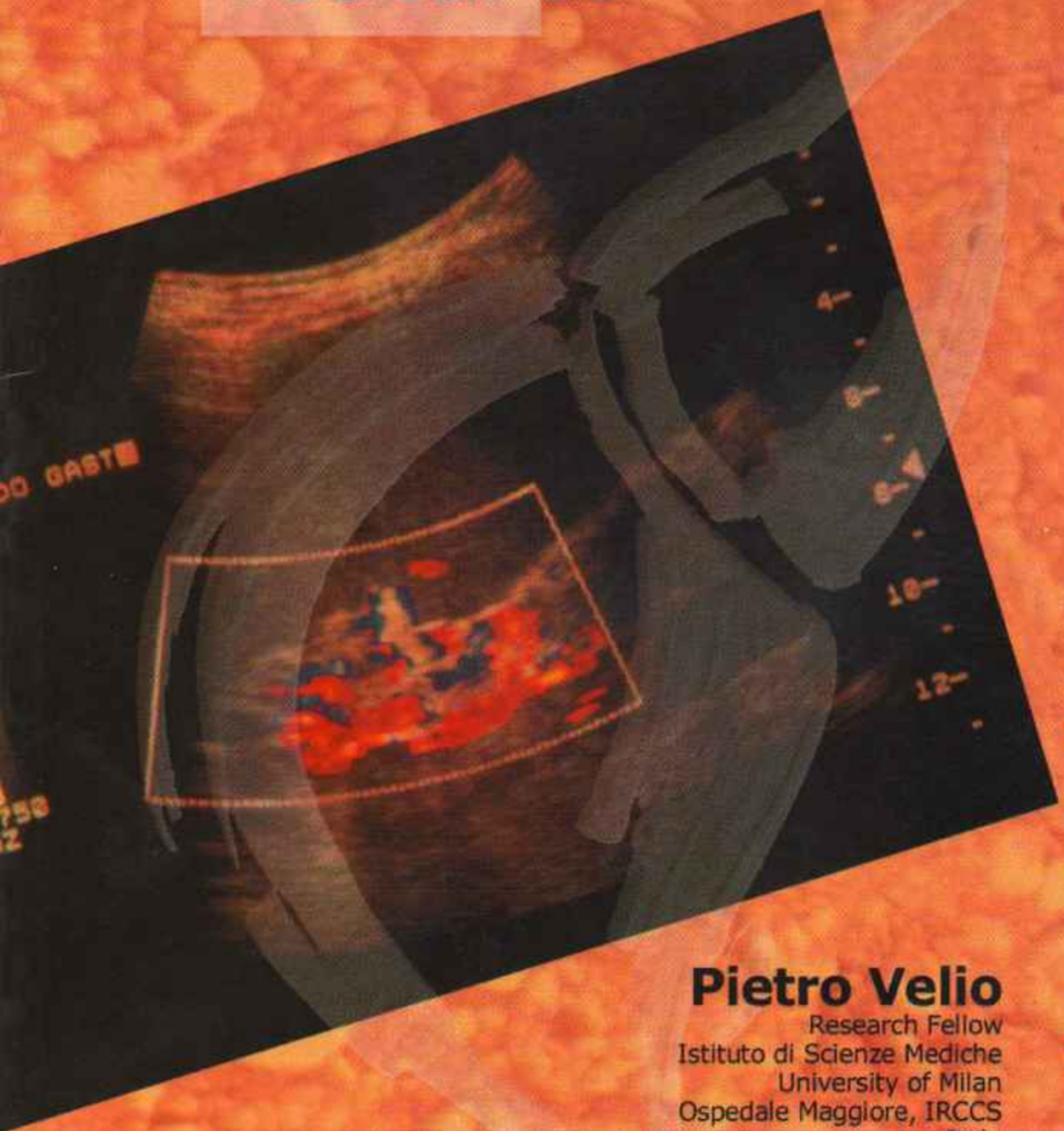
Main Liver Diseases

Imaging, endoscopy and histological features



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GRUPPO ROTTA RESEARCH

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Introduction

Liver diseases are very frequent. Hepatocellular carcinoma is the principal cause of cancer deaths worldwide and is mainly related to the endemic occurrence of viral hepatitis. In the USA, the number of new cases/year of viral hepatitis are: HAV 32,000, HBV 300,000, HCV 150,000, HDV 70,000; the prevalence of chronic liver disease and gallstones is respectively 400,000 and 22 million.

The liver is the largest body mass of glandular tissue. It receives 20% of the cardiac output (three-quarters of it from the veins of the digestive tract, pancreas and spleen) through the portal vein which conveys nutrients, drugs, toxins and bacteria absorbed from the digestive tract. As it provides the first chance to metabolize these substances, it is the first organ to be exposed to ingested toxic compounds. Hepatocytes can degrade these toxic compounds but are also damaged by them. Moreover, biliary excretion is the only way to eliminate lipophilic substances such as drugs and cholesterol.

