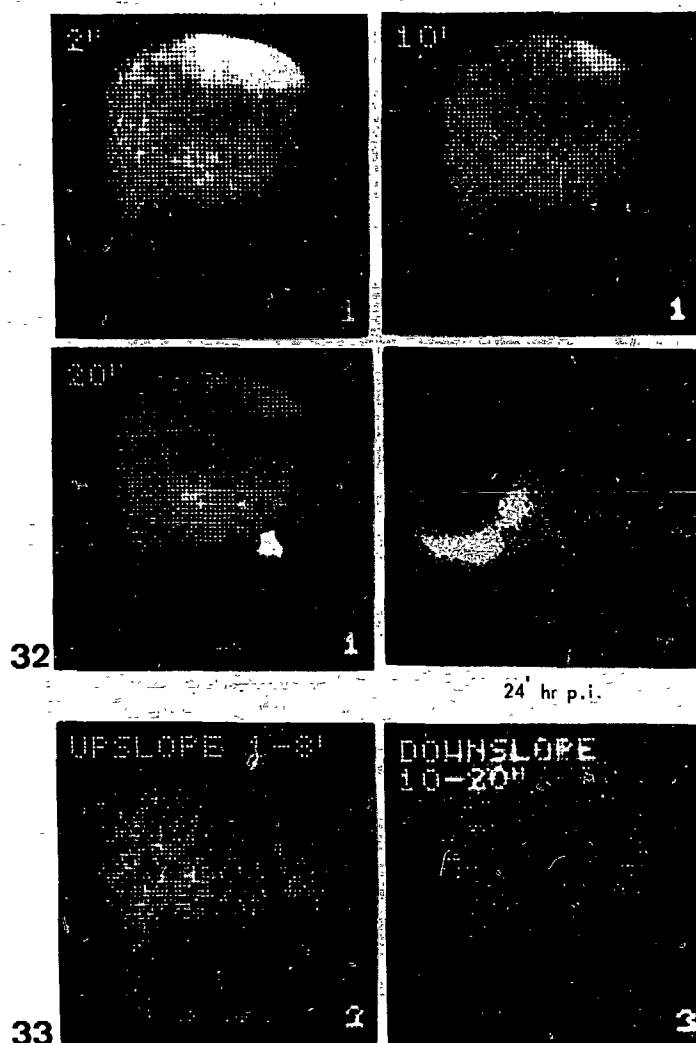


Fig. 12:32-33 Cholescintigraphy in a patient with alcoholic hepatitis.

Cholescintigraphy was repeated after clinical improvement had set in, but before the biochemical liver functions were fully normalized.

#### Cholescintigraphy II

serial scintigraphy:  
( figure 12-34 )

Clear visualisation of the liver without persistent blood pool activity, visibility of bile ducts, no gallbladder ( later confirmed by I.V.C. ) and normal intestinal excretion of the radiopharmaceutical.

time-activity curves:  
( figure 12-35 )

Normal uptake and excretion patterns.

functional images:  
( figure 12-36 )

Normalized uptake phase and practically normalized excretion phase.

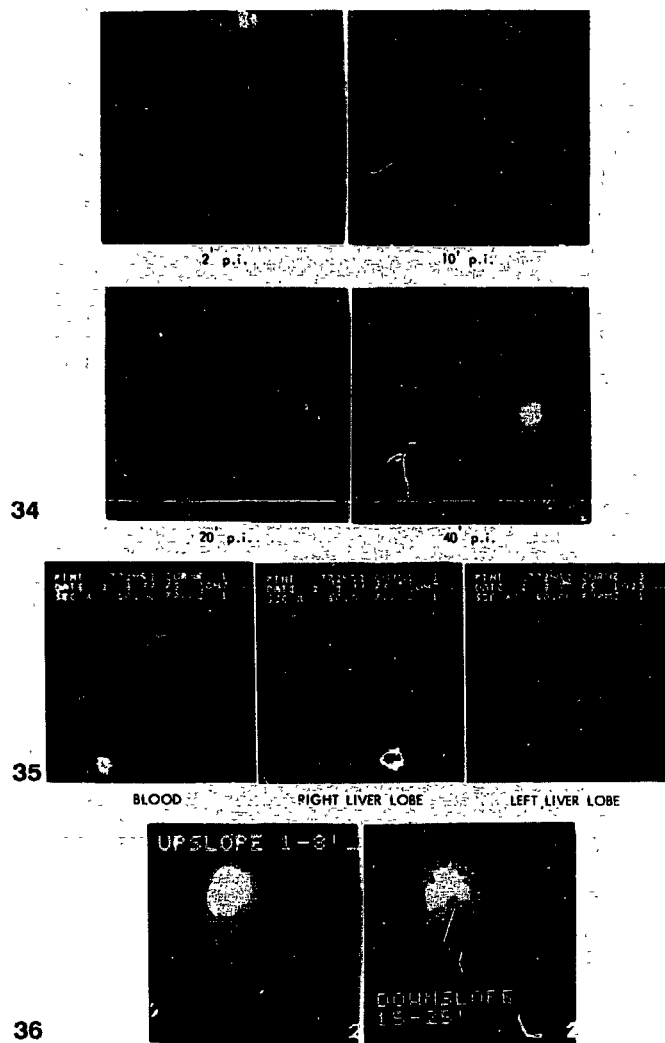


Fig. 12:34-36 Cholescintigraphy in a patient with alcoholic hepatitis; after clinical improvement.

Case history no. 10

A 20-year-old male was admitted with a suspicion of acute viral hepatitis.

Laboratory findings: Total bilirubin 32  $\mu\text{mol/l}$ , direct reacting bilirubin 10  $\mu\text{mol/l}$ , alkaline phosphatase 181  $\text{mU/ml}$ , S.G.O.T. 60  $\text{mU/ml}$ , S.G.P.T. 310  $\text{mU/ml}$ .

Abdominal plain film: No calcifications in right upper abdomen.

Cholescintigraphy I serial scintigraphy: ( figure 12-37 ) Normal visualisation of the liver, bile ducts and gallbladder. There was no persistent blood pool activity; excretion of the radio-pharmaceutical in the intestine was normal.

time-activity curves: ( figure 12-38 ) Normal uptake and excretion patterns.

functional images: ( figure 12-39 ) Normal uptake phase for the right liver lobe, a slightly disturbed uptake phase for the left liver lobe and disturbed excretion phase for both liver lobes.

conclusion: Diffuse disturbance of liver parenchyma; left liver lobe more involved than right liver lobe.

Liver biopsy: Patterns of hepatitis with cholestasis.

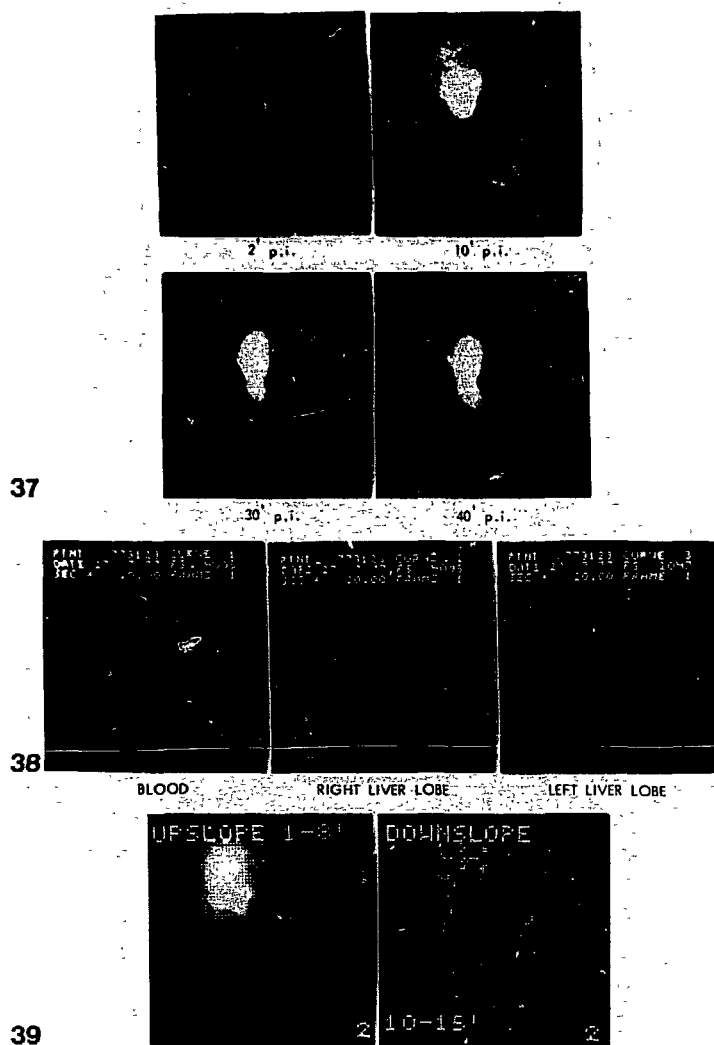


Fig. 12:37-39 Cholescintigraphy in a patient with probably acute viral hepatitis.

Cholescintigraphy was repeated after clinical improvement had set in, but before biochemical liver functions were fully normalized.

Cholescintigraphy II

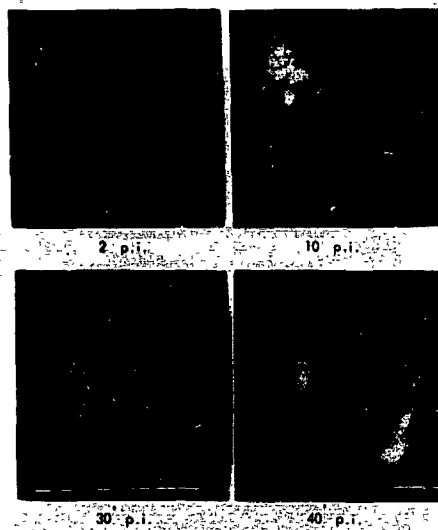
serial scintigraphy:  
( figure 12-40 )

An unchanged, normal picture;  
this was also with the time-  
activity curves.

functional images:  
( figure 12-41 )

Improvement of uptake phase of  
right liver lobe and improvement  
of excretion phase of both liver  
lobes.

40



41

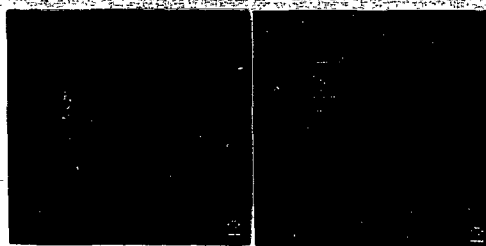


Fig. 12:40-41 Cholescintigraphy in a patient with probably acute viral hepatitis; after clinical improvement.



Case history no. 11

A 25-year-old male was admitted because of jaundice two weeks after taking prescribed medicaments.

Laboratory findings:	Total bilirubin 26 $\mu\text{mol/l}$ , direct reacting bilirubin 11 $\mu\text{mol/l}$ , alkaline phosphatase 317 $\text{mU/ml}$ , S.G.O.T. 203 $\text{mU/ml}$ , S.G.P.T. 439 $\text{mU/ml}$ .
Abdominal plain film:	No calcifications in the abdomen.
Cholescintigraphy serial scintigraphy: ( figure 12-42 )	Good visualisation of the liver, there was no persistent blood pool activity; intrahepatic bile ducts and gallbladder were visible. Intestinal excretion of the radiopharmaceutical was normal.
time-activity curves: ( figure 12-43 )	Normal uptake patterns for right and left liver lobes. The excretion phase of the right liver lobe is slightly delayed whilst that of the left lobe is normal.
functional images: ( figure 12-44 )	Normal uptake phase and disturbed excretion phase in both liver lobes, in the left lobe more than the right.
conclusion:	No obstruction; suspected of generally disturbed liver parenchyma.
Liver biopsy:	Patterns that agreed with a diagnosis of drug induced hepatitis.

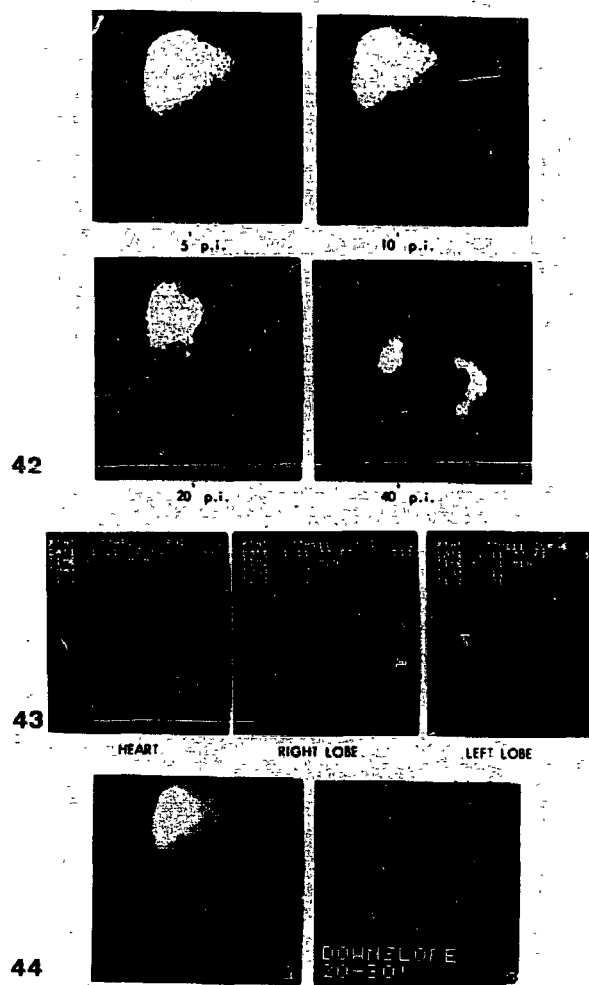


Fig. 12:42-44 Cholescintigraphy in a patient with drug induced hepatitis.

### 12.3.2. Results in patients with various other diseases.

In this series 16 patients were investigated. They suffered from jaundice due to various diseases not classified in the groups of patients discussed earlier. Table 12-18 shows the diagnoses, biochemical blood patterns and the intestinal excretion of the radiopharmaceutical.

patient no.	clinical diagnoses	bilirubin total direct umol/l		alkaline phosphatase mU/ml	S.G.O.T. mU/ml	S.G.P.T. mU/ml	intestinal excretion
1.	metastasis	175	155	392	34	70	N
2.	liver cell carcinoma	30	17	1130	25	23	D
3.	liver cell carcinoma	22	20	334	37	26	N
4.	metastasis	24	16	163	149	37	N
5.	Hodgkin	452	216	198	38	37	C
6.	gallbladder carcinoma + metastasis	250	125	440	43	44	D
7.	gallbladder carcinoma + metastasis	243	197	565	35	63	C
8.	stone in cystic duct	95	90	156	35	52	N
9.	cholecystitis	58	14	657	61	117	N
10.	stone in cystic duct, cholecystitis	46	23	171	12	24	N
11.	cholelithiasis	38	17	314	68	99	N
12.	pernicious anaemia	78	18	47	18	9	N
13.	jaundice e.c.i.	38	20	199	12	12	N
14.	Gilbert's syndrome	33	3	99	11	26	N
15.	heart failure	72	23	133	34	24	N
16.	hemolytic anaemia	37	7	50	19	25	N

Table 12-18 Biochemical blood patterns and intestinal excretion of diethyl-IDA in 16 patients with jaundice due to various diseases.

N=normal, D=delayed and C=complete obstruction.

Serial scintigraphy showed 12 patients to have normal intestinal excretion of the radiopharmaceutical; in two patients a delayed excretion and in a further two patients a complete obstruction was observed. One of these latter patients ( no.5 ) produced a poorly visualised liver, difficult to distinguish from blood pool activity and an other patient ( no.7 ) showed a relatively "good" visualisation of the liver without visible bile ducts or gallbladder. Patient no.13 suffering from jaundice of unknown origin showed clinical signs of obstruction, but neither initial investigations nor operation could establish the cause of the jaundice. The liver biopsy of the patient with heart failure ( no.15 ) showed a pattern of cardiac congestion; post mortem examination showed no other abnormality.

Time-activity curves and functional images for the right and left liver lobes of the patients investigated are shown in table 12-19 and are compared with total bilirubin values and intestinal excretion of the radiopharmaceutical as shown by the serial scintigram. These group of patients with miscellaneous diseases shows a great variety of patterns in time-activity curves and functional images.

In 11 patients there was disagreement between functional imaging and the pattern of time-activity curves. In 9 patients the time-activity curves show slightly delayed uptake patterns for the right liver lobes whilst the upslope image shows a normal uptake phase; in two patients there was a normal time-activity curve for the right liver lobe and an abnormal upslope image. In 5 patients there is a normal upslope image for the left liver lobe in spite of slightly disturbed uptake patterns in the time-activity curves. In one patient ( no.13 ) there were abnormal downslope images in spite of normal time-activity curves. Patient no.6 showed on the serial scintigram a delayed excretion and on the functional images a disturbed uptake and excretion phase.

Nevertheless time-activity curves in this patient did not rise above the level of the blood pool curve.

In this series 4 patients showed normal intestinal excretion on the serial scintigram although the time-activity curves showed a delayed excretion pattern for both liver lobes.

patient no.	total bilirubin $\mu\text{mol/l}$	intestinal excretion	T-max liver lobes		T- $\frac{1}{2}$		upslope		downslope	
			right	left	right	left	right	left	right	left
1.	175	N	10	15	22	23	N	N	A	A
2.	30	D	AC	AC	AC	AC	N	A	A	A
3.	22	N	10	11	L	L	A	N	A	A
4.	24	N	12	12	L	L	A	A	A	A
5.	425	C	BPA		BPA		BPA		BPA	
6.	250	D	BPA		BPA		A	A	A	A
7.	243	C	15	16	L	L	N	N	A	A
8.	95	N	16	23	L	L	N	N	A	A
9.	53	N	11	12	22	24	N	N	N	N
10.	46	N	14	AC	21	AC	N	A	N	A
11.	38	N	24	20	L	L	N	N	A	A
12.	78	N	14	21	17	29	N	N	N	N
13.	38	N	14	14	17	19	N	N	A	A
14.	33	N	20	AC	13	AC	N	N	N	A
15.	72	N	16	19	L	L	N	N	A	A
16.	37	N	10	12	18	19	N	N	N	N

Table 12-19 Computer data of 16 patients with jaundice due to various diseases in comparison with total bilirubin values and intestinal excretion on the serial scintigram.

Intestinal excretion on serial scintigram. N=normal, D=delayed, C=complete obstruction, AC=ascending curve, L=lengthened, BPA=blood pool activity, N=normal, A=abnormal. Right=right liver lobe. Left=left liver lobe. T-max and T- $\frac{1}{2}$  are in minutes.

In this group of 16 patients 33 investigations other than biochemical blood examinations were performed to establish the diagnosis ( table 12-20 ).

diagnostic investigation	no.patients	visualisation liver and/or bile ducts	
		success	failure
abdominal plain film	6	-	-
oral cholecystography	1	0	1
intravenous cholangiography	5	5	0
endoscopic cholangiography	1	1	0
colloid liver scintigraphy	8	8	-
ultra sound study	5	5	0
laparoscopy	1	-	-
transcutaneous liver biopsy	6	6	0

Table 12-20 Investigations in 16 patients with jaundice due to various disease; success rate in visualising liver and/or bile ducts.

In 2 patients the abdominal plain film showed calcifications in the right upper abdomen; this could not be verified. In two patients with gallbladder stones abdominal plain film showed no abnormalities.

Oral cholecystography in one patient failed to visualise the gallbladder, nor did intravenous cholangiography show a gallbladder. The patient was found to be suffering from a stone in the cystic duct.

Table 12-21 shows the results of cholescintigraphic investigation compared with the results of other investigations in correct distinction between parenchymal and obstructive disease as the cause of jaundice.

diagnostic investigation	no.patients	correct diagnosis
intravenous cholangiography	5	3
endoscopic cholangiography	1	1
colloid liver scintigraphy	8	6
ultra sound study	5	3
transcutaneous liver biopsy	6	6
cholescintigraphy	16	12

Table 12-21 Results of cholescintigraphy and various other investigations in 16 patients with jaundice due to various diseases.

In two patients intravenous cholangiography gave incorrect information; in one patient there was no visualisation of bile ducts ( total bilirubin only 22  $\mu\text{mol/l}$  ), the other showed no abnormality. However the latter patient was found to have multiple stones in the gallbladder ( patient no.11 ). Colloid liver scintigraphy showed in one patient accumulation of radiocolloid in bone marrow although there was no proven parenchymal disease ( no.12 ) and in an other patient no abnormality, although the liver contained foci of Hodgkins disease. In one patient ultra sound showed no abnormality although there existed a space occupying lesion in the left liver lobe ( no.2 ); in another patient there was a suspicion of obstruction ( no.6 ) but this could not be confirmed. In 4 patients in whom cholescintigraphy was performed serial scintigram and computer data showed abnormal patterns, but no agreement with the clinical findings was found. In these patients there was a suspicion of parenchymal disturbance ( no.8 and 11 ) and a suspicion of obstructive disease ( no. 10 and 14 ).

However the first three patients ( no. 8, 10 and 11 ) showed no visualisation of the gallbladder on the serial scintigram. This could be in agreement with the final diagnosis and may be due to gallbladder pathology. It is not clear why the patient with Gilberts syndrome ( no.14 ) showed abnormal computer data.

#### *15.3.2.1. Discussion.*

The patients included in these series can be divided into the following main groups:

- a. patients with jaundice due to malignant involvement of the liver.
- b. patients with jaundice suffering from gallbladder disorders.
- c. patients with jaundice not due to liver or biliary tract disease.

The results of the study revealed the following patterns of cholescintigraphy in patients with various diseases.

#### Serial scintigraphy

Group a:                   normal intestinal excretion was observed in 44%  
                              delayed intestinal excretion was observed in 28%  
                              complete obstruction was observed in 28%  
Patients with complete obstruction and with delayed intestinal excretion showed:

- good visualisation and slight persistent blood pool activity in 50%
- bad liver visualisation and persistent high blood pool activity in 50%



Space occupying processes could be observed on the serial scintigram in 43% of the patients studied.

Group b: All patients showed normal intestinal excretion without persistent blood pool activity.

No visualisation of the gallbladder was observed in 75%

Group c: All patients showed normal turnover patterns.

#### Computer data

Time-activity curves obtained from patients with malignancy involving of the liver showed:

- high normal T-max for both liver lobes in 80%.
- normal  $T-\frac{1}{2}$  for both liver lobes in 20%.
- delayed  $T-\frac{1}{2}$  for both liver lobes in 60%.
- ascending curve for both liver lobes in 20%.

Functional images in this group of patients revealed the following patterns:

- an abnormal excretion phase for both liver lobes was observed in 100%.
- normal uptake phase for both liver lobes in 33%.
- abnormal uptake phase for right or left liver lobe in 33%.
- abnormal uptake phase for both liver lobes in 33%.

In one patient the computer data did not provide further information because of persistent high blood pool activity and in another patient it was only possible to generate functional images.

Time-activity curves obtained from patients suffering from gallbladder disorder showed:

- normal uptake and excretion patterns in 25%.
- delayed T-max for both liver lobes in 75%.
- lengthened  $T-\frac{1}{2}$  was observed in 50%.
- ascending curve for left liver lobe was observed in 25%.

Functional images in this group of patients revealed the following patterns:

- normal uptake and excretion phase for both liver lobes in 25%.
- abnormal excretion phase for both liver lobes in 50%.
- abnormal excretion phase for the left liver lobe in 25%.

The computer data obtained from the patients with jaundice not due to liver parenchymal disease showed slightly delayed uptake patterns in the time-activity curves in 67% of the patients studied, however in all these patients the functional images were normal.

Time-activity curves showed normal excretion patterns in 67% also the functional images of the excretion phase were normal.

#### Clinical reliability

A malignant involvement of the liver can be detected on the serial scintigram as space occupying processes. In 43% of the patients these could be diagnosed on the serial scintigram alone.

In 43% of the patients studied the computer showed patterns suspect for bile duct obstruction and in 57% patterns suspect for liver parenchymal disease. Both patterns can indicate malignant involvement of the liver but are not specific for malignancy.

The combination of non-visualisation of the gallbladder in fastened patients and normal computer data is indicative of gallbladder disorders.

The success rate of serial scintigraphy combined with computer patterns for demonstrating normal liver and biliary tract function in the group of jaundiced patients without liver disease in 67%. In 33% there was an inexplicable suspicion of bile duct obstruction.

#### 12.3.2.2. CASE HISTORIES

Case history no. 12

A 67-year-old female was admitted because of painless jaundice.

Patient was known to suffer from heart failure.

Laboratory findings: Total bilirubin 72  $\mu\text{mol/l}$ , direct reacting bilirubin 23  $\mu\text{mol/l}$ , alkaline phosphatase 133  $\text{mU/ml}$ , S.G.O.T. 34  $\text{mU/ml}$ , S.G.P.T. 24  $\text{mU/ml}$ .

Colloid liver scintigraphy: Normal liver with accumulation of radiocolloid in the R.E.S. of the bone marrow.

Cholescintigraphy

serial scintigraphy:  
( figure 12-45 )

Relatively good visualisation of the liver with persistent blood pool activity. The bile ducts and gallbladder are visible. There is normal intestinal excretion of the radiopharmaceutical.

cumulative image:  
( figure 12-46 )

1 to 8 minutes image shows supplying veins from the arm to the heart. 24 to 31 minutes image shows the intrahepatic bile ducts and the gallbladder.

time-activity curves:  
( figure 12-47 )

Slightly delayed uptake patterns in both liver lobes and the excretion patterns are even more delayed.

functional images:  
( figure 12-48 )

Normal uptake phase for the right liver lobe and slightly disturbed left lobe. The excretion phase shows abnormalities in both liver lobes.

conclusion: Suspected disturbance of liver parenchyma functions with delayed blood flow to the heart from the injection side.

Liver biopsy: Patterns matched by cardiac congestion. Post mortem investigations confirmed these findings.

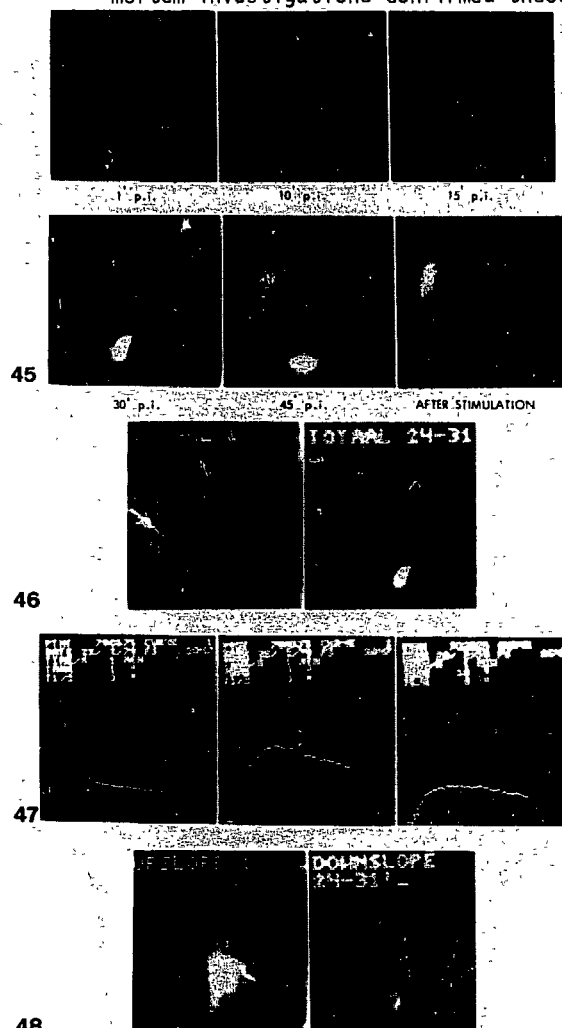


Fig. 12:45-48 Cholangiography in a patient with cardiac congestion.

Case history no. 13

A 44-year-old female was admitted with biochemical tests indicating disturbed liver function. The patient was known to be suffering from breast cancer.

Laboratory findings:	Total bilirubin 24 $\mu\text{mol/l}$ , direct reacting bilirubin 16 $\mu\text{mol/l}$ , alkaline phosphatase 163 $\text{mU/ml}$ , S.G.O.T. 149 $\text{mU/ml}$ , S.G.P.T. 37 $\text{mU/ml}$ .
Colloid liver scintigraphy:	Multiple space occupying processes.
Cholescintigraphy	
serial scintigraphy: ( figure 12-49 )	Good visualisation of an enlarged liver with defects in the right liver lobe, no visibility of bile ducts or gallbladder, normal intestinal excretion of the radiopharmaceutical.
time-activity curves: ( figure 12-50 )	The defect in the right liver lobe showed a normal uptake pattern while the excretion pattern was delayed. The uptake pattern of the left liver lobe was normal but the excretion pattern was delayed.
functional images: ( figure 12-51 )	Abnormal uptake phase in the right liver lobe with a normal uptake phase in the left liver lobe. The excretion phase in both lobes was disturbed, the right worse than the left.
conclusion:	Suspected liver metastases.
Liver biopsy:	Patterns of metastases of breast cancer.

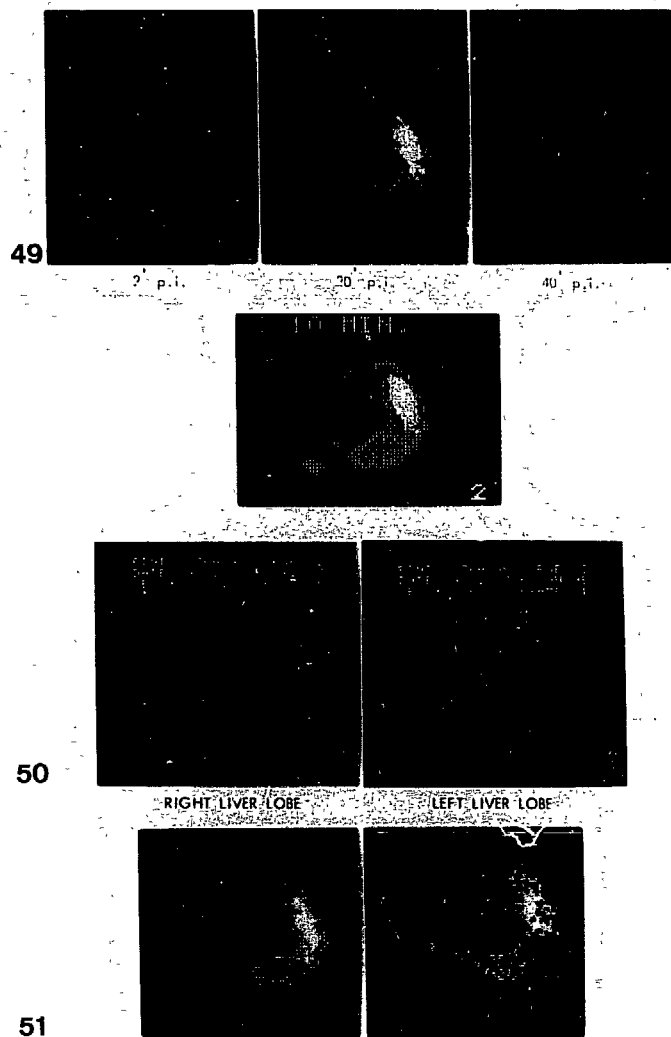


Fig. 12:49-51 Cholescintigraphy in a patient with liver metastases.



Case history no. 14

A 58-year-old man was admitted with jaundice and fever associated with pain in right upper abdomen.

Laboratory findings: Total bilirubin 58  $\mu\text{mol/l}$ , direct reacting bilirubin 14  $\mu\text{mol/l}$ , alkaline phosphatase 657  $\text{mU/ml}$ , S.G.O.T. 61  $\text{mU/ml}$ , S.G.P.T. 117  $\text{mU/ml}$ .

Abdominal plain film: No calcifications in the upper abdomen.

Intravenous cholangiography: Stenosed cystic duct.