Enzymatic detoxication of the liver is a two-step microsomal process. The first phase (toxification) is based on cytochrome P-450 mediated biotransformation reactions (oxidation, reduction, and deacetylation) and yields active intermediate metabolites that may still be responsible for hepatic injury. In the second phase of conjugation reactions (detoxification), the active metabolites from the first phase are conjugated to other compounds by means of sulfation, acetylation, glucuronidation and methylation, and converted to non-toxic

substances. Metabolites are generally less toxic than the parent compound. For instance, metabolites from phase 1 reactions are sometimes more toxic and cannot be conjugated immediately. These toxic intermediate substances bind to cell proteins or oxidize cell components and may cause cell damage or death.
Many factors influence xenobiotic metabolism. Phase 1 reactions can be reduced by liver diseases, acute alcohol ingestion, smoking, the use of oral contraceptives and old age, or may be increased by some drugs or chronic alcohol intake by means of the induction of P-450 systems; phase 2 reactions are diminished by congenital enzymopathies or fasting. The analgesic agent acetaminophen is a cardinal example of a drug leading to hepatic damage. It has few side effects if taken at daily therapeutic doses of 1-4 g., but its active metabolite (phase 1) can induce acute hepatocyte necrosis when it is taken in single large doses of 15 g. or more, or even at low doses (6 to 10 g.) in chronic alcoholics or fasting subjects because these factors increase phase 1 toxication.

The main liver diseases are hepatitis, cirrhosis, hepatocellular carcinoma (HCC), and biliary stone disease. Other conditions frequently observed are steatosis, benign congenital lesions and post-cholecystectomy syndrome.

Diagnostic procedures. The diagnosis of a liver disease is usually based on routine chemistry, immunological assays and abdominal ultrasound (US); other diagnostic procedures are indicated only in selected conditions. Liver biopsy is considered essential in establishing the nature and severity of histologic damage. It is commonly performed by inserting a needle through the abdominal wall into the liver and removing a

tissue specimen that can be processed and stained before microscopic examination. A biopsy can also be taken from very small focal lesions, during laparoscopy. However, this procedure is not without risks, of which the greatest is a severe, sometimes fatal, bleeding. In clinical practice, the liver biopsy is not always necessary for diagnostic purpose, particularly when serologic tests are unequivocal, as in the routine diagnosis of chronic viral hepatitis. Biopsy plays a role only if it gives information that help to make therapeutic decisions and to assess the effects of the therapy (Table 1). Clinicians are often surprised to find a considerable discrepancy between the clinically apparent stage and biochemical parameters (which may underestimate the severity of the disease) and lesions observed at histology.
Sonography (US) and color doppler-sonography are being more frequently used. No specific preparation is needed, and the quality of the examination greatly depends on the experience of the sonologist. US is generally considered the first procedure in patients with biliary pain or cholestasis, and can be helpful when performing routine percutaneous liver biopsy. NMR and CT-scans are more sensitive than US in some situations, but are more invasive, expensive, and indicated only after specialist consultation.
The main indication for arteriography is in suspected liver neoplastic disease; it also allows a therapeutic approach (chemoembolization) and the follow-up of treated patients. Other endoscopic diagnostic or therapeutic procedures (ERCP with or without papillotomy, endosonography and PTC) are sometimes used.

STEATOSIS (Fatty liver)

Fat is the most frequently observed hepatic storage material. It accumulates in hepatocytes under a wide variety of circumstances (steatosis), and reflects an imbalance between the synthesis and secretion of lipids. Steatosis may be the only liver abnormality or one component of a more severe injury (e.g. alcoholic liver disease, HCV-hepatitis, non alcoholic steato-hepatitis). It may be macrovesicular, microvesicular or mixed. Macrovesicular steatosis consists of large fat droplets enlarging the liver cells and peripherally displacing the nucleus; lipogranulomas can occur from the rupture of fat cysts and are reported in 30-40% of patients with alcoholic liver disease (ALD). Distribution is usually more prominent in acinar zone 3 when it is alcohol related, but it may be pan-acinar. It is often associated with exposure to drugs (Table 2), toxins, alcohol intake, obesity, diabetes, and malnutrition. Macrovesicular steatosis is a clinically asymptomatic and reversible benign condition. Liver function tests are normal in most patients and it does not tend to progress to cirrhosis (uncomplicated fatty liver). Nevertheless, cases of related sudden death have been reported. Microvesicular steatosis consists of numerous small fat droplets in swollen hepatocytes with centrally placed pyknotic nuclei; it may also be associated with focal necrosis and lipogranulomas. It may be patchy or diffuse and is most often observed in acinar zone 3. It is typically caused by toxic injuries (e.g., alcohol, tetracycline iv, valproic acid), pregnancy and Reye' syndrome. Fatty liver is generally diagnosed US and liver biopsy is usually unnecessary.

Table 2. *Drug-induced steatosis and related drugs*

Microvesicular	*Macrovesicular*
Acetylsalicylic acid	Alcohol
Aflatoxin	Asparaginase
Alcohol	Corticosteroids
Amiodarone	Mercury poisoning
Cocaine	Methotrexate
Desferrioxamine	Minocycline
Ipobrufen	Parenteral nutrition
Tetracyclines	Phosphorous poisoning