Cholescintigraphy

serial scintigraphy:  
( figure 12-52 )

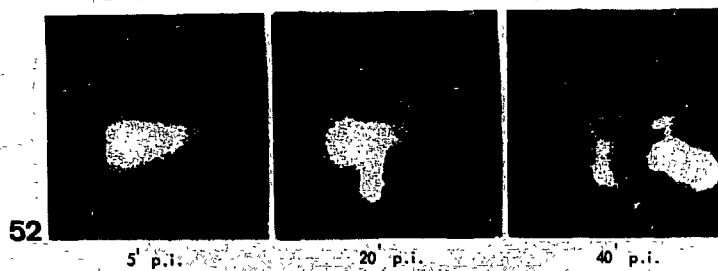
Good visualisation of the liver without persistent blood pool activity, visibility of the bile ducts with some dilated common bile duct, no visibility of the gallbladder, normal intestinal excretion of the radiopharmaceutical.

time-activity curves and functional images:  
( figure 12-53 )

Normal accumulatory and excretory phases.

conclusion: Suspected gallbladder pathology.

Surgery: Cholecystitis and stones in the gallbladder.

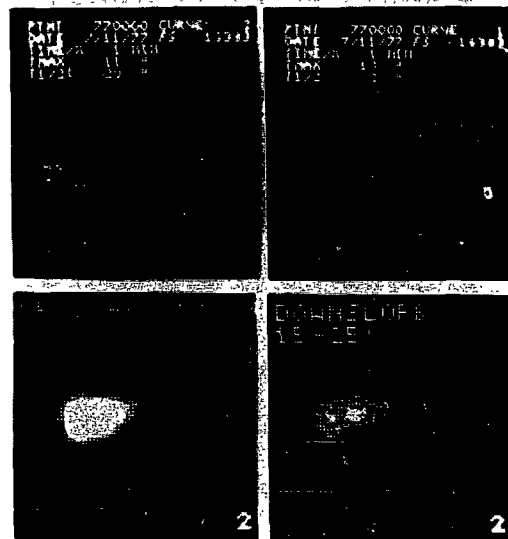


52

5' p.i.

20' p.i.

40' p.i.



53

Fig. 12:52-53 Cholescintigraphy in a patient with cholecystitis and stones in the gallbladder.

Case history no. 15

A 86-year-old female was admitted with jaundice and upper abdominal pain.

Laboratory findings:	Total bilirubin 250 $\mu\text{mol/l}$ , direct reacting bilirubin 125 $\mu\text{mol/l}$ , alkaline phosphatase 440 $\text{mU/ml}$ , S.G.O.T. 43 $\text{mU/ml}$ , S.G.P.T. 44 $\text{mU/ml}$ .
Abdominal plain film:	Calcifications in right upper abdomen.
Ultra sound study:	Stones in the gallbladder and dilated bile ducts.
Cholescintigraphy serial scintigraphy: ( figure 12-54 )	Poor visualisation of the liver with persistent blood pool activity. No bile ducts or gallbladder visible. In the gallbladder region diminished accumulation of activity, a so called "cold" area was visible. There was delayed intestinal excretion of the radiopharmaceutical.
cumulative image: ( figure 12-55 )	The 10 to 30 minutes image confirmed the "cold" area at the site of the gallbladder.
time-activity curves: ( figure 12-56 )	The curves did not rise above blood pool activity.
functional images: ( figure 12-57 )	A disturbed accumulation and excretory phase for both liver lobes.

conclusion:

Suspected gallbladder pathology,  
diffuse disturbance of liver  
parenchyma.

Surgery:

Carcinoma of the gallbladder  
with multiple liver metastases.

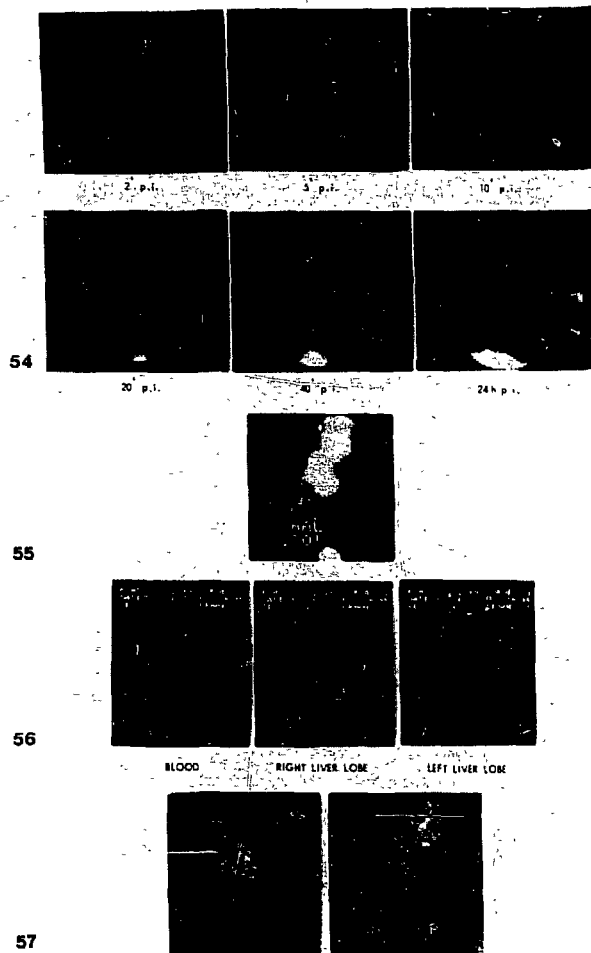


Fig. 12:54-57 Cholescintigraphy in a patient with carcinoma of the gallbladder and multiple liver metastases.

Case history no. 16

A 58-year-old male was admitted because of jaundice associated with a tumour in right upper abdomen.

Laboratory findings: Total bilirubin 37  $\mu\text{mol/l}$ , direct reacting bilirubin 20  $\mu\text{mol/l}$ , alkaline phosphatase 334  $\text{mU/ml}$ , S.G.O.T. 37  $\text{mU/ml}$ , S.G.P.T. 26  $\text{mU/ml}$ .

Abdominal plain film: No calcifications in right upper abdomen.

Intravenous cholangiography: No common bile duct visible.

Colloid liver scintigraphy: Large space occupying process in the right liver lobe.

Cholescintigraphy

serial scintigraphy:  
( figure 12-58 )

Good visualisation of the liver with a defect in the right liver lobe. There was no clear indication of activity in the bile ducts but normal excretion of the radiopharmaceutical into the intestine was observed.

time-activity curves:  
( figure 12-59 )

A region corresponding to the defect in the right lobe showed a normal uptake but much delayed excretion patterns. The left liver lobe showed normal turnover patterns.

functional images:  
( figure 12-60 )

An abnormal uptake and excretion phase for the right liver lobe and a normal uptake phase and slight disturbed excretion phase for the left liver lobe.

conclusion:

Suspected for tumour in right  
liver lobe, disturbed function  
left liver lobe.

Liver biopsy:

Patterns of liver cell carcinoma.

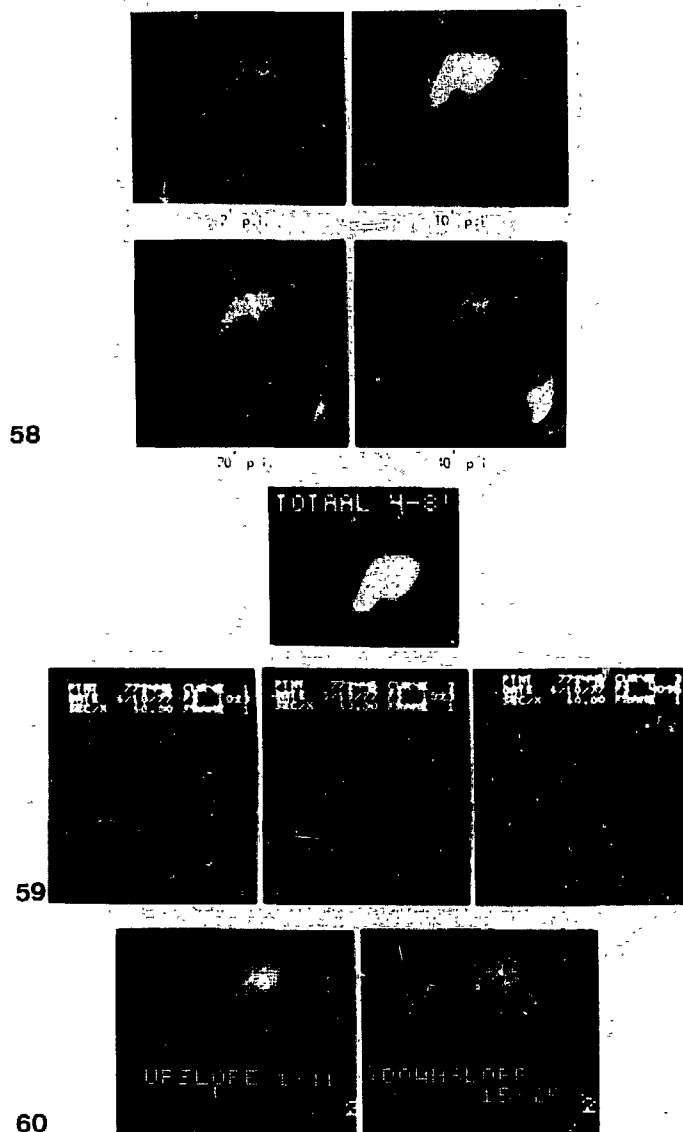


Fig. 12:58-60 Cholescintigraphy in a patient with liver cell carcinoma.

CHAPTER XIII  
CHOLESCINTIGRAPHY IN NON-JAUNDICED PATIENTS WITH LIVER AND/OR  
BILIARY TRACT DISEASE.

*13.1. Introduction.*

Fifty two patients with various disturbances of liver and biliary tract were investigated. With the exception of three patients all patients showed disturbances in biochemical parameters of liver function, without hyperbilirubinaemia. The cholescintigraphic investigation was performed routinely to confirm the findings of other diagnostic investigations and to exclude liver parenchyma disturbance or aberrations in biliary tract or gallbladder. The classification of these patients is shown in table 13-1.

No. patients	Group of diseases
32	parenchymal disease
7	malignant involvement of the liver
10	biliary duct and/or gallbladder disease
3	various abnormalities

Table 13-1 Classification of 52 non-jaundiced patients studied by cholescintigraphy.

*13.2. Results in patients with parenchymal liver disease.*

The classification of the patients with liver parenchyma disturbance including malignant involvement is shown in table 13-2.

No. patients	diagnosis
10	steatosis
1	cirrhosis
4	reactive hepatitis
5	drug induced hepatitis
3	chronic hepatitis
8	aspecific liver function disturbance
7	malignant involvement
1	siderosis

Table 13-2 Classification of 39 non-jaundiced patients with parenchymal liver disease.

The final diagnosis was made by liver biopsy, operation or laparoscopy. The eight patients with aspecific liver function disturbances all showed biochemical aberrations although liver biopsy could not give further information.

Table 13-3 shows the biochemical parameters of the patients studied compared with the findings on the serial scintigram. From the latter intestinal excretion of the radiopharmaceutical and visibility of the bile duct and gallbladder are considered. The normal value for alkaline phosphatase is maximal 108 mU/ml, for S.G.O.T. 26 mU/ml, for S.G.P.T. 26 mU/ml and for gamma glutamyl transpeptidase 4-28 mU/ml.



As can be seen from table 13-3 in 10 patients the liver biochemistry was normal. These patients were admitted with disturbed biochemical liver function but at the time of cholescintigraphy they were already normalised. Cholescintigraphy was performed to study in how far this investigation could contribute to the diagnosis.

In nine patients the gallbladder could not be visualised. In three patients ( no.: 7, 26 and 28 ) cholecystectomy had been carried out previously. In the other six patients, where the gallbladder could not be visualised, intravenous cholangiography confirmed these findings in three cases ( no.: 22, 23 and 34 ). In the other three no further information about the gallbladder was obtained, it was possible that these patients were not fasting from six hours before the examination. In one patient whose gallbladder could not be visualised laparoscopy showed that it had grown together with the intestines ( no. 34 ).

In all of the patients investigated in this series the intestinal excretion of the radiopharmaceutical was normal. In 4 patients there was no clear visualisation of the bile ducts, although in three of them the gallbladder could be seen.

diagnosis	patient no.	alk.phosph. mU/ml	S.G.O.T. mU/ml	S.G.P.T. mU/ml	Y-G.T. mU/ml	intestinal excretion	serial scintigram	
							bile ducts	gallbladder
steatosis hepatitis	1.	56	36	57	-	N	V	V
	2.	98	42	71	-	N	V	V
	3.	46	21	52	14	N	V	V
	4.	74	20	17	-	N	V	V
	5.	48	56	54	31	N	V	V
	6.	99	22	55	91	N	V	V
	7.	61	36	51	-	N	V	O
	8.	100	22	19	-	N	V	V
	9.	94	40	39	196	N	V	V
	10.	156	26	63	-	N	V	V
cirrhosis	11.	150	49	44	-	N	V	V
reactive hepatitis	12.	360	23	48	-	N	V	NV
	13.	294	82	103	34	N	NV	V
	14.	116	77	135	29	N	V	V
	15.	174	30	43	-	N	V	V
drug induced hepatitis	16.	249	71	163	141	N	NV	V
	17.	59	178	300	71	N	V	V
	18.	159	23	30	-	N	V	V
	19.	309	29	53	-	N	V	V
	20.	35	152	220	-	N	V	V
chronic hepatitis	21.	301	25	23	136	N	V	V
	22.	154	221	160	-	N	V	NV
	23.	20	17	29	-	N	V	NV
siderosis	24.	104	11	10	-	N	V	V
aspecific liver function disturbance	25.	90	19	17	-	N	V	V
	26.	96	9	13	-	N	V	O
	27.	170	13	15	-	N	V	V
	28.	39	38	43	157	N	V	O
	29.	33	18	19	-	N	V	V
	30.	49	9	4	-	N	V	V
	31.	147	10	9	-	N	V	V
	32.	203	72	30	-	N	NV	V
malignant liver involvement	33.	500	52	44	-	N	V	V
	34.	153	13	11	-	N	NV	NV
	35.	17	13	12	-	N	V	NV
	36.	136	24	30	-	N	V	NV
	37.	112	10	27	-	N	V	V
	38.	34	9	9	-	N	V	V
	39.	149	13	12	-	N	V	V

Table 13-3 Biochemical blood patterns and findings on the serial scintigram in 39 non-jaundiced patients with parenchymal liver disease, including malignant involvement of the liver.

N=normal, V=visible, NV=non visible, O=operated.

In 38 patients of the patients investigated time-activity curves and functional images were generated ( table 13-4 ). Contrary to the other groups of discussed patients abnormality of the functional images in this series was also viewed for diffuse or focal disturbances.

In four patients no aberrations were found either in the time-activity curves or in the functional images ( no.: 4, 24, 26 and 31 ). Patient no. 31 showed a slight elevation of the alkaline phosphatase level and in the other three patients the biochemical blood parameters were normal.

In nine patients there was an agreement between the patterns of the time-activity curves and the findings in functional imaging. In six patients there were normal time-activity curves although the downslope functional images for one or both liver lobes were disturbed ( no.: 1, 2, 5, 14, 35 and 36 ). Patient no. 7 showed abnormal downslope images in spite of a normal time-activity curve and in addition an abnormal upslope image was also produced in spite of a normal maximum uptake time for the left liver lobe; the patient was suffering from an extensive steatosis of the liver.