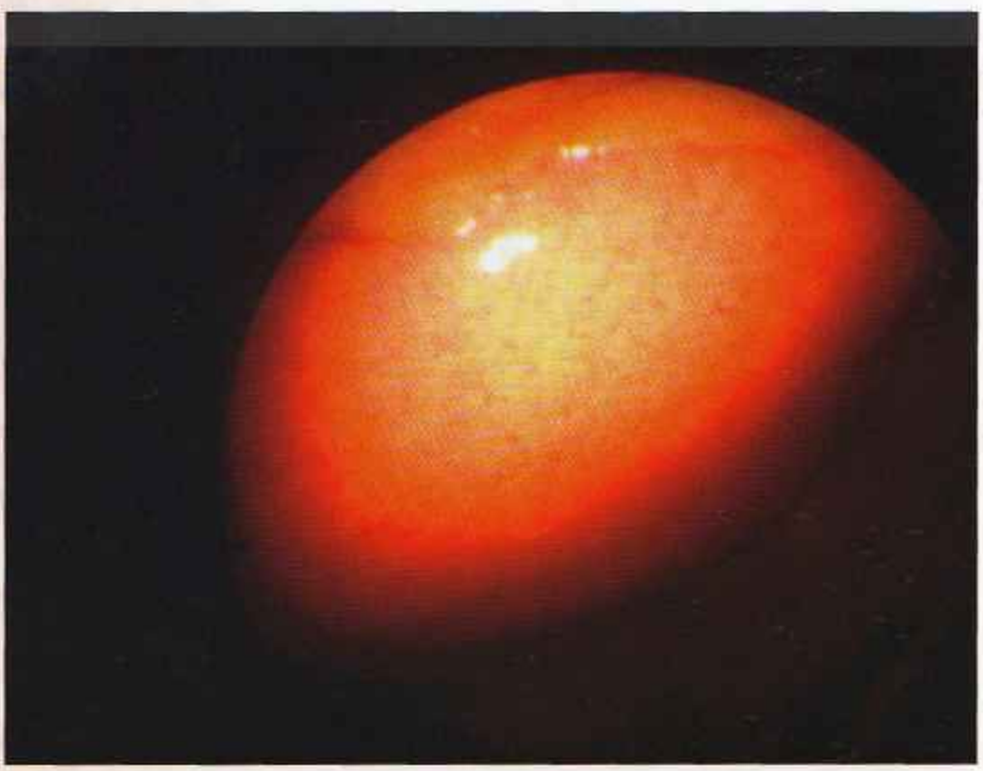


Fig. 4 Laparoscopy: alcoholic fatty liver. The liver is enlarged and soft, its surface is regular and the colour is orange-yellow; this appearence (called "en motte de beurre" by French authors), is characteristic of fatty liver at laparoscopy.

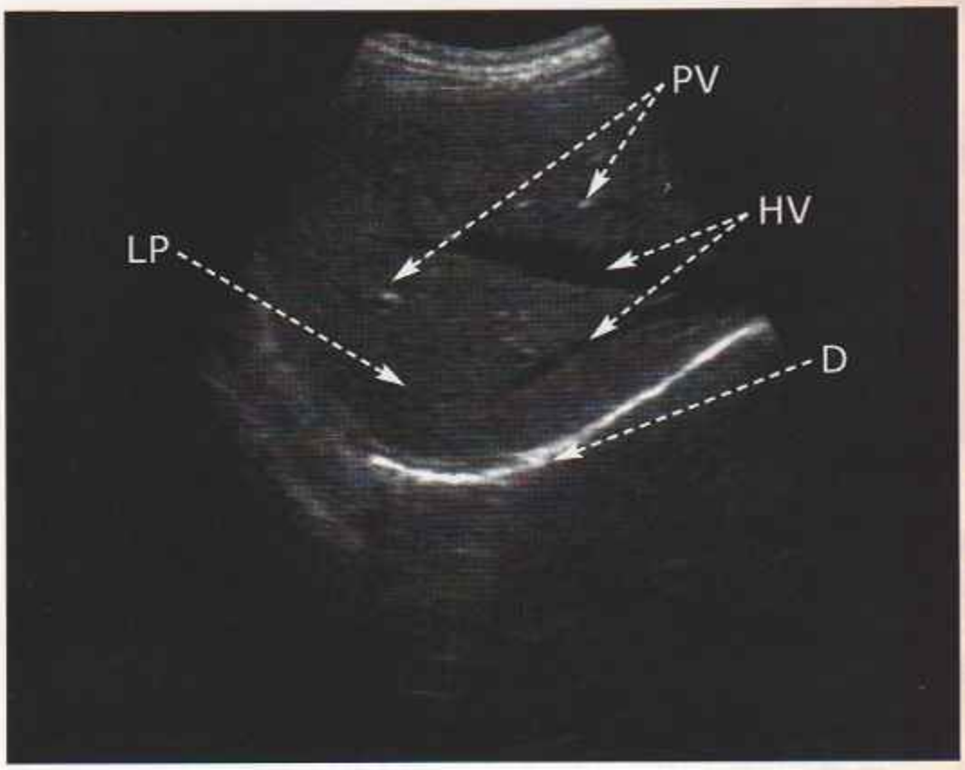


Fig.5 Ultrasound (US): normal liver, right lobe. Liver parenchyma (LP) and diaphragm (D); the hepatic veins (HV) have poorly defined margins, whereas the portal vein radicles (PV) have dense walls. The intrahepatic biliary ducts are not visible.