In three patients existed disturbed downslope images in spite of normal half value times of the curves, however in these patients the maximum uptake time for the liver was delayed ( no.: 15, 27 and 30 ). In two of these patients ( no.: 15 and 27 ) the upslope image was normal although the maximum uptake time was slightly delayed. This latter finding was also seen in 14 other patients in whom the time-activity curve implied a delayed uptake of the reagent by the liver; the upslope functional image however was normal.

diagnosis	patient no.	T-max		T- $\frac{1}{2}$		Upslope		Downslope		
		right	left	right	left	right	left	right	left	
steatosis hepatitis	1.	9	9	17	20	N	N	A	A	F
	2.	11	14	29	26	N	N	A	A	D
	3.	13	15	L	L	N	N	A	A	F
	4.	11	12	24	25	N	N	N	N	
	5.	10	12	22	27	N	N	A	A	F
	6.	9	15	L	17	N	N	A	N	F
	7.	12	13	21	32	N	A	A	A	D
	8.	13	14	27	23	N	A	N	A	F
	9.	13	12	32	33	N	N	A	A	F
	10.	14	23	L	L	N	N	A	A	D
cirrhosis	11.	18	17	L	L	N	N	A	A	D
reactive hepatitis	12.	9	12	20	33	N	N	A	A	F
	13.	-	-	-	-	-	-	-	-	-
	14.	9	9	18	18	N	N	N	A	F
	15.	14	14	20	L	N	N	A	A	D
drug induced hepatitis	16.	10	11	34	32	N	N	A	A	D
	17.	13	19	22	L	N	N	A	A	F
	18.	13	10	L	34	N	N	A	A	D
	19.	22	36	L	L	N	N	N	A	F
	20.	15	13	L	L	N	N	A	A	D
chronic hepatitis	21.	14	15	L	L	N	N	A	A	D
	22.	23	14	L	L	N	N	A	A	D
	23.	23	33	L	L	N	N	A	A	F
siderosis	24.	3	10	19	17	N	N	N	N	
aspecific liver function disturbance	25.	14	15	L	L	N	N	A	A	F
	26.	6	11	27	24	N	N	N	N	
	27.	15	19	23	35	N	N	A	A	D
	28.	16	19	L	17	N	N	A	N	F
	29.	15	14	L	23	N	N	A	A	D
	30.	19	AC	27	AC	A	A	A	A	D
	31.	12	11	22	23	N	N	N	N	
	32.	30	33	L	L	N	N	A	A	D
malignant liver involvement	33.	AC	AC	AC	AC	N	A	A	A	D
	34.	15	18	30	L	N	N	A	A	F
	35.	9	8	23	22	N	N	N	A	F
	36.	8	10	27	30	N	N	A	A	D
	37.	21	AC	L	A	N	N	A	A	F
	38.	14	26	31	L	N	N	A	A	F
	39.	4	32	L	L	N	N	A	A	F

Table 13-4 Computer data of 39 non-jaundiced patients with parenchymal liver disease, including malignant involvement of the liver.

AC=ascending curve, L=lengthened, N=normal, A=abnormal, F=focal, D=diffuse. T-max and T- $\frac{1}{2}$  are in minutes.

Table 13-5 shows the other diagnostic investigations performed in this group of patients with parenchymal disturbance of the liver.

no. patients	diagnostic investigation	visualisation of liver and/or biliary tract	
		success	failure
27	percutaneous liver biopsy	27	-
25	colloid liver scintigraphy	25	-
6	abdominal plain film	-	-
12	oral cholecysto- graphy	9	3
10	intravenous cholangiography	7	3
4	ultra sound study	4	-
1	arteriography	1	-
3	laparoscopy	3	-

Table 13-5 Diagnostic investigation in 39 non-jaundiced patients with liver parenchyma disturbance.

One patient with failure to visualise the gallbladder in oral cholecystography was suffering from liver cirrhosis ( table 13-4 no.11 ). I.V.C. could not be performed in this patient because he was allergic for intravenously administered contrast material.

Two patients with non-visualisation of the gallbladder on oral cholecystography also showed no gallbladder on intravenous cholangiography ( no. 23 and 24 ). The non-visualisation of the gallbladder could not be confirmed by surgery.

Intravenous cholangiography showed in one patient, suffering from aspecific liver function disturbance ( no. 28 ), excretion of the contrast material by the kidneys and a very poor visualisation of the bile ducts.

Table 13-6 compares the results of cholescintigraphy and the results of some investigations in diagnosing a parenchymal disturbance of the liver.

no. patients	diagnostic investigation	no abnormalities	correct diagnosis	other diagnosis
27	percutaneous liver biopsy	2 (5)	20	-
25	colloid liver scintigraphy	9	15	1
4	ultra sound study	3	-	1
3	laparoscopy	2	1	-
38	cholescintigraphy	4	34	-

Table 13-6 Frequency of correct diagnosing of investigations in non-jaundiced patients with parenchymal liver disease.

Colloid liver scintigraphy was performed in 25 patients. In 16 patients the scintigraphic findings were suspected for pathology of the liver i.e. enlarged liver, inhomogeneous distribution of the radiocolloid and/or space occupying processes. In one patient a lesion in the right liver lobe was suspected; this could not be confirmed.

Percutaneous liver biopsy showed no abnormalities in two patients: one patient was suffering from reactive hepatitis, another had multiple metastases in the liver. In five patients liver biopsy showed atypical patterns; no diagnosis could be made on the specimen obtained (table 13-6 between brackets).

Ultra sound study showed no aberrations in three patients suffering respectively from steatosis, chronic hepatitis and metastases. In one patient an ultra sound study was positive for multiple cystic processes but surgery showed multiple solid metastases in the liver.

Cholescintigraphy showed no aberrations in 4 patients, either in the serial scintigram or in time-activity curves or functional images. In all other patients there was a disturbed downslope phase in functional imaging in spite of a normal intestinal excretion of the reagent on the serial scintigram. Time-activity curves were also normal in 7 patients in whom functional imaging showed a disturbed excretion phase.

#### *13.2.1. Discussion.*

The results of the study revealed the following patterns of cholescintigraphy in patients with biochemical indications of liver function disturbance without jaundice.

##### **Serial scintigraphy:**

All patients showed normal intestinal excretion. No persistent blood pool activity was observed. Bile ducts were visible in 90% of the patients studied. In 86% of the patients with malignant involvement of the liver the serial scintigram showed no abnormalities. In 14% space occupying processes were observed.

##### **Computer data:**

In one patient no computer data could be obtained because of technical disorder of the computer.

Time-activity curves:

34% of the patients studied showed normal maximum uptake time and normal half value time for both liver lobes.

- normal T-max for both liver lobes was observed in 47% of the patients studied.
- delayed T-max for both liver lobes was observed in 24%.
- delayed T-max for only the right liver lobe was observed in 16%.
- delayed T-max for only the left lobe was observed in 5%.
- ascending curve for both liver lobes was observed in 3%.
- ascending curve for left lobe and delayed T-max for right lobe was observed in 5%.
- normal  $T-\frac{1}{2}$  for both liver lobes was observed in 34% of the patients studied.
- lengthened  $T-\frac{1}{2}$  for both liver lobes was observed in 34%.
- lengthened  $T-\frac{1}{2}$  for only the right lobe was observed in 11%.
- lengthened  $T-\frac{1}{2}$  for only the left lobe was observed in 13%.
- ascending curve for both liver lobes was observed in 3%.
- ascending curve for left liver lobe was observed in 5%.

Functional imaging:

- the upslope and downslope images were normal for both liver lobes in 10%.
- the upslope and downslope images were abnormal for both liver lobes in 3%.
- the upslope images normal, downslope images abnormal for both liver lobes in 66%.
- the downslope image was abnormal for one of the liver lobes when other functional images were normal in 13%.
- the upslope image was normal for the right liver lobe whilst other images were abnormal in 5%.
- the upslope and downslope image of the right lobe were normal whilst upslope and downslope image of the left lobe were abnormal in 3%.



#### Clinical reliability:

All patients in this study showed a normal intestinal excretion on the serial scintigram; diagnosing parenchymal liver disease on the serial scintigram only was not possible in this study. The computer data showed an indication of bile duct obstruction in 8% of the patients studied whilst no liver function disturbance was indicated in 10% of the patients studied. The success rate for the computer data in diagnosing liver parenchyma disturbance was therefore 82%.

In comparison the success rate in diagnosing parenchymal disease was for percutaneous liver biopsy 74%, for colloid liver scintigraphy 60%, for laparoscopy 33%. Ultra sound could not diagnose parenchymal disease in the patients studied.

### 13.2.2. CASE HISTORIES

Case history no. 17.

A 45-year-old female was admitted because of slight biochemical liver function disturbance and an enlarged liver. There was a prior history of alcohol abuse.

Laboratory findings: Total bilirubin 15  $\mu\text{mol/l}$ , direct reacting bilirubin 2  $\mu\text{mol/l}$ , alkaline phosphatase 136  $\text{mU/ml}$ , S.G.O.T. 42  $\text{mU/ml}$ , S.G.P.T. 24  $\text{mU/ml}$ .

Colloid liver scintigraphy: Enlarged liver with inhomogeneous activity distribution; space occupying processes could not be excluded.

Cholescintigraphy

serial scintigram:  
( figure 13-1 )

Enlarged liver, visibility of intrahepatic bile ducts and gallbladder, inhomogeneous distribution of the radiopharmaceutical. Normal intestinal excretion of the reagent.

time-activity curves:  
( figure 13-2 )

Normal uptake and excretion patterns.

functional images:  
( figure 13-3 )

Disturbed uptake left liver lobe, slight disturbed excretion phase right liver lobe, strongly disturbed excretion left liver lobe.

conclusion:

Suspicion of liver parenchyma disturbance.

Liver biopsy:

Alcoholic hepatitis and steatosis.

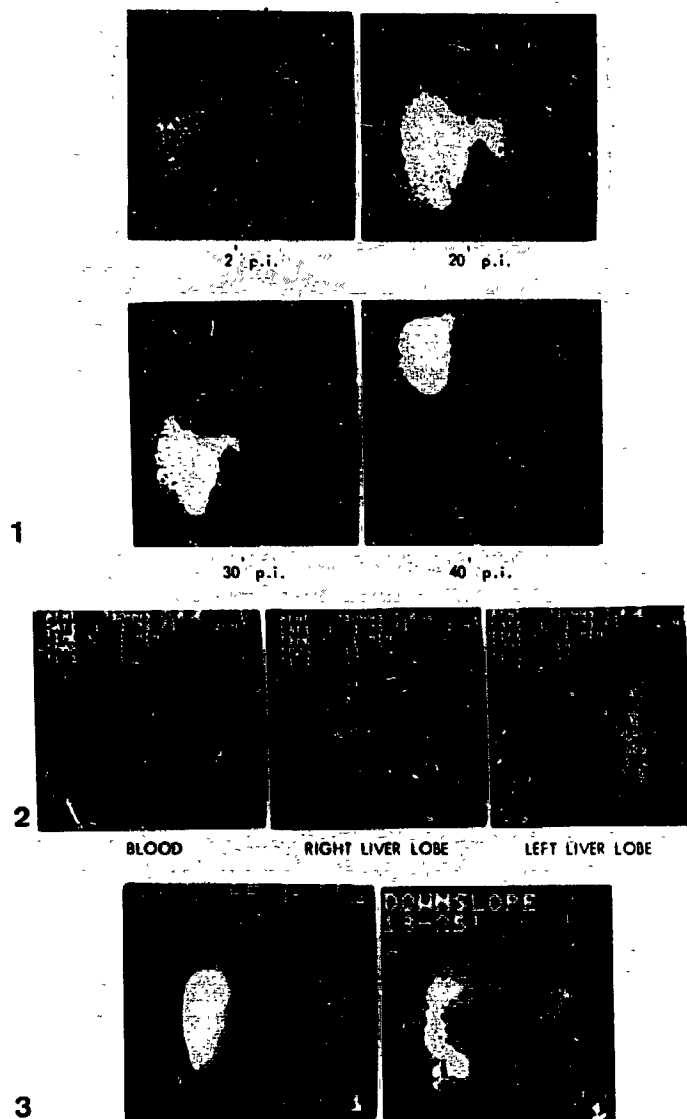


Fig. 13:1-3 Cholescintigraphy in a patient with alcoholic hepatitis and steatosis.

Case history no. 18.

A 56-year-old male was admitted because of enlarged liver and disturbed liver biochemistry.

Laboratory findings:	Total bilirubin 13 $\mu\text{mol/l}$ , direct reacting bilirubin 2 $\mu\text{mol/l}$ , alkaline phosphatase 301 $\text{mU/ml}$ , S.G.O.T. 25 $\text{mU/ml}$ , S.G.P.T. 23 $\text{mU/ml}$ , gamma-G.T. 136 $\text{mU/ml}$ .
Colloid liver scintigraphy:	Enlarged liver, no further aberrations.
Cholescintigraphy	
serial scintigram: ( figure 13-4 )	Good visualisation of the liver, gallbladder and bile ducts. Normal intestinal excretion of the reagent.
time-activity curves: ( figure 13-5 )	Slightly delayed maximum uptake time in the right liver lobe, normal maximum uptake time in left liver lobe, lengthened half value time in both liver lobes.
functional images: ( figure 13-6 )	Upslope image showed normal uptake phase, downslope image showed diffuse disturbed excretion phase.
conclusion:	Suspicion of diffuse liver parenchyma disturbance.
Liver biopsy:	Chronic active hepatitis.

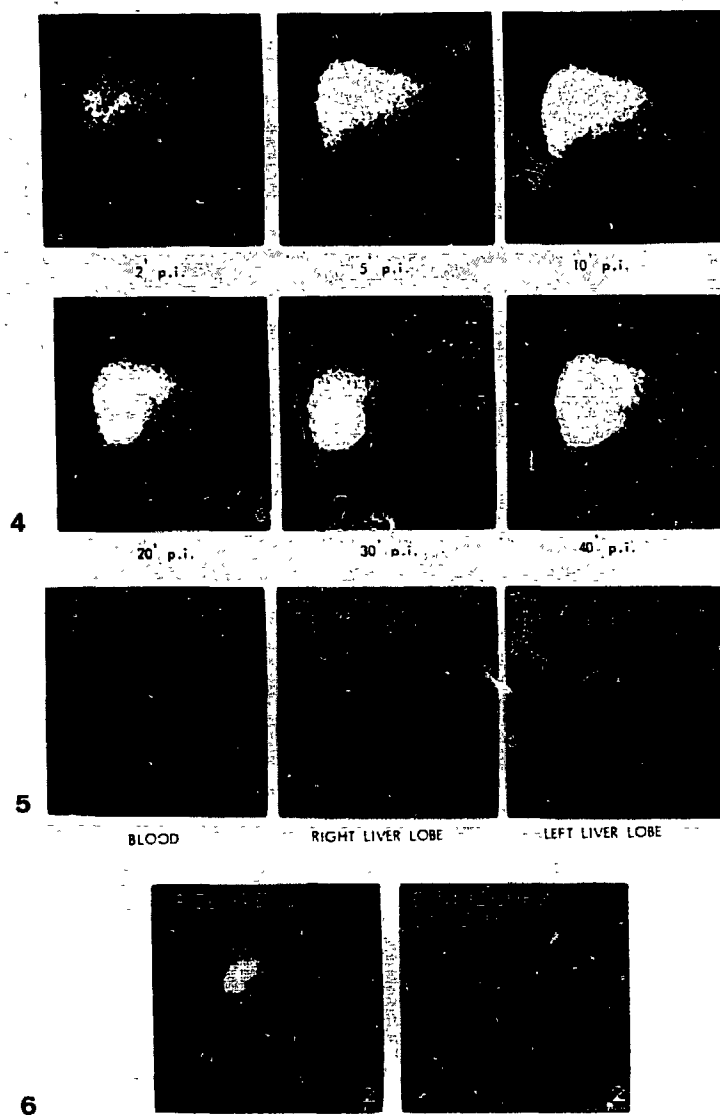


Fig. 13:4-6 Cholescintigraphy in a patient with chronic active hepatitis.

Case history no. 19.

A 58-year-old female was admitted because of disturbed liver biochemistry.

Laboratory findings:	Total bilirubin 13 $\mu\text{mol/l}$ , direct reacting bilirubin 2 $\mu\text{mol/l}$ , alkaline phosphatase 85 $\text{mU/ml}$ , S.G.O.T. 152 $\text{mU/ml}$ , S.G.P.T. 220 $\text{mU/ml}$ .
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Cholescintigraphy

serial scintigram:  
( figure 13-7 )

Good visualisation of the liver, bile ducts and gallbladder:

Normal intestinal excretion of the radiopharmaceutical.

time-activity curves:  
( figure 13-8 )

Normal maximum uptake time for both liver lobes, lengthened half value time for both liver lobes.

functional images:  
( figure 13-9 )

Upslope image shows normal uptake phase, downslope image shows general disturbed excretion phase.

conclusion:

Suspect for liver parenchyma disturbance.

Liver biopsy:

Patterns suspect for a drug-induced hepatitis.