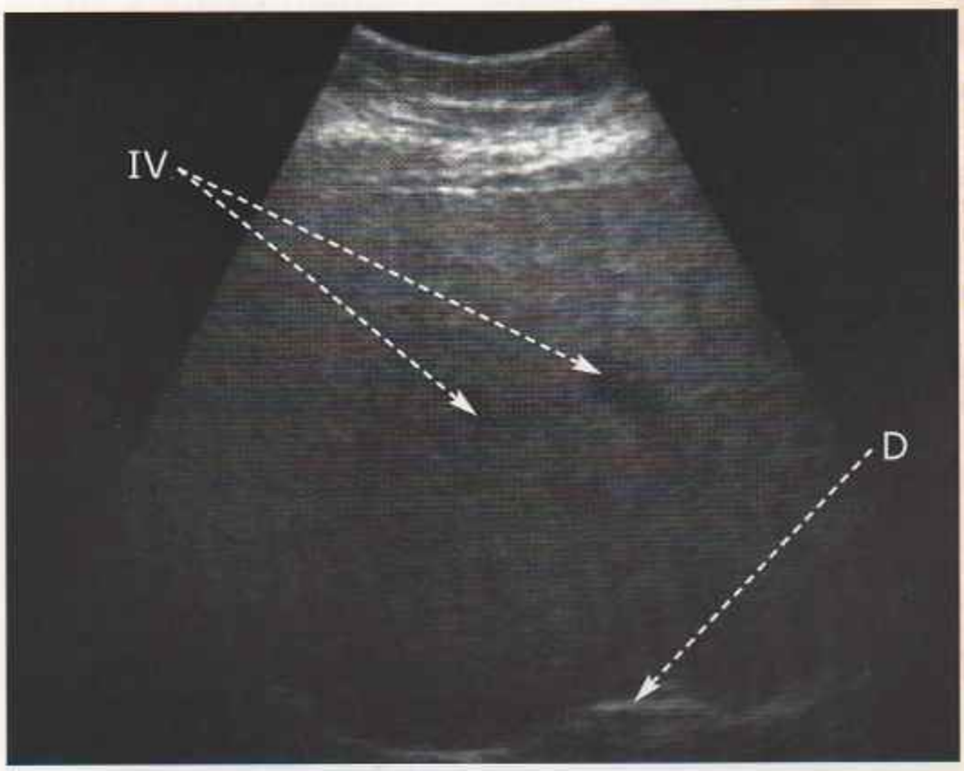


Fig. 6 Liver US: alcoholic steatosis (moderate degree). The uniform and brightly reflective echopattern slightly impairs the visualization of the intrahepatic vessels (IV) and diaphragm (D). The sensitivity of US in detecting fatty infiltration is as much as 90% in moderate or severe disease.

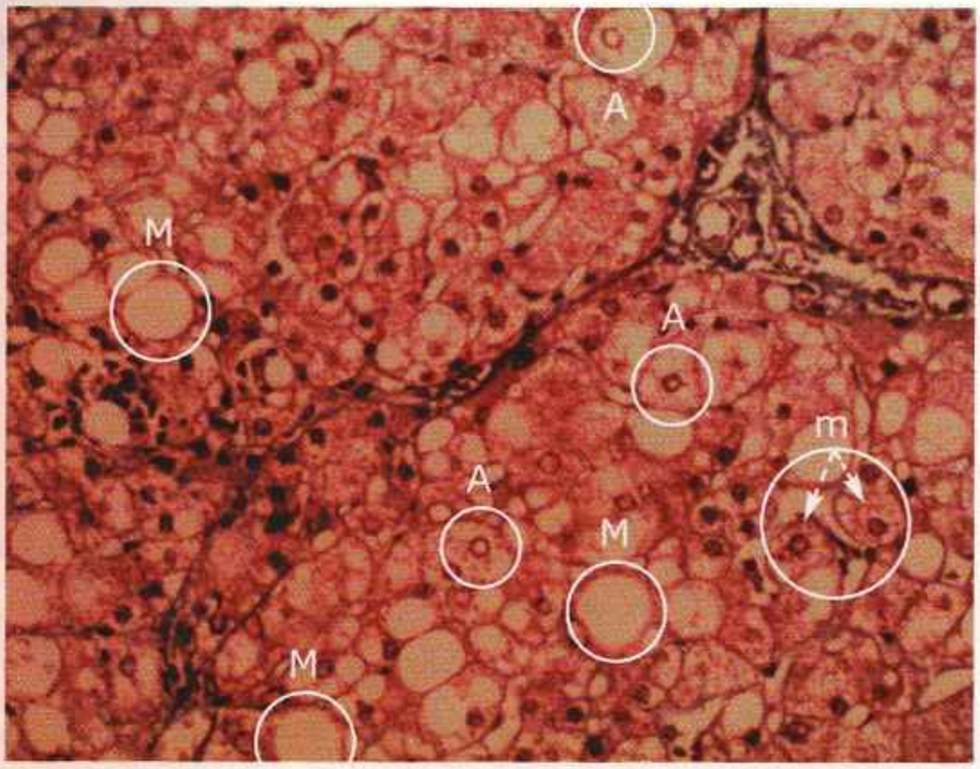


Fig. 7 Liver biopsy: mixed steatosis (Wilson's disease). Macrovesicular steatosis is characterized by a single large fat droplet distending the hepatocyte and displacing the nucleus to the periphery (M). A few of the hepatocytes show miscrovesicular steatosis (m) and central nuclei. Some nuclei appear clear because they are glycogenated (A). Trichrome stain.

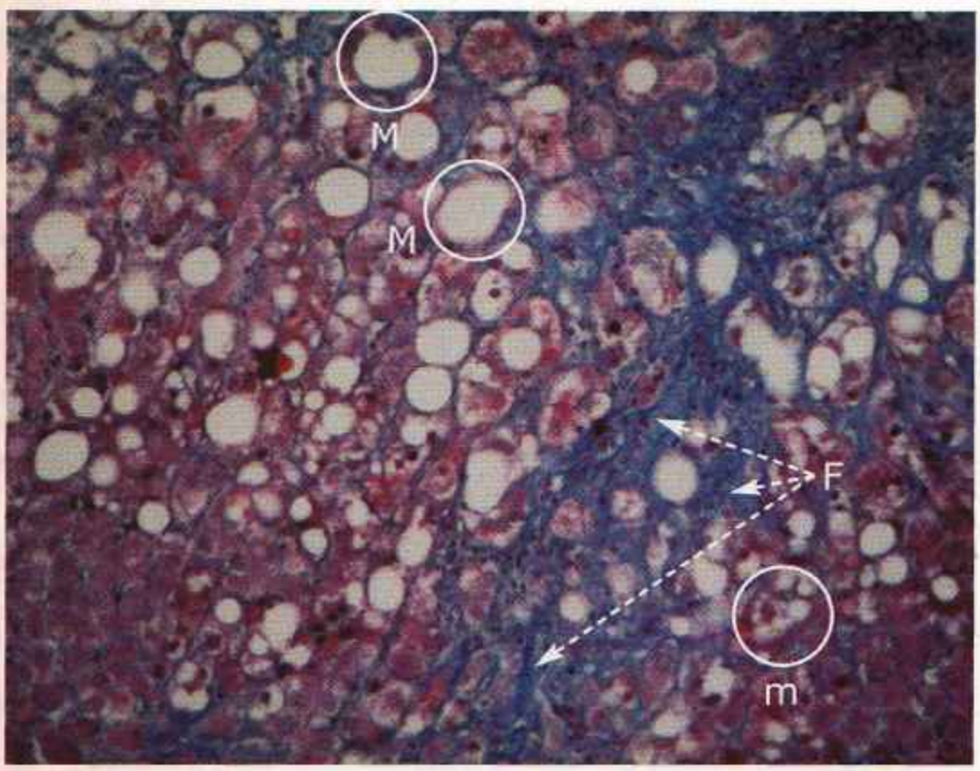


Fig.8 Liver biopsy: alcoholic liver disease. Macrovesicular (M) and microvesicular steatosis (m) are associated with diffuse and severe pericellular fibrosis (F). H & E stain.

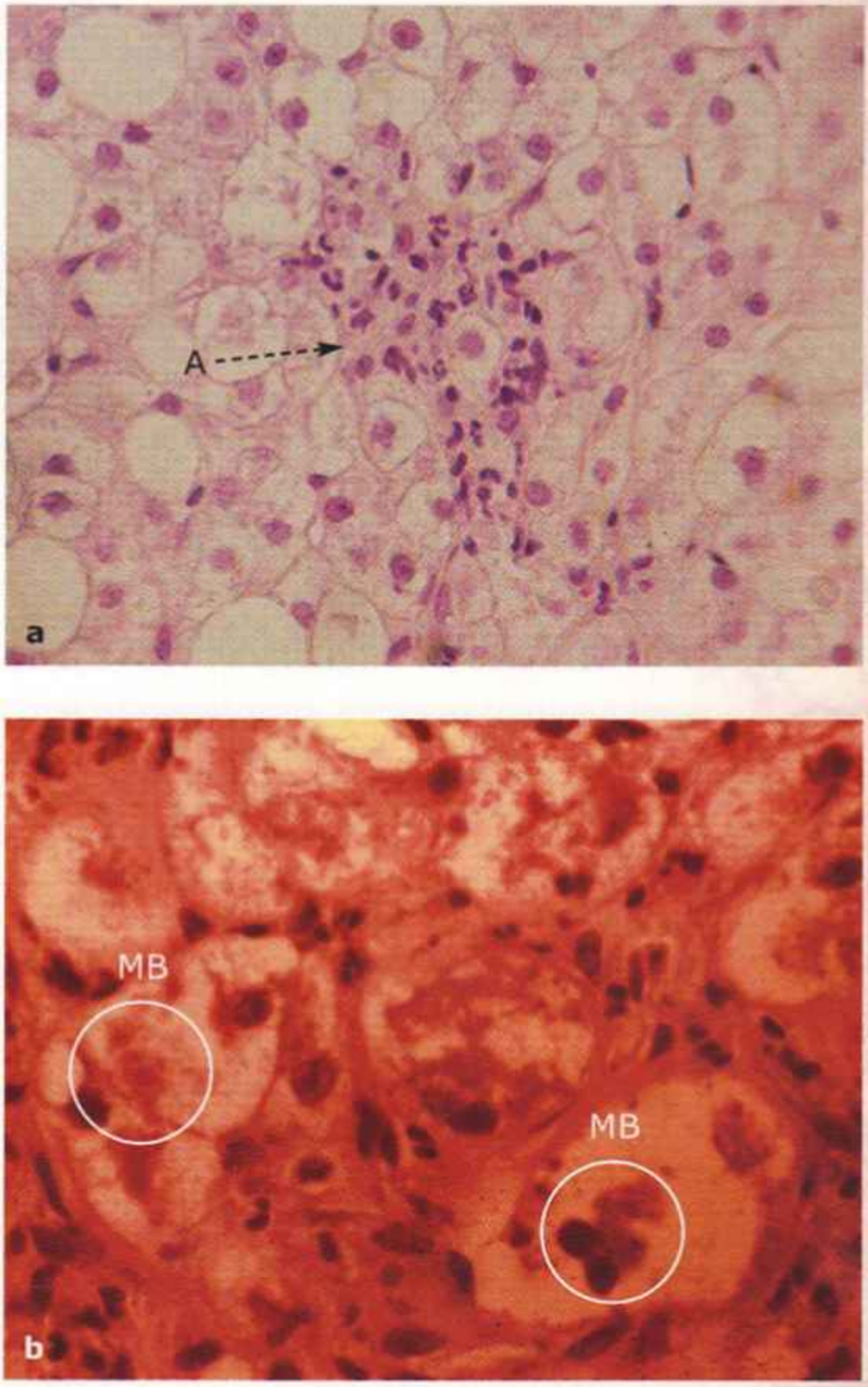


Fig. 10 Liver biopsy: non-alcoholic steatohepatitis (NASH) in an obese male. (a) Diffuse macrovesicular fatty change and focal acute hepatitis (A); one hepatocyte is surrounded by neutrophil polymorphs. Some hepatocytes contain pale Mallory bodies.
(b) The enlarged hepatocytes containing Mallory bodies and with pericellular fibrosis are more clearly seen at higher magnification (Mb). H&E.