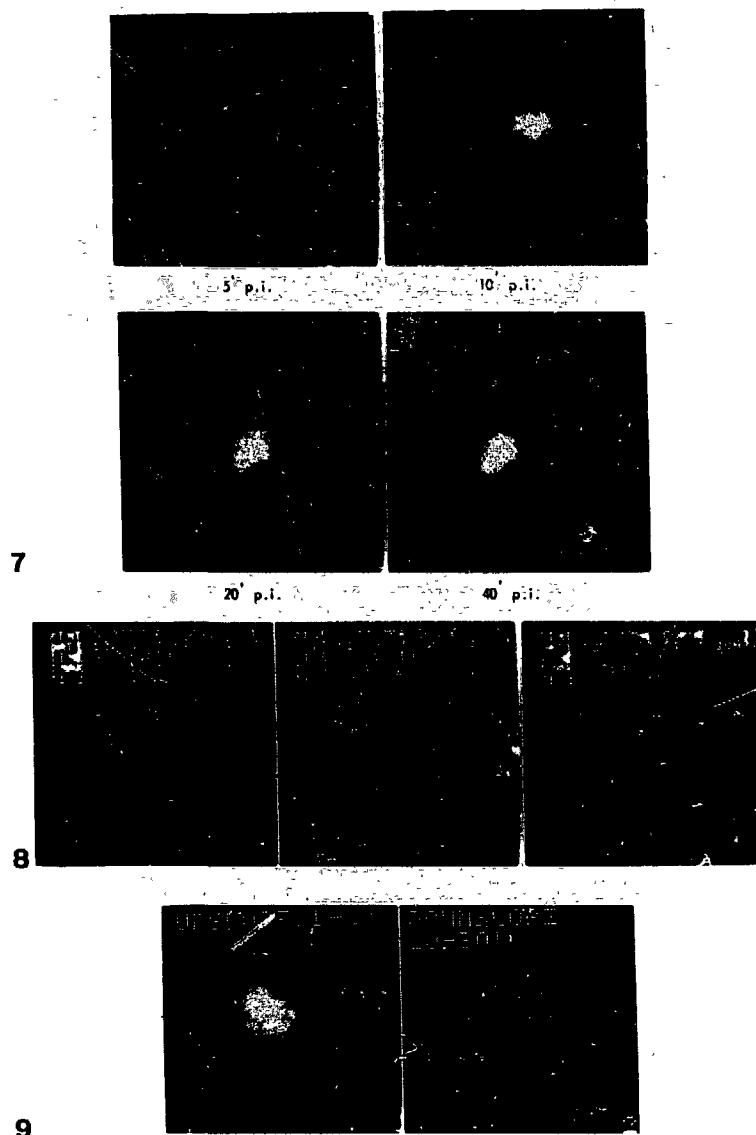


Fig. 13:7-9 Cholescintigraphy in a patient with a drug induced hepatitis.



Case history no. 20.

A 68-year-old male was admitted because he was suffering from progressive pain in the upper abdomen. Earlier he had been operated upon a carcinoma of the colon.

Laboratory findings: Total bilirubin 12  $\mu\text{mol/l}$ , direct reacting bilirubin 2  $\mu\text{mol/l}$ , alkaline phosphatase 500  $\text{mU/ml}$ , S.G.O.T. 52  $\text{mU/ml}$ , S.G.P.T. 44  $\text{mU/ml}$ .

Colloid liver scintigraphy: Suspect for a space occupying process in left liver lobe.

Cholescintigraphy  
serial scintigram:  
( figure 13-10 )

Good visualisation of the liver, gallbladder and common bile duct. Intestinal excretion of the radiopharmaceutical 6 hours after administration.

time-activity curves:  
( figure 13-11 )

Ascending curve for both liver lobes during the total time of the study.

functional images:  
( figure 13-12 )

Upslope image shows slightly disturbed uptake in right liver lobe, and strongly disturbed uptake in the left liver lobe. Downslope image was disturbed demonstrating a generally disturbed excretion phase.

conclusion:

Diffuse liver parenchyma involvement, space occupying process in left liver lobe, bile duct obstruction.

Liver biopsy: Congested liver cells, no tumour found.  
 Post mortem investigation: Diffuse liver metastases and  
 metastasis in liver hilus with subtotal obstruction of the  
 common hepatic duct. Also a cholangitis was found.

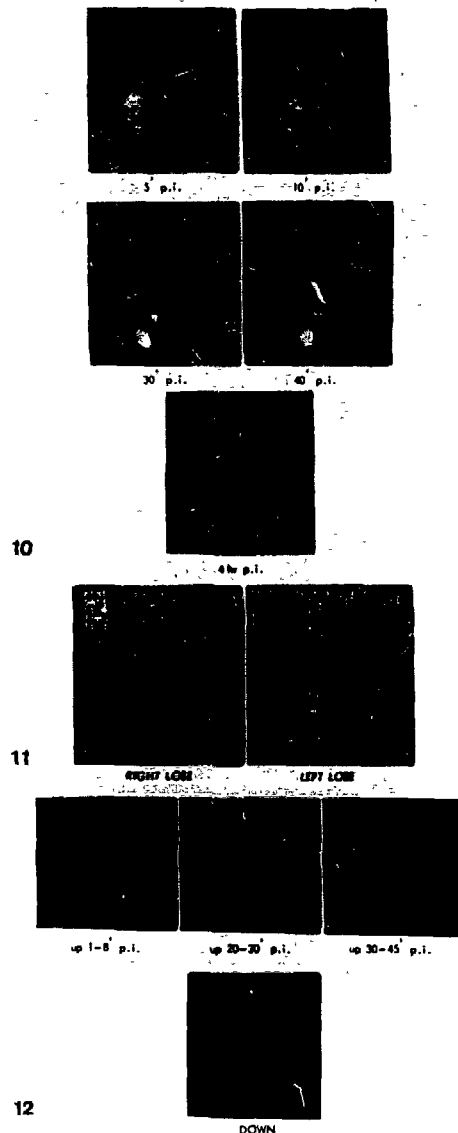


Fig. 13:10-12 Cholescintigraphy in a patient with diffuse liver metastases.

Case history no. 21.

A 66-year-old male was admitted because of a tumour in the upper abdomen.

Laboratory findings:	Total bilirubin 7 $\mu\text{mol/l}$ , direct reacting bilirubin 2 $\mu\text{mol/l}$ , alkaline phosphatase 121 $\text{mU/ml}$ , S.G.O.T. 22 $\text{mU/ml}$ , S.G.P.T. 26 $\text{mU/ml}$ .
Abdominal plain film:	No aberrations.
Intravenous cholangiography:	No aberrations.
Arteriography:	Suspect for cystic lesions in right and left liver lobe but especially in the left liver lobe.
Colloid liver scintigraphy:	Great space occupying process in the left liver lobe, several lesions in the right liver lobe.
Ultra sound study:	Multiple cystic lesions.
Cholescintigraphy serial scintigram: ( figure 13-13 )	Good visualisation of the liver, gallbladder and common bile duct. Space occupying process in left liver lobe. Intestinal excretion of the radiopharmaceutical 6 hours after administration of the reagent.
cumulative image: ( figure 13-14 )	Space occupying lesion in left liver lobe. Lesion cranial in right liver lobe.
time-activity curves: ( figure 13-15 )	Lengthened maximum uptake time and half value time for the right liver lobe; ascending curve for the left lobe.

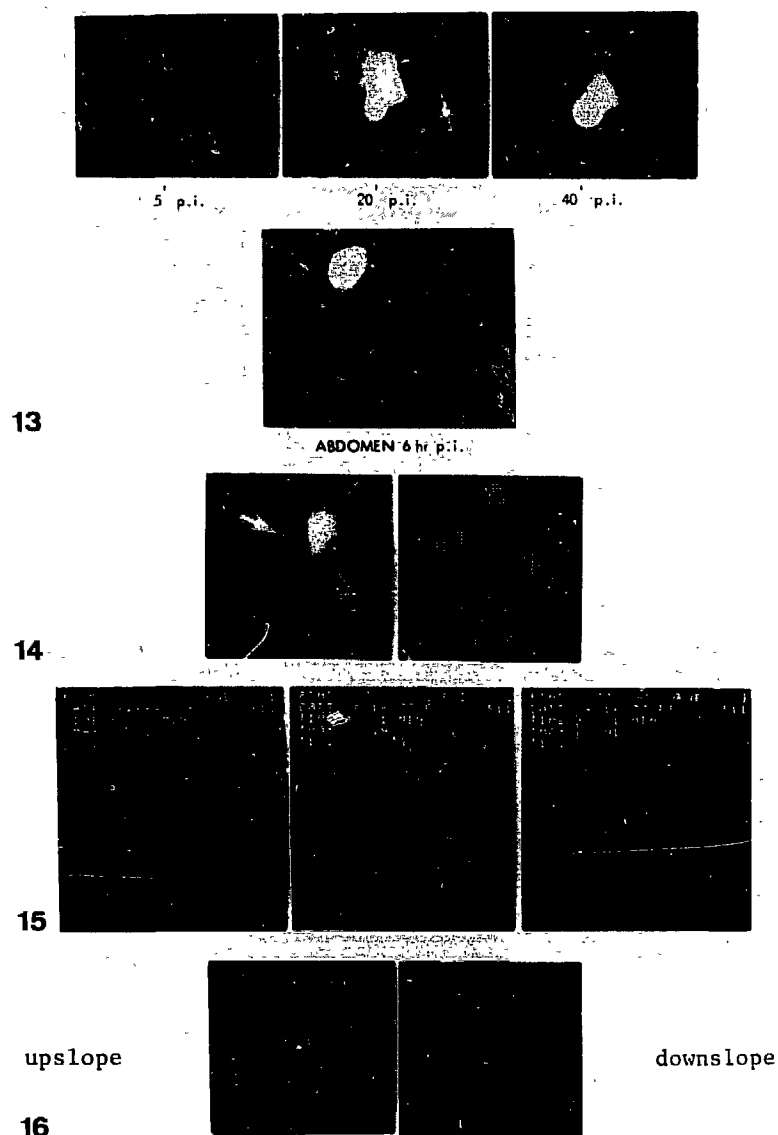


Fig. 13:13-16 Cholescintigraphy in a patient with several metastases in right and left liver lobe.

functional images:  
( figure 13-16 )

Upslope image shows a slightly disturbed uptake phase for the right liver lobe and a strongly disturbed uptake phase for the left liver lobe. Downslope image shows disturbed excretion phase for both liver lobes.

conclusion:

Parenchymal involvement right liver lobe, suspected for a tumour in left liver lobe.

Surgery:

In left liver lobe great metastasis from a leiomyosarcoma of the jejunum, in right liver lobe several little metastases.

Case history no. 22.

A 69-year-old male suffering from carcinoma of the larynx, was admitted because of weight loss and dehydration.

Laboratory findings:

Alkaline phosphatase 74 mU/ml,  
S.G.O.T. 9 mU/ml, S.G.P.T.  
8 mU/ml.

Ultra sound study:

Normal liver, normal gallbladder, space occupying process in pancreas.

Pancreascintigraphy:

Suspect for pancreas lesion.

Cholescintigraphy

serial scintigraphy:  
( figure 13-17 )

Good visualisation of the liver, bile ducts and gallbladder. No stimulation of the gallbladder took place; intestinal excretion of the radiopharmaceutical was observed after 6 hours post injection.

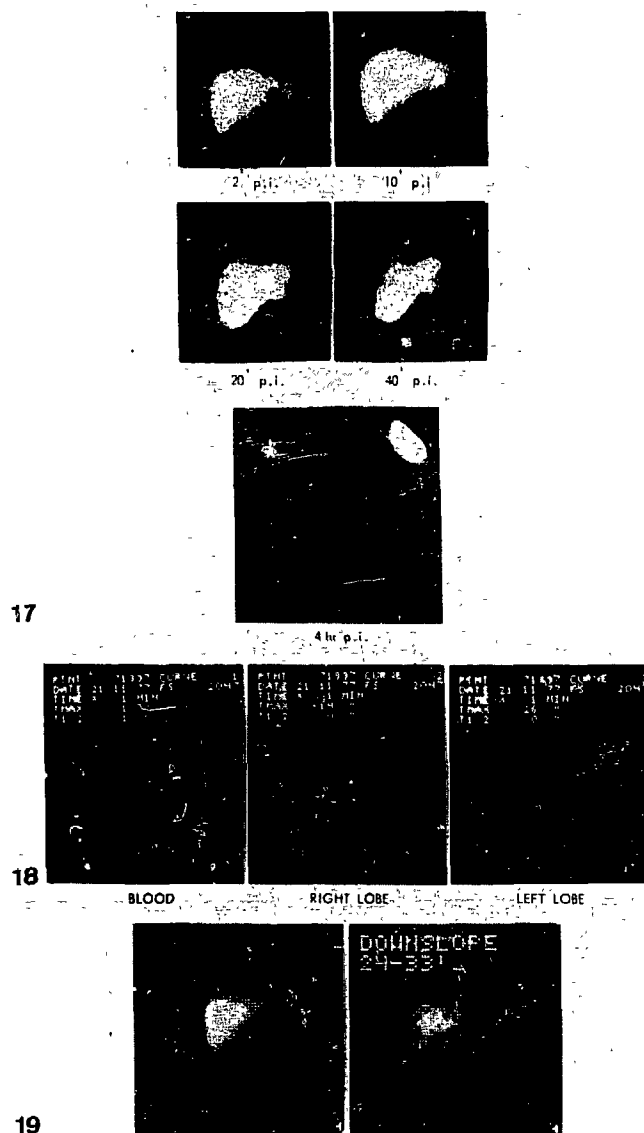


Fig. 13:17-19 Cholescincigraphy in a patient with metastases in right and left liver lobe.

time-activity curves:  
( figure 13-18 )

Normal uptake patterns for the right liver lobe, delayed maximum uptake time for the left liver lobe. Lengthened half value time for the right liver lobe and a very slow excretion for the left liver lobe.

functional images:  
( figure 13-19 )

Upslope image shows normal uptake phase for right and left liver lobe, downslope image shows slightly disturbed excretion phase for right liver lobe and strongly disturbed excretion phase for the left liver lobe.

conclusion:

Diffuse involvement of liver parenchyma; left liver lobe more disturbed than right liver lobe.

Surgery:

Tumour in pancreas and metastases in right and left liver lobe.

### *13.3. Results in patients with pathology of bile duct or gallbladder.*

The classification of the patients investigated with proven bile duct obstruction or gallbladder stones is shown in table 13-7 together with biochemical blood parameters and findings on the serial scintigram. In several of these patients cholescintigraphy was performed after improvement in the clinical condition and biochemical blood parameters. On admission some patients showed initial jaundice and all patients were admitted because of pain in right upper abdomen. As can be seen from

this table two patients show a delayed intestinal excretion of the radiopharmaceutical. In patient no.1 cholangiography performed during operation showed no entrance of contrast material into the duodenum. In patient no.4 only slight entrance of contrast from distal common bile duct into duodenum was observed. In this patient there was a stenosis due to a histologically benign tumour of distal common bile duct.

patient no.	diagnosis	alk.phosph. mU/ml	S.G.O.T. mU/ml	S.G.P.T. mU/ml	Y-G.T. mU/ml	serial scintigram		
						intestinal excretion	bile ducts	gallbladder
1.	stones in common bile duct	162	17	108	342	D	NV	NV
2.	stones in common bile duct	94	14	8	-	N	V	V
3.	cholangitis	107	16	15	-	N	NV	NV
4.	benigne tumour in common bile duct	210	65	138	-	D	V	O
5.	stone in right hepatic branche	64	10	10	-	N	V	V
6.	gallbladder stones	57	12	10	-	N	V	V
7.	gallbladder stones	68	19	24	-	N	V	NV
8.	gallbladder stones	87	21	119	-	N	V	V
9.	gallbladder stones	128	12	10	-	N	V	NV
10.	gallbladder stones	70	11	9	-	N	V	NV

Table 13-7 Classification of patients with pathology of the bile ducts or gallbladder with biochemical blood parameters and patterns on serial scintigram.

D=delayed, N=normal, NV=non-visualised, V=visualised, O=operated.



Stones in the gallbladder may cause non-visualisation of the gallbladder on the serial scintigram, although visibility of the gallbladder may occur in patients with gallstones.

In table 13-8 the results of time-activity curves and functional imaging are shown. In four patients there are normal time-activity curves and normal functional images ( no. 5, 7, 8 and 9 ). Two patients with obstruction in the common bile duct show ascending time-activity curves ( no. 1 and 4 ), in one patient the curve of left liver lobe showed a plateau ( no. 2 ). In two patients there were abnormal downslope images ( no. 3 and 6 ) in spite of normal time-activity curves. In two patients normal upslope functional images ( no. 6 and 10 ) were found in spite of abnormal uptake patterns in time-activity curves.

In patient no.3 in whom an abnormal excretion phase on the functional image was seen, intravenous cholangiography also showed excretion of contrast material by the kidneys. Although no definite information about liver parenchyma disturbance was obtained each of these patterns in cholescintigraphy and intravenous cholangiography is suspect for liver parenchyma disturbance. In patient no.6 intravenous cholangiography might also agree with liver parenchyma disturbance.

patient no.	T-max		T- $\frac{1}{2}$		Upslope		Downslope	
	right	left	right	left	right	left	right	left
1.	15	AC	L	AC	N	N	A	A
2.	20	22	L	P	N	N	A	A
3.	10	10	10	10	N	N	A	A
4.	AC	AC	AC	AC	N	N	A	A
5.	13	16	30	32	N	N	N	N
6.	16	12	19	25	N	N	A	A
7.	11	15	24	L	N	N	N	N
8.	8	11	22	20	N	N	N	N
9.	6	9	22	31	N	N	N	N
10.	18	36	27	L	N	N	N	A

Table 13-8 Time-activity curves and functional imaging in 10 non-jaundiced patients with pathology of biliary tract and gallbladder.

AC=ascending curve, L=lengthened, P=plateau, N=normal, A=abnormal.

In this group of patients, 22 other diagnostic investigations were performed. Table 13-9 shows the results of these investigations in relation to the diagnostic accuracy in answering the question whether the liver function disturbance was due to pathology of the biliary tract and/or the gallbladder. The results of the cholescintigraphic investigation in this group of patients are also given.

diagnostic investigation	no. patients	no. abnormalities	correct diagnosis	other diagnosis
oral cholecystography	2	-	1	1
intravenous cholangiography	10	-	9	1
abdominal plain film	2	2	-	-
ultra sound study	3	1	1	1
colloid liver scintigraphy	3	3	-	-
percutaneous liver biopsy	1	-	1	-
endoscopic cholangiography	1	-	1	-
cholescintigraphy	10	2	6	2

Table 13-9 Frequency of correct diagnosis of various diagnostic investigations in 10 non-jaundiced patients with pathology of bile ducts and/or gallbladder.

In one patient oral cholecystography and intravenous cholangiography showed no visualisation of gallbladder or common bile duct. The patient was clinical suspected of cholangitis; no obstruction in common bile duct or stones in the gallbladder could be demonstrated at surgery.

In one patient ultra sound showed a lesion in the right liver lobe; this could not be confirmed.

In 6 patients cholescintigraphy showed patterns which were in agreement with the final diagnosis.

In three patients ( no. 7,9 and 10 ) the serial scintigram patterns, which showed no visualisation of the gallbladder, were in agreement with the demonstration of gallbladder stones.

In two patients ( no. 5 and 8 ) serial scintigram patterns as well computer data showed no aberration although pathology could be demonstrated. In two patients the cholescintigraphic findings were indicative of parenchymal disease. Although this possibility could not be excluded the final diagnosis was cholangitis and gallbladder stones ( no. 3 and 6 ).

#### *13.3.1. Discussion.*

The results of the study revealed the following patterns of cholescintigraphy in patients with disorders of biliary duct or gallbladder. The group of patients is subdivided into patients with bile duct disorders and in patients with stones in the gallbladder.

##### *Serial scintigraphy*

All patients showed intestinal excretion of the radiopharmaceutical. No persistent blood pool activity was observed in the patients studied. Normal intestinal excretion with visibility of the bile ducts was observed in 80%. Delayed intestinal excretion without visibility of the bile ducts was observed in 20%.

Patients with gallbladder stones showed no visualisation of the gallbladder in 60%. In two patients with common bile duct obstruction and in whom the bile ducts could be visualised, dilated bile ducts were observed.

#### Computer data

Time-activity curves from patients with bile duct disorders.

- a normal maximum uptake time and half value time for both liver lobes was observed in 40%.
- an ascending curve for both liver lobes was found in 20%.
- delayed T-max for both liver lobes was observed in 20% of the patients studied.
- delayed T-max for right liver lobe and ascending curve for left lobe was observed in 20%.
- a lengthened T- $\frac{1}{2}$  for the right liver lobe was observed in 40%.
- an ascending curve or plateau for the left liver lobe only was observed in 40%.

#### Functional images

- normal upslope and downslope images for both lobes were observed in 20%.
- abnormal upslope and downslope images for both lobes were observed in 80%.

Time-activity curves from patients with gallbladder disorders.

- normal maximum uptake time and half value time was observed in 40%.
- delayed T-max for the right liver lobe only was observed in 20%.
- lengthened T- $\frac{1}{2}$  for the left lobe only was observed in 40%.

#### Functional images

- normal upslope and downslope images for both liver lobes were observed in 60%.
- abnormal downslope image for both liver lobes was observed in 20%.
- abnormal downslope image for the left liver lobe only was observed in 20%.

#### Clinical reliability.

Extrahepatic obstruction was suspected on the serial scintigram if there was visualisation of dilated bile ducts. In relation to this parameter in this series of patients extrahepatic obstruction was indicated on the serial scintigram alone in 20%. Extrahepatic obstruction could be diagnosed from the computer data if time-activity curves from one or both liver lobes showed a plateau or were ascending during the whole study. When serial scintigrams and computer data were combined the overall success rate for cholescintigraphy in diagnosing extrahepatic obstruction in patients with biochemical liver function disturbance without jaundice was 60%.

Gallbladder pathology could be identified if no gallbladder could be visualised on the serial scintigram and the computer data was normal in fasting patients. The success rate for diagnosing gallbladder pathology was therefore 20%.

The success rate in this study in diagnosing obstructive disease for intravenous cholangiography is 90% and for ultrasound study 33%.

### 13.3.2. CASE HISTORY

Case history no. 23.

A 77-year-old male was admitted because of pain in right upper abdomen.

Laboratory findings: Total bilirubin 10  $\mu\text{mol/l}$ , direct reacting bilirubin 2  $\mu\text{mol/l}$ , alkaline phosphatase 94  $\text{mU/ml}$ , S.G.O.T. 14  $\text{mU/ml}$ , S.G.P.T. 8  $\text{mU/ml}$ .

Intravenous cholangiography: Dilated common bile duct with stones; gallbladder with multiple stones.

Ultra sound study: Cystic process right liver lobe; no stones in gallbladder or common bile duct.

Colloid liver scintigraphy: No abnormalities.

Cholescintigraphy  
serial scintigram:  
( figure 13-20 )  
Clear liver visualisation with visibility of dilated bile ducts and common bile duct; visibility of gallbladder. No intestinal excretion was seen 50 minutes post injection; stimulation of the gallbladder was omitted.

time-activity curves:  
( figure 13-21 )  
Normal uptake patterns from right and left liver lobe; delayed excretion right liver lobe and the curve from the left liver lobe reaches a plateau.

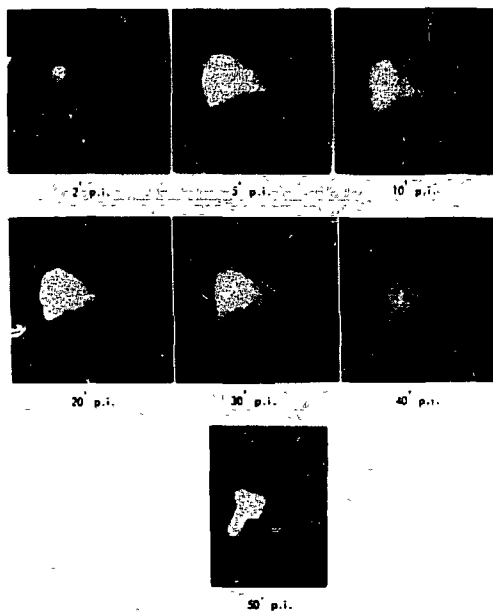
functional images:  
( figure 13-22 )  
Normal uptake phase; diffuse disturbed excretion phase.

conclusion:

Suspicion of common bile duct  
obstruction, diffuse liver  
parenchyma involvement.

Surgery:

Stones in common bile duct and  
gallbladder; liver metastases  
due to carcinoma of the prostate.



20

21

22

Fig. 13:20-22 Cholescintigraphy in a patient with stones in  
common bile duct and liver metastases.



#### *13.4. Results in patients with various other diseases.*

Cholescintigraphy was performed in three patients without biochemical pattern indicating liver function disturbance. Two showed defects on the colloid liver scintigram indicative of malignancy. Further investigation could neither confirm or refute the suspicion of malignancy; cholescintigraphy was performed in an attempt to obtain more information before the patients were operated upon. The third patient was suffering from multiple myeloma. Serum electrophoresis showed pathological proteins i.e. an increase of gamma- and beta-globulines. Cholescintigraphy was performed to investigate whether an increase of ( pathological ) proteins could prevent uptake of the radiopharmaceutical by the liver. Beside the cholescintigraphic investigation serum electrophoresis was carried out after injection of the reagent. No abnormal binding of the reagent to the proteins was found. In case histories no. 23, 24 and 25 the results in these patients are shown.

#### 13.4.1. CASE HISTORIES

Case history no. 23.

A 51-year-old female was admitted because of loss of weight and progressive tiredness. Physical examination revealed an enlarged liver.

Laboratory findings:	Total bilirubin 12.0 $\mu\text{mol/l}$ , alkaline phosphatase 35 mU/ml, S.G.O.T. 8 mU/ml, S.G.P.T. 8 mU/ml.
Oral cholecystography:	Several stones in the gallbladder.
Colloid liver scintigraphy:	Space occupying process in right liver lobe.
Ultra sound study:	Non-cystic lesion in right liver lobe.
Cholescintigraphy serial scintigram: ( figure 13-23 )	Good visualisation of an enlarged liver and intrahepatic bile ducts. No visualisation of the gall- bladder, normal intestinal excretion of the radiopharma- ceutical. Space occupying process in the right liver lobe.
time-activity curves: ( figure 13-24 )	Normal uptake patterns for both liver lobes, normal excretion pattern for the left liver lobe, delayed excretion pattern for the right liver lobe.
functional images: ( figure 13-25 )	Disturbed uptake phase for the right liver lobe, normal uptake phase left liver lobe. Disturbed excretion phase right liver lobe, slightly disturbed excretion phase left liver lobe.

conclusion:

Space occupying process in right  
liver lobe with functional  
capacities.

Laparoscopy and  
liver biopsy:

Great benign hemangioma of the  
right liver lobe.

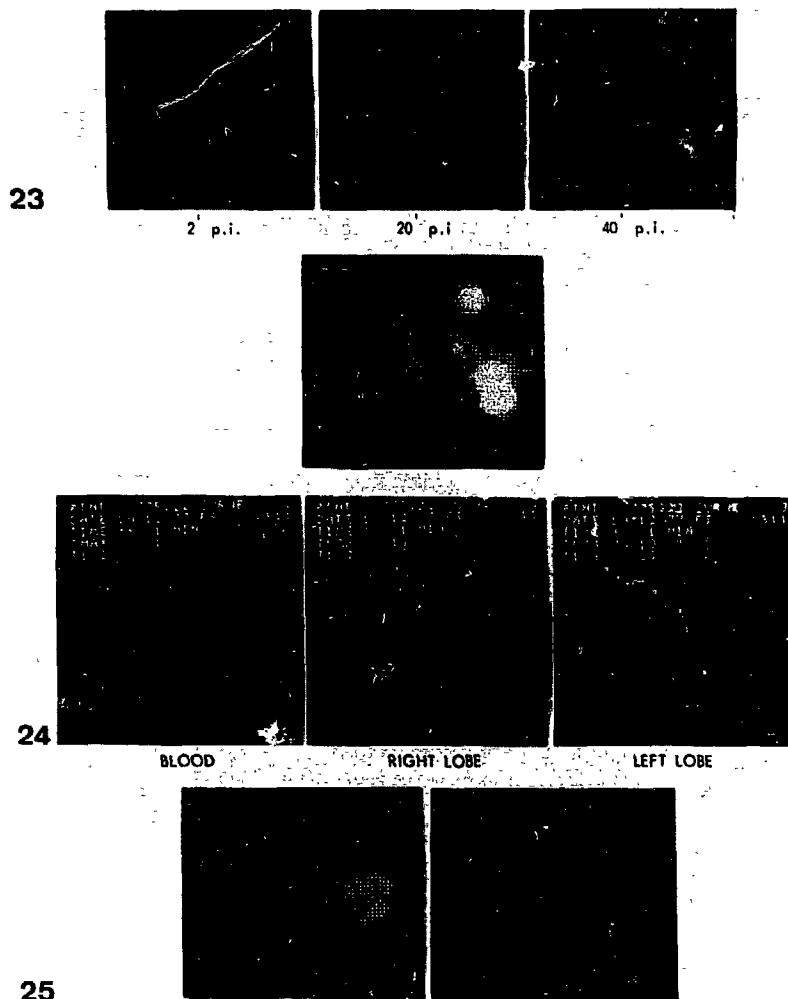


Fig. 13:23-25 Cholescintigraphy in a patient with a hemangioma  
of the right liver lobe.

Case history no. 24.

A 81-year-old female was admitted because of rheumatoid arthritis. Patient revealed no disturbed biochemical blood parameters indicative for liver or bile duct disease. Colloid liver scintigraphy was performed because of pain in right upper abdomen.

Diminished accumulation of activity in the gallbladder region was observed.

To evaluate this cold area and to exclude malignancy cholescintigraphy was performed.

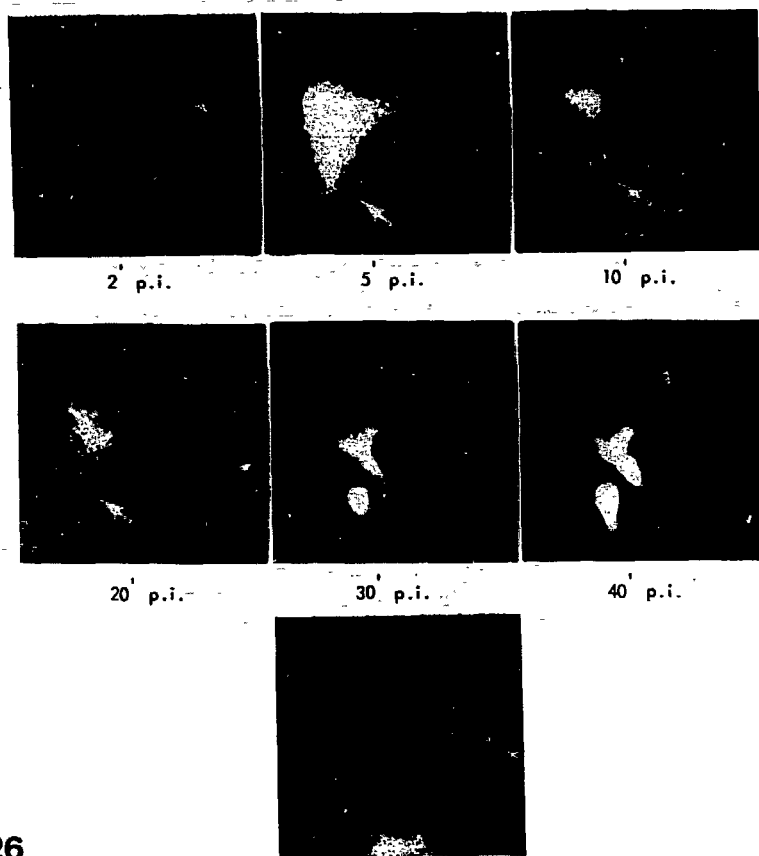
Cholescintigraphy

serial scintigraphy:  
( figure 13-26 )

Good visualisation of the liver and bile ducts. Until 20 minutes post injection the cold area in the gallbladder region is visible; after 30 minutes post injection the cold area is filled with activity indicating the gallbladder. No stimulation of the gallbladder took place; intestinal activity was observed 4 hours post injection.

conclusion:

The cold area seen on the colloid liver scintigram and in the early images of the serial scintigram is caused by the gallbladder.