CHRONIC HEPATITIS

Chronic hepatitis (CH) is histopathologically defined as a chronic necroinflammatory disease of variable severity that is not associated with the features of chronic cholestasis or steatosis and Mallory body formation.

The nomenclature of chronic hepatitis has been recently revised with the term chronic hepatitis (associated with the degree of activity and emphasizing the etiology) replacing the formerly used terms of chronic active hepatitis, chronic aggressive hepatitis, chronic persistent hepatitis and chronic lobular hepatitis.
The course and evolution of chronic hepatitis depend on its etiology but it is generally a progressive disease that can be reversed only in rare cases (e.g. after drug-withdrawal if drug-induced). Chronic hepatitis can be caused by only one of a number of different etiologic agents, but the interaction of two or more causes is becoming increasingly evident; the most common associations are HCV and HBV, alcohol and HBV or HCV, and HCV and porphyria cutanea tarda.
The causes of chronic hepatitis are HBV (Delta virus negative or positive), HCV, HGV, autoimmunity, alcohol, drugs, inherited metabolic liver diseases (Wilson's disease, alpha1-antitrypsin deficiency), and celiac disease.

Viruses are responsible for more than 90% of the cases of chronic hepatitis. Regardless of its etiology, the histopathological aspects of chronic hepatitis are piecemeal necrosis (the most important lesion), portal area inflammation, periportal bridging and fibrosis, and intra-acinar degeneration and necrosis. Piecemeal necrosis is a

necroinflammatory lesion that destroys the limiting plate of the liver cells mainly around portal areas (expanding portal areas into the parenchima) and is followed by fibrosis; it can also last in the cirrhotic liver due to chronic hepatitis. The portal tracts are infiltrated by lymphocytes and plasma cells and show a histopathologic characteristic that is pathognomic of chronic hepatitis: the isolation and entrapment of a single group of hepatocytes in the expanded portal tract. Intra-acinar apoptotic necroinflammatory lesions of variable severity are frequent, and liver cell regeneration is almost always present.

Continuous piecemeal necrosis of portal and bridging or multiacinar type, leads to fibrosis and eventually to macronodular or mixed macro-micronodular cirrhosis. The histopathological characteristics of hepatitis C are more intense chronic portal inflammation (often with follicles or lymphoid aggregates), hepatocellular fat accumulation, and inflammation of the ductal epithelial cells without destruction ("Poulsen's lesion"). Only some patients with HVC infection have acute self-limiting hepatitis; 70-80% have chronic disease. About 40% of the patients with chronic HCV develop liver cirrhosis and 15-20% develop hepatocellular carcinoma (HCC). The B virus usually causes acute, and very occasionally fulminant, hepatitis; chronic hepatitis develops in about 10% of the patients and represents about 25% of all chronic forms. In some cases, the lesions progress to cirrhosis, and HCC may be the final event. HDV is a defective RNA virus that needs the presence of HBV as a helper; it can therefore only infect individuals who are also infected with HBV. Simultaneous coinfection with HBV and HDV tends to cause more severe disease,

and there is a high likelihood of fulminant hepatitis. There are no morphologically specific features of HDV, and only immunostaining can reveal the delta antigen in the hepatocyte nuclei. Autoimmune hepatitis account for less than 10% of all forms of CH and have been primarly distinguished on the basis of their autoantibody profile. The histopathological aspects include severe hepatocellular injury, rosettes and giant cell transformation. Cryptogenic hepatitis account for about 17% of the cases of CH.

Liver biopsy plays an important role in confirming diagnosis and guiding therapy.
In the opinion of most hepatologists, histology remains the gold standard for evaluating the effects of therapy on CH even if its role is now debated because some serological tests seem to provide a more precise measure of therapeutic efficacy, such as a sustained loss of serum HBV DNA and the disappearance of HbcAg in chronic HBV, or HCV RNA negativization in chronic HCV.