26

Fig. 13:26 Normal serial scintigram of a patient with a cold area in the gallbladder region on the colloid liver scintigram.

Case history no. 25.

A 55-year-old female was hospitalized because of multiple myeloma. Serum electrophoresis demonstrated an increase of gamma globulines showing the characteristic spike.

A half year earlier patient showed slightly disturbed liver biochemistry; at the moment of investigation the biochemical blood parameters indicative for liver function were normal.

Intravenous cholangiography showed no abnormalities.

Cholescintigraphy was performed to be informed about parenchymal disturbance and to study if the reagent would be bound to an excess of ( abnormal ) proteins.

Cholescintigraphy

serial scintigram:  
( figure 13-27 )

Good visualisation of liver, bile ducts and gallbladder. No stimulation of the gallbladder took place. Intestinal activity was observed 24 hours post injection.

time-activity curves:  
( figure 13-28 )

Normal uptake patterns for both liver lobes; normal excretion pattern for left liver lobe. Slightly lengthened half value time for right lobe.

functional images:  
( figure 13-29 )

Normal uptake phase for both liver lobes, slightly disturbed excretion phase right liver lobe, normal excretion phase left liver lobe.

conclusion:

Slightly disturbed parenchyma right liver lobe. Normal cholescintigraphic performance in spite of an excess of proteins. Electrophoresis of the serum after administration of the radiopharmaceutical revealed no abnormal findings.

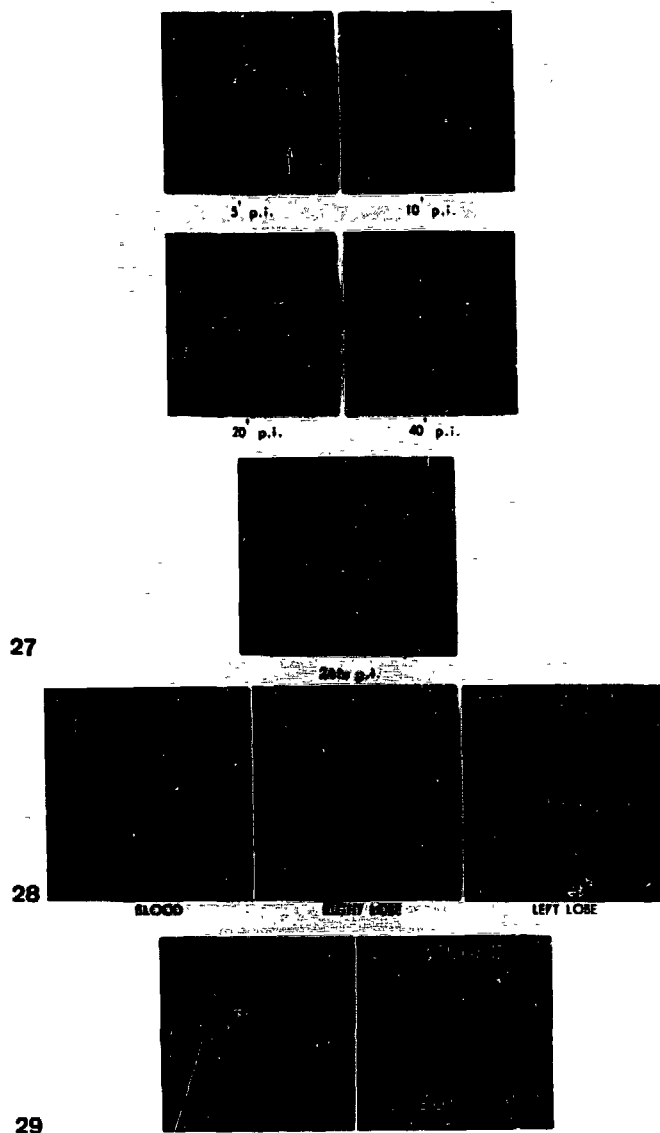


Fig. 13:27-29 Cholescintigraphy in a patient with abnormal serum proteins due to multiple myeloma.



### *13.5. Three additional case histories.*

The results of serial scintigraphy in three additional cases are demonstrated in case histories no. 26, 27 and 28.

These reports permit the following conclusions:

Cholescintigraphy has to be performed in a fasted patient, Cholescintigraphy can give additional information about dubious lesions observed on the colloid liver scintigram, Cholescintigraphy can test the passage of bilio-digestive anastomoses.

#### **Case history no. 26.**

In figure 13-30 the serial scintigram of a person without disease of liver or biliary tract is demonstrated. There is a good visualisation of the liver, bile ducts and intestinal activity. No gallbladder was observed.

In figure 13-31 the repeated investigation is demonstrated when the patient was fasted. In constrast to the former serial scintigram the gallbladder is well visualised.

This finding demonstrates the necessity of performing cholescintigraphy only in a fastened patient because otherwise no conclusion can be drawn from non-visualisation of the gallbladder.

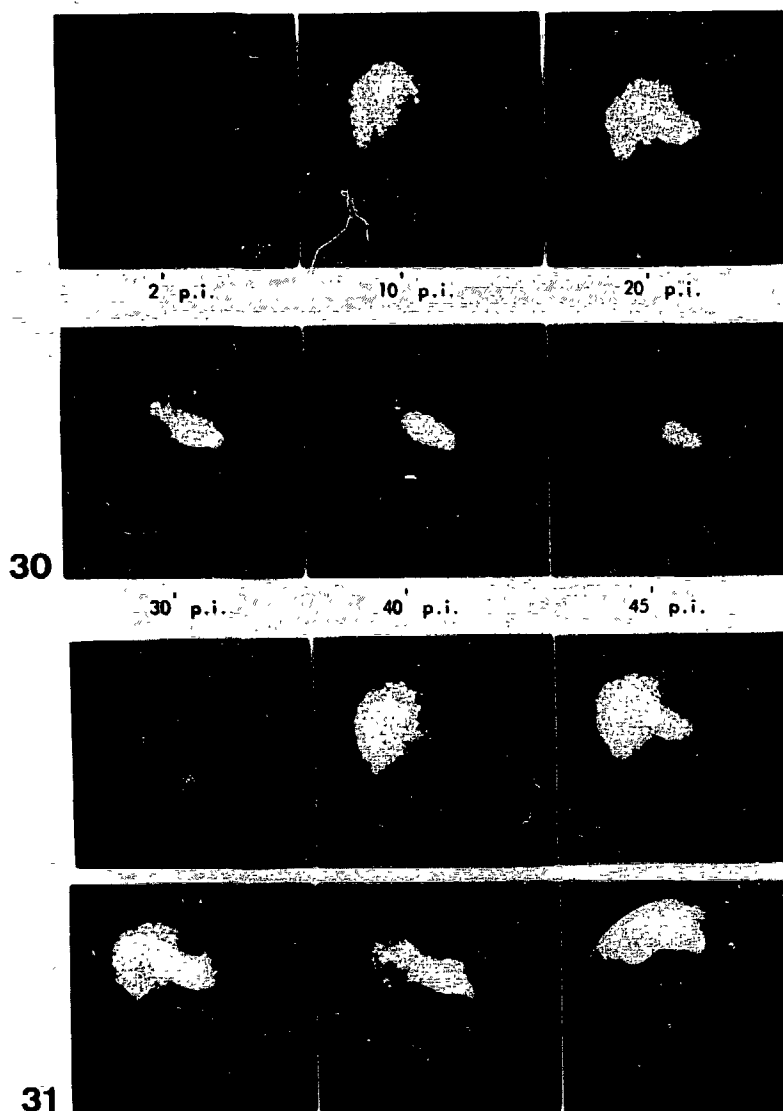


Fig. 13:30 Serial scintigram of a non-fasted patient without liver or biliary tract disease.

Fig. 13:31 Serial scintigram of the same patient when he was fasted.

Case history no. 27.

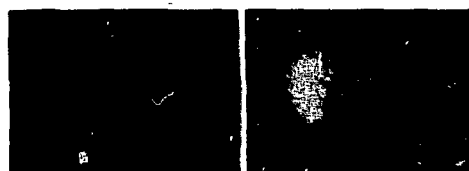
A 89-year-old male was admitted because of pain in right upper abdomen and slight jaundice.

Laboratory findings:	Total bilirubin 24 $\mu\text{mol/l}$ , direct reacting bilirubin 13 $\mu\text{mol/l}$ , alkaline phosphatase 219 $\text{mU/ml}$ , S.G.O.T. 16 $\text{mU/ml}$ , S.G.P.T. 17 $\text{mU/ml}$ .
Abdominal plain film:	No aberrations.
Intravenous cholangiography:	Dilated common bile duct, no gallbladder visible.
Colloid liver scintigraphy: ( figure 13-32 )	Enlarged liver, inhomogeneous distribution of radio activity, suspicion of a space occupying process in liver hilus.
Cholescintigraphy serial scintigram: ( figure 13-33 )	Good visualisation of the liver, dilated bile ducts, good visualisation of the gallbladder. No stimulation of the gallbladder took place. Intestinal activity 4 hours post injection.
time-activity curves: ( not demonstrated here )	Ascending curve for both liver lobes.
conclusion:	Suspicion of common bile duct obstruction.
Surgery:	Stone in common bile duct, dilated bile ducts, no space occupying processes in liver hilus.

The suspicion of a space occupying process in the liver observed on the colloid liver scintigram could not be confirmed by surgery. Findings on serial scintigram make it probable that this findings is caused by dilated bile ducts.



32



2' p.i.

5' p.i.



10' p.i.

20' p.i.



30' p.i.

40' p.i.

33

Fig. 13:32-33 Colloid liver scintigram and serial scintigram of a patient with dilated bile ducts and stone in the common bile duct.

Case history no. 28.

A 28-year-old female was operated upon because of progressive jaundice due to an islet cell carcinoma of the pancreas. Figure 13-34 shows the computer display of the serial scintigram before surgery. There is a bad visualisation of the liver with persistent high blood pool activity and renal excretion of the radiopharmaceutical. No intestinal excretion was observed after 40 minutes and 24 hours post injection.

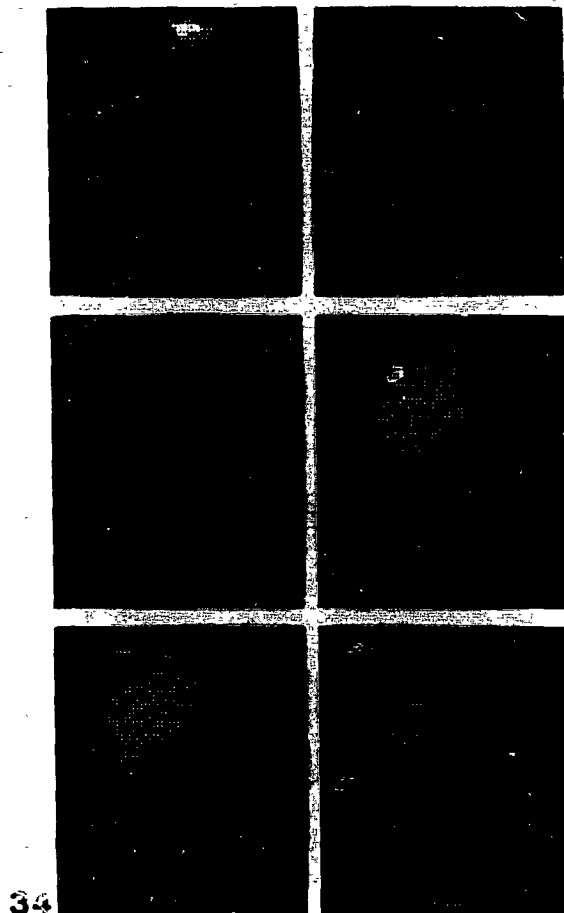


Fig. 13:34 Computer display of a serial scintigram of a patient with bile duct obstruction due to islet cell carcinoma of the pancreas.

Figure 13-35 shows the computer display of the serial scintigram after surgery. To relief jaundice cholecysto-jejunostomy was performed. There is a good visualisation of the liver, bile ducts and the bilio-digestive anastomosis and therefore a good improvement in comparison with the former study.

Cholescintigraphy can be performed to test the function and passage via bilio-digestive anastomosis.

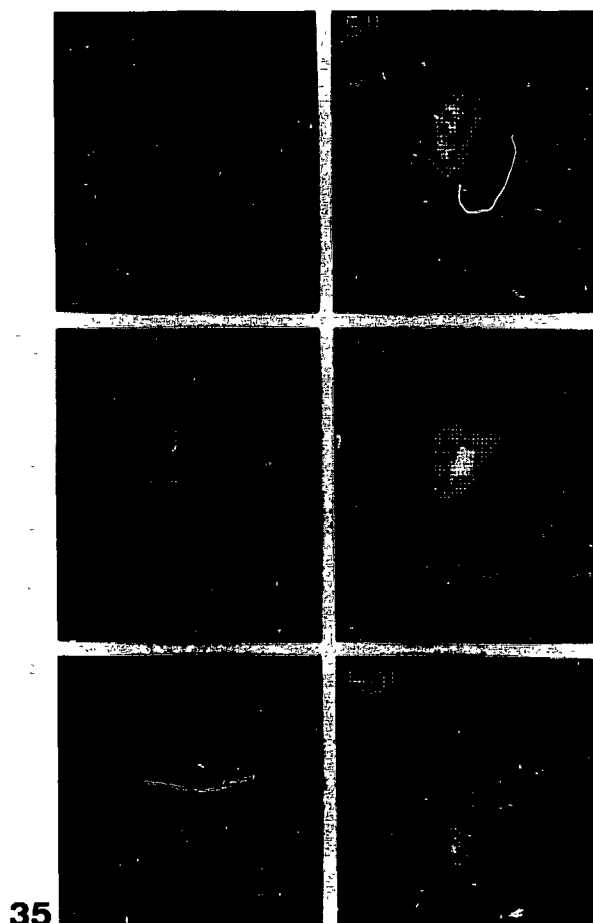


Fig. 13:35 Computer display of the serial scintigram of the patient from fig. 13:34 after performing cholecysto-jejunostomy.

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#### CHAPTER XIV.

#### DISCUSSION AND CONCLUSIONS.

Diethyl-acetanilido iminodiacetic acid is a hepatobiliary agent that is cleared from the blood by the polygonal cells of the liver and excreted via the biliary system into the intestines. In cholescintigraphy the labelled reagent is used for measurement of hepatocyte function and in establishing hepatobiliary disorders. Animal studies reveal a very rapid clearance from the blood, the distribution in the liver and a rapid excretion via the bile ducts into the intestine. The extraction from the blood in man by the liver cells, the transit through the liver cells and the excretion of the reagent into the bile is slightly slower than in rats, nevertheless in normal individuals information about liver and bile system can be provided within 45 minutes after administration of the reagent.

In contrast to routinely used radiologic investigations as intravenous cholangiography and oral cholecystography, the applicability of cholescintigraphy is less dependent on the serum bilirubin level. Intravenous cholangiography is not able to visualise the bile system when the serum bilirubin value exceeds 60  $\mu\text{mol/l}$ , whilst in cholescintigraphy bile duct visualisation is possible up to 150  $\mu\text{mol/l}$  and intestinal excretion of the radiopharmaceutical is possible up to bilirubin levels of 400  $\mu\text{mol/l}$ .

In this thesis cholescintigraphic investigation encompassed serial scintigraphy with analogue images supplemented with cumulative images, time-activity curves and functional images generated from computer data.

The serial scintigrams obtained from normal individuals showed liver, bile ducts, gallbladder and intestinal excretion within 45 minutes post injection. Blood pool activity and renal excretion of the reagent can be observed, however when still present 5 minutes post injection, they may indicate impaired liver function and/or bile duct obstruction. The degree of intestinal excretion of the radiopharmaceutical and the persistence of blood pool activity can be used to a certain extent as a parameter in the diagnosis of obstructive or parenchymal liver disease.

Complete obstruction patterns were observed in 30 jaundiced patients studied. From these 30 patients 93.3% were suffering from an obstructive process in the hepatic duct or common bile duct; the rest of the patients were suffering from diffuse metastatic disease in the liver. In complete obstruction persistence of slight or high blood pool activity can be observed. Complete obstruction did not occur in patients with jaundice due to parenchymal disease or in patients with liver and biliary tract disease without jaundice.