HBV and HCV hepatitis treatment. The recommendations for treating HBV hepatitis are:

- Healthy carriers with normal ALT should not be treated
- Interferon is the first-line choice for compensated liver disease
- Lamivudine must be considered in patients with hepatic decompensation or who undergo liver transplantation
- Combination therapy: no data available
- Treated patients should be carefully followed (blood counts, mental adjustment, avoidance of pregnancy)

The recommendations for treating HCV hepatitis are:

- Combination therapy with interferon and ribavirin for 6-12 months, using standard interferon 3 mu TIW dosing
- Protease inhibitors may be useful in the future
- Follow treated patients with great care

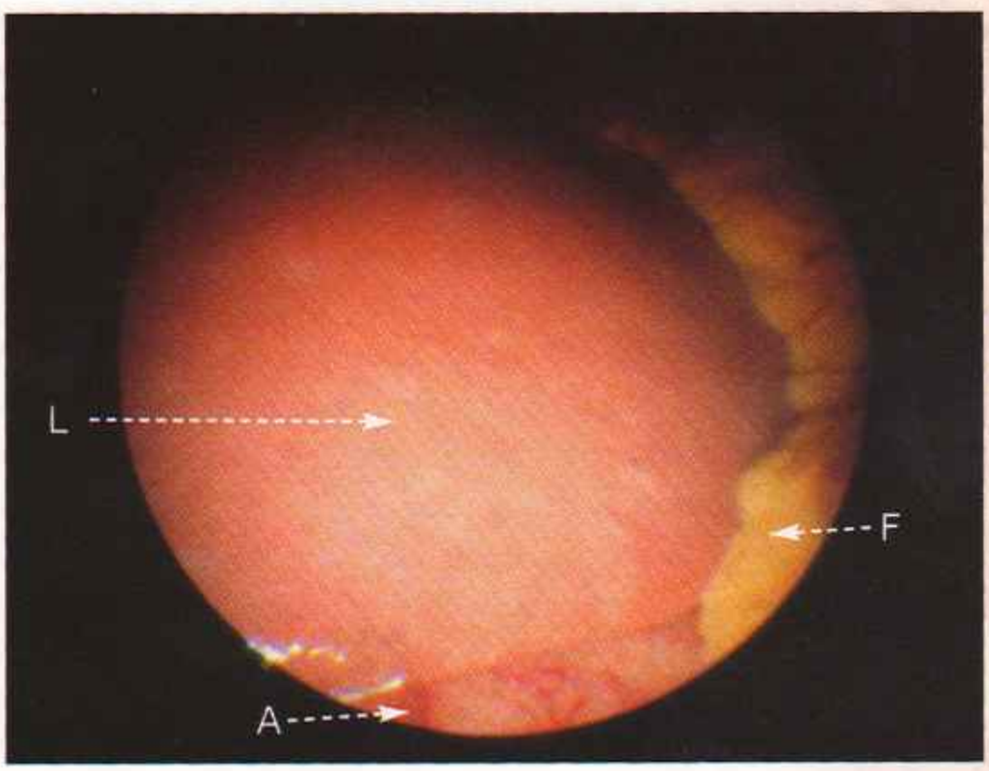


Fig. 11 Laparoscopy: chronic hepatitis. The liver appears almost normal (L); its colour is pale red and the small white areas are post-necrotic scars. Mild ascites (A) and peritoneal fat (F) can also be seen.

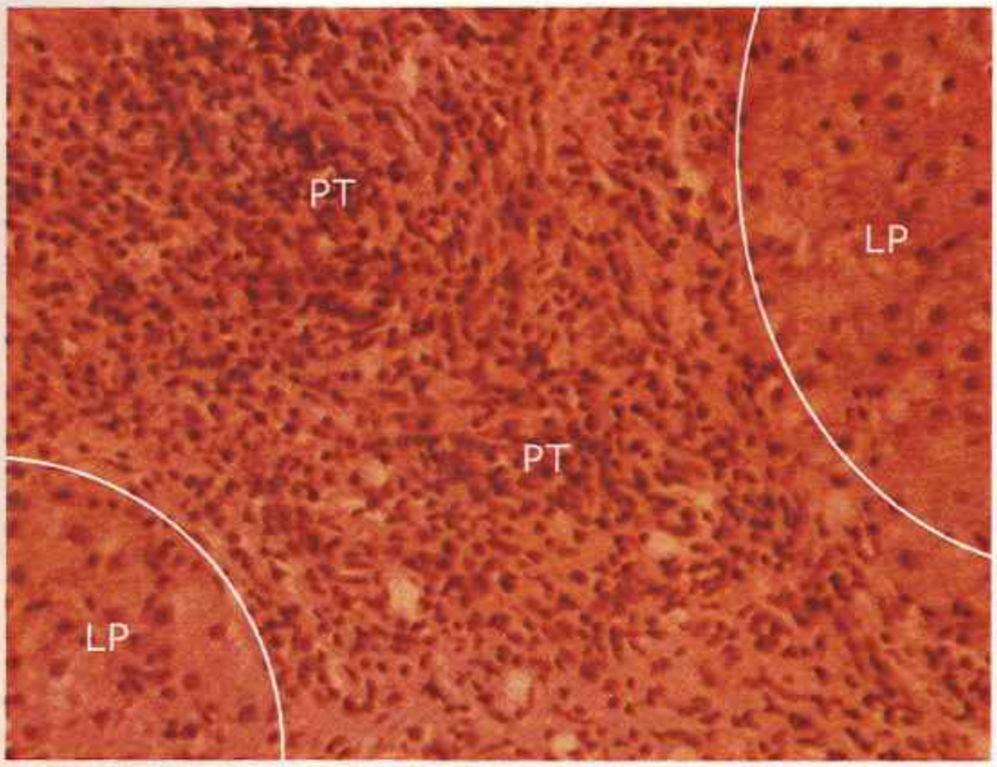


Fig. 12 Liver biopsy: chronic HCV hepatitis. The portal tract (PT) is expanded, infiltrated with inflammatory mononucleated cells and presents piecemeal necrosis; bile ducts cannot be seen. Liver parenchyma (LP) shows mild inflammation and steatosis. H&E stain.