Delayed intestinal excretion of the radiopharmaceutical could be observed in patients with obstructive disease as well as in patients with parenchymal disease. In 9% of all 151 patients studied delayed intestinal excretion was due to an obstructive process in the hepatic duct or common bile duct. In another 9% of all patients studied the delayed intestinal excretion was due to jaundiced patients with parenchymal liver disease and malignant involvement of the liver.

All patients with delayed intestinal excretion due to an obstruction showed none or slight persistence of blood pool activity. On the other hand in 77% of the patients with delayed intestinal excretion due to parenchymal or malignant liver disease a persistence of a high blood pool activity was observed.



Delayed intestinal excretion did not occur in patients with liver function disturbance without jaundice nor in patients with disorders of the gallbladder.

It can be deduced from this study that normal intestinal excretion of the radiopharmaceutical was present in patients with non-malignant common bile duct obstruction, patients with parenchymal disease and in patients with a malignant involvement of the liver. In 20% of the patients with bile duct obstruction and in 33% of the patients with jaundice due to parenchymal disease a persistence of a slight blood pool activity was observed. Solely normal intestinal excretion was observed in non-jaundiced patients with liver function disturbance and/or malignant involvement of the liver as well in all patients with non-malignant disorders of the gallbladder. Not a single case with normal intestinal excretion was observed in patients with a malignant obstructive process in the hepatic duct or common bile duct.

There are still some other patterns on the serial scintigram which can contribute to the diagnosis. A persistent cold area in the liver is suspect for a space occupying process. Dilated bile ducts or a clear interruption in the common bile duct is suspect for a bile duct obstruction. When the gallbladder is not visualised on the serial scintigram of a fasted patient without previous cholecystectomy it is suspect for a gallbladder disorder and/or obstruction of the cystic duct.

Only a limited number of patterns on the serial scintigram can be used in distinguishing obstructive disease from disorders of the liver parenchyma. With the aid of the computer it is possible to provide additional information.

The cumulative image provides a clear image of the liver and bile duct system and can support information about the presence of dubious aberrations observed on the serial scintigram.

This can be useful in patients with suspected space occupying lesions in the liver or interruptions in the common bile duct. Generated time-activity curves show distinct patterns for several liver and bile duct disorders. From this study it can be concluded that in patients with an obstructive disease the maximum uptake time for one or both liver lobes is usually delayed even more often than in patients with a parenchymal liver disease. However two typical patterns of the time-activity curves were exclusively observed in patients with an obstruction in the hepatic duct or common bile duct. The curve shows a continuously ascent during the whole study or a plateau following the maximum uptake time. One or both liver lobes can show these patterns.

Functional imaging is able to provide additional information, especially in patients with normal uptake and/or excretion patterns in the time-activity curves.

The study revealed that in 14% of all patients with parenchymal disease functional imaging showed a disturbed uptake phase whilst uptake patterns in the time-activity curves were normal. In 23% of these patients functional imaging showed a disturbed excretion phase in spite of normal excretion patterns in the time-activity curves.

In patients with an obstructive disease normal uptake patterns in the time-activity curves and disturbed uptake phase in functional imaging was observed in 6% of the patients studied and in 8% there were normal excretion patterns in the time-activity curves and disturbed excretion phase in the functional images. It was striking that in patients with an obstructive disease and a delayed uptake in the time-activity curve, a normal uptake phase in functional imaging was observed.

## Conclusion.

1. Diethyl-acetanilido iminodiacetic acid is a hepato-biliary agent with excellent biological properties. The reagent accumulates readily in the hepatocytes and is rapidly excreted via the biliary system into the intestine. No reabsorption from the intestinal mucosa is observed. The radiopharmaceutical can easily be prepared using an " instant labelling kit " and shows a high labelling yield with  $^{99m}\text{Tc}$ . No detectable free pertechnetate is observed.
2. Cholescintigraphy with  $^{99m}\text{Tc}$ -diethyl-IDA is a reliable investigation in the diagnosis of patients with liver or biliary tract disorders. In contrast to other investigations it provides dynamic information about liver and biliary tract. The study can be completed without inconvenience for the patient within 45 minutes after administration of the reagent. Application of the reagent showed no adverse reactions at the dose level used and no contra-indications are known.
3. In jaundiced patients it is possible to differentiate between parenchymal disease and bile duct obstruction. The serial scintigrams however reveal only limited differentiation but the uptake and excretion curves obtained by the computer from different regions of interest and the generated functional images provide additional information. Cholescintigraphy can be performed in an early phase of the jaundiced illness because it is hardly dependent on the bilirubin level.
4. In patients with liver function disturbance without jaundice cholescintigraphy can also differentiate between or confirm a suspicion of parenchymal or obstructive disease.

Serial scintigraphy alone is of limited value in these patients, but computer data may indicate parenchymal or obstructive disease. Gallbladder pathology can be diagnosed when in fasting patients no gallbladder visualisation is seen on the serial scintigram and all the other patterns on the serial scintigrams are normal. A well visualised gallbladder however does not exclude gallbladder pathology.

5. Several case histories revealed that repeated cholescintigraphy can be used as a test for recovery of the patient. Serial scintigrams can normalise before the biochemical liver function tests are normal. The time-activity curves and functional images however follow the biochemical patterns. These data may be a measure for the prognosis of liver disease.

6. Cholescintigraphy may also be used in examining the passage of bilio-digestive anastomoses. With the aid of this investigation it is possible to acquire additional information about ( dubious ) lesions in the liver observed on the colloid liver scintigram.

7. Cholescintigraphy is restricted by the fact that it is usually not able to localise an obstructing process in the bile system; stones cannot be demonstrated.

## SUMMARY

This thesis describes the clinical application of cholescintigraphy with  $^{99m}\text{Tc}$ -diethyl-IDA as hepato-biliary radiopharmaceutical.

After a review of some anatomical and physiological properties of liver and biliary tract ( chapter II and III ) the conceptions jaundice and cholestasis are defined ( chapter IV ). Various clinical investigations in patients with liver and biliary tract disorders are discussed such as biochemical blood examinations ( chapter V ), liver biopsy ( chapter V ) and radiological investigations ( chapter VI ). The applications and limitations of colloid liver scintigraphy in patients with focal or diffuse liver diseases are reviewed in chapter VII. Furthermore in this chapter the diagnostic value of this investigation in jaundiced patients is discussed. The literature study ends with a review of the application of various hepato-biliary radiopharmaceuticals and the development, properties and first application of IDA-derivates ( chapter VIII ). Chapter IX describes the synthesis, preparation and quality control of diethyl-IDA which is available as an " instant labelling kit " ( Solco-HIDA<sup>R</sup> ). The biological properties of the radiopharmaceutical are studied by means of kinetic and autoradiographic investigations in rat ( chapter IX ). As introduction to the clinical studies the technical basis of cholescintigraphy is described that encompasses the performance of the serial scintigrams and the generation of time-activity curves and functional images by a computer. Cholescintigraphic patterns in individuals without liver or biliary tract disorders are shown ( chapter X ).

The retrospective investigation includes the cholescintigraphic patterns in 151 patients subdivided in 99 jaundiced patients and 52 non-jaundiced patients with liver and biliary tract diseases. It is evident that the performance of cholescintigraphy is highly independent of the total serum bilirubin level ( chapter XI ).

The jaundiced patients include patients with a bile duct obstruction from a malignant or non malignant cause, patients with a primary liver parenchymal disease and patients with various liver and/or bile duct disorders. In chapter XII the various patterns on the serial scintigram, the time-activity curves and the functional images in these patients are discussed. To differentiate obstructive from parenchymal disease a combination of the obtained parameters is often necessary. The clinical reliability of cholescintigraphy in these patients is compared with the diagnostic accuracy of other investigations. In chapter XIII the results are discussed of cholescintigraphy in 52 patients without jaundice but with various liver and bile duct diseases. In these patients the contribute of cholescintigraphy to the diagnosis was studied, especially the differentiation between obstructive and parenchymal disease as the cause of biochemical liver function disturbance. Chapter XIV contains the final discussion and furthermore in this chapter the conclusions are summarised.

## SAMENVATTING

Dit proefschrift beschrijft de klinische toepassingen van cholelescintigrafie met het  $^{99m}\text{Tc}$ -Technetium-diethyl-IDA als hepatobiliair radiofarmacon.

Na een overzicht van enkele anatomische en fysiologische eigenschappen van lever en galwegen ( hoofdstukken II en III ) worden de begrippen icterus en cholestase nader gedefinieerd ( hoofdstuk IV ). Diverse klinische onderzoeksmethoden bij patiënten met lever- en galwegaandoeningen worden beschreven zoals biochemische bepalingen in bloed ( hoofdstuk V ), leverbiopsie ( hoofdstuk V ) en radiologische onderzoeken ( hoofdstuk VI ). De toepassingen en beperkingen van leverscintigrafie bij patiënten met focale en diffuse leverafwijkingen alsmede de diagnostische waarde van leverscintigrafie bij patiënten met icterus worden beschreven ( hoofdstuk VII ). De literatuurstudie besluit met een overzicht van de toepassingen van diverse hepatobiliaire radiofarmaca en de ontwikkeling, eigenschappen en eerste toepassingen van de IDA-derivaten ( hoofdstuk VIII ). Het eigen onderzoek beschrijft de synthese, bereiding en kwaliteitscontrole van het diethyl-IDA, dat beschikbaar is als een zg. " instant labelling kit " ( Solco-HIDA<sup>R</sup> ).

De biologische eigenschappen van het radiofarmacon worden bestudeerd aan de hand van kinetische en autoradiografische onderzoeken in de rat ( hoofdstuk IX ). Ter inleiding van het klinische onderzoek wordt een beschrijving gegeven van de gebruikte methode van cholelescintigrafie welke omvat het vervaardigen van zg. serie scintigrammen en het genereren van tijd-activiteits curven en functionele beelden met behulp van een computer. De cholelescintigrafische parameters bij individuen zonder lever- of galwegafwijkingen worden weergegeven ( hoofdstuk X ).

Het retrospectieve onderzoek omvat de cholescintigrafische bevindingen bij 151 patienten waarvan 99 icterische patienten met lever- en galwegaandoeningen en 52 niet icterische patienten met lever- en galwegaandoeningen. Het cholescintigrafisch onderzoek blijkt in hoge mate onafhankelijk te zijn van de totale serum bilirubine waarde ( hoofdstuk XI ). De icterische patienten worden onderverdeeld in patienten met een galwegobstructie door een maligne of niet maligne oorzaak, patienten met een primaire aandoening van het leverparenchym en patienten met diverse lever- en galwegafwijkingen. De diverse patronen op het serie scintigram, in de tijd-activiteits curven en in de functionele beelden van deze patienten worden besproken ( hoofdstuk XII ). Om tot de differentiatie obstructie of parenchymaandoening te komen is meestal een combinatie van gevonden parameters noodzakelijk. De klinische waarde van cholescintigrafie in deze patienten groepen wordt vergeleken met die van enkele andere onderzoeken.

Vervolgens worden de resultaten beschreven van cholescintigrafie in 52 patienten met lever- en galwegaandoeningen zonder icterus. Nagegaan werd in hoeverre het onderzoek tot de diagnose kon bijdragen, met name of het onderzoek ook in deze categorie kan differentieren tussen obstructie of parenchymaandoening als oorzaak voor de gevonden biochemische leverfunctie stoornissen ( hoofdstuk XIII ).

Hoofdstuk XIV geeft de eindbespreking en de conclusies weer welke laatste als volgt samengevat kunnen worden:

1.  $^{99m}\text{Tc}$ -diethyl-IDA heeft uitstekende biologische eigenschappen als hepato-biliar radiofarmacon; het wordt snel door de levercel uit het bloed opgenomen en uitgescheiden via de galwegen in de darmen. Er vindt geen reabsorptie plaats door het darmslijmvlies.



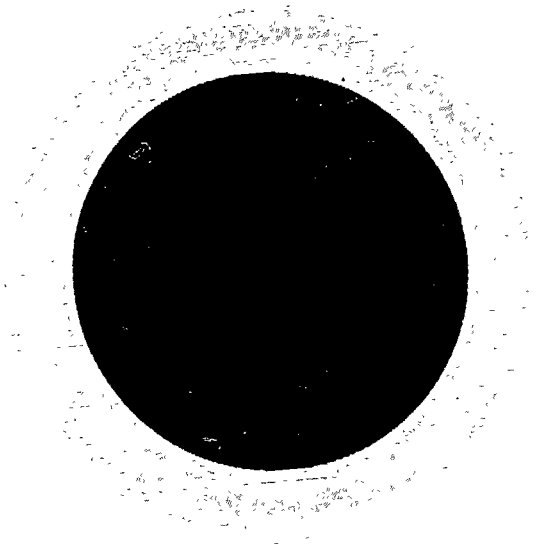
2. Cholescintigrafie is een weinig belastend onderzoek voor de patient en kan vrijwel onafhankelijk van de ernst van de leverfunctiestoornis worden uitgevoerd; tot bilirubine waarde van 400  $\mu\text{mol/l}$  kan het radiofarmacon nog door de lever worden uitgescheiden. Het onderzoek kent geen nadelige bijwerkingen en contra-indicaties zijn niet bekend.

3. Het serie scintigram allèen kan slechts in beperkte mate informeren over een obstructieve of parenchymateuze aandoening als oorzaak voor icterus. Het serie scintigram gecombineerd met de gegevens verkregen uit de computer maakt een grote betrouwbaarheid in de differentiatie tussen obstructieve of parenchymateuze aandoening mogelijk. Het is derhalve mogelijk in een vroeg stadium van een icterische aandoening informatie te verkrijgen over de aard van de icterus.

4. In niet-icterische patienten met leverfunctie stoornissen kan cholescintigrafie een bijdrage leveren tot de diagnose. Behalve voor de differentiatie tussen obstructie of parenchymaandoening kunnen de cholescintigrafische parameters ook dienen als maat voor het herstel van de leverfunctie.

5. Cholescintigrafie kan informeren over de doorgankelijkheid van bilio-digestieve anastomosen en nadere informatie verschaffen over ( dubieuze ) defecten die gezien worden op het lever-scintigram. De betrouwbaarheid in het diagnostiseren van de galblaaspathologie is beperkt.

6. Cholescintigrafie is meestal niet in staat om de plaats van een obstructief proces in de galwegen aan te tonen; ook stenen kunnen niet worden aangetoond.



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#### Note

1 mg % bilirubin = 17.1  $\mu$ mol/l bilirubin.

1 mCi = 37 MBq.

## CURRICULUM VITAE.

De schrijver van dit proefschrift werd geboren op 28 maart 1944 te Venlo.

In 1961 deed hij eindexamen H.B.S.-B aan het St.Thomascollege te Venlo.

Het doctoraal examen Geneeskunde werd in 1968 afgelegd aan de Katholieke Universiteit te Nijmegen; in mei 1970 werd het arts-examen behaald aan de Medische Faculteit te Rotterdam. De opleiding tot internist vond plaats van september 1970 tot september 1975 op de interne afdeling van het militair hospitaal "Dr.A.Matthijssen" te Utrecht, de dialyse afdeling van het St.Lucas ziekenhuis te Amsterdam en de interne afdeling van het St.Franciscus Gasthuis te Rotterdam.

De nucleair geneeskundige scholing vond plaats tijdens een 6-maandse opleiding in de nucleaire geneeskunde ( 1974/1975 ) waarbij tevens de "deskundigheid stralenbescherming C" werd verkregen en door stages op de afdelingen nucleaire geneeskunde van het Wilhelmina Gasthuis te Amsterdam en het Rotterdamsch Radio-Therapeutisch Instituut ( 1975/1976 ).

In juli 1976 volgde een benoeming tot internist-stafid in het St.Franciscus Gasthuis te Rotterdam, tevens volgde een part-time aanstelling als nucleair geneeskundige op de afdeling nucleaire geneeskunde van het Rotterdamsch Radio-Therapeutisch Instituut. Per januari 1978 vond inschrijving plaats als nucleair deelspecialist in het voorlopige B-register voor in-vivo van de Nederlandse Vereniging voor Nucleaire Geneeskunde.