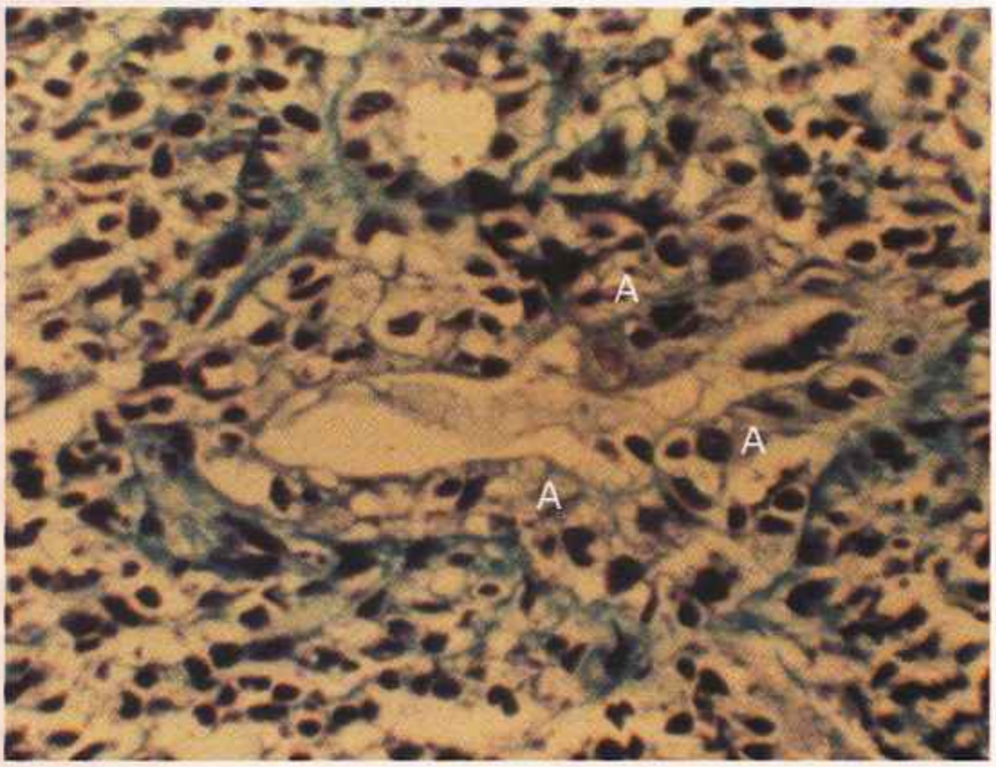


Fig. 13 Liver biopsy: chronic HCV hepatitis, portal tract. There is dense infiltration by lymphocytes associated with bile duct damage (Poulsen's lesion (A)): the epithelium is multilayered, swollen and vacuolated, and the cells are infiltrated by lymphocytes. H&E stain.

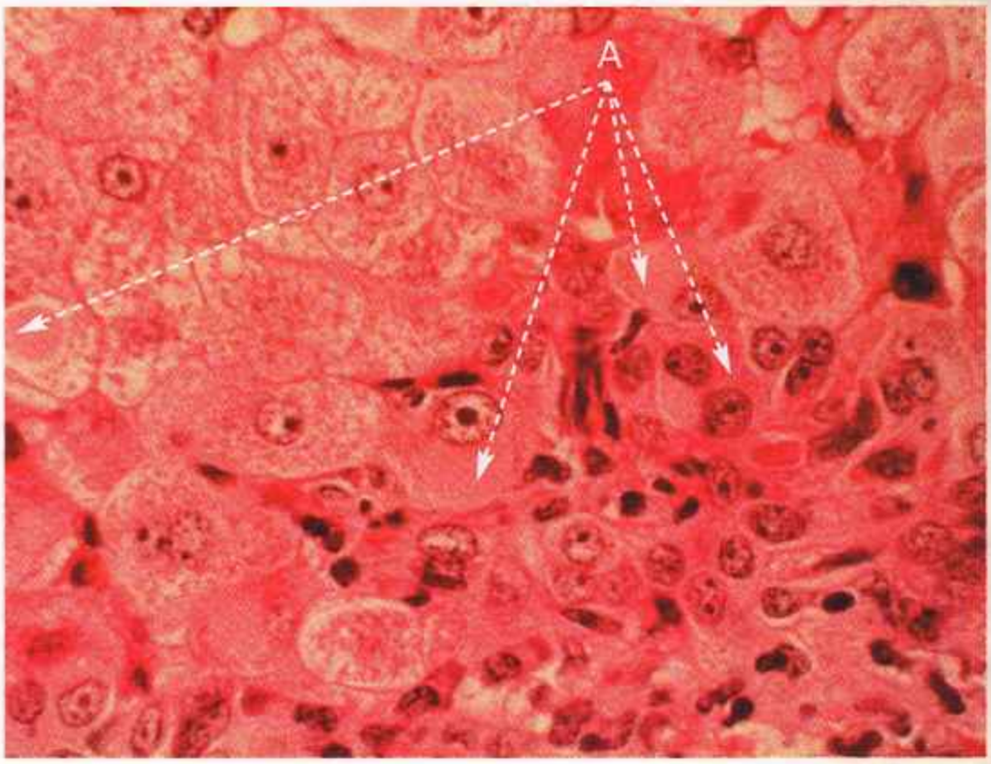


Fig. 14 Liver biopsy: chronic HBV hepatitis. Mild periportal piecemeal necrosis (bottom) and many HBV-containing ground-glass hepatocytes (A); some of the hepatocytes are picnotic. H&E stain.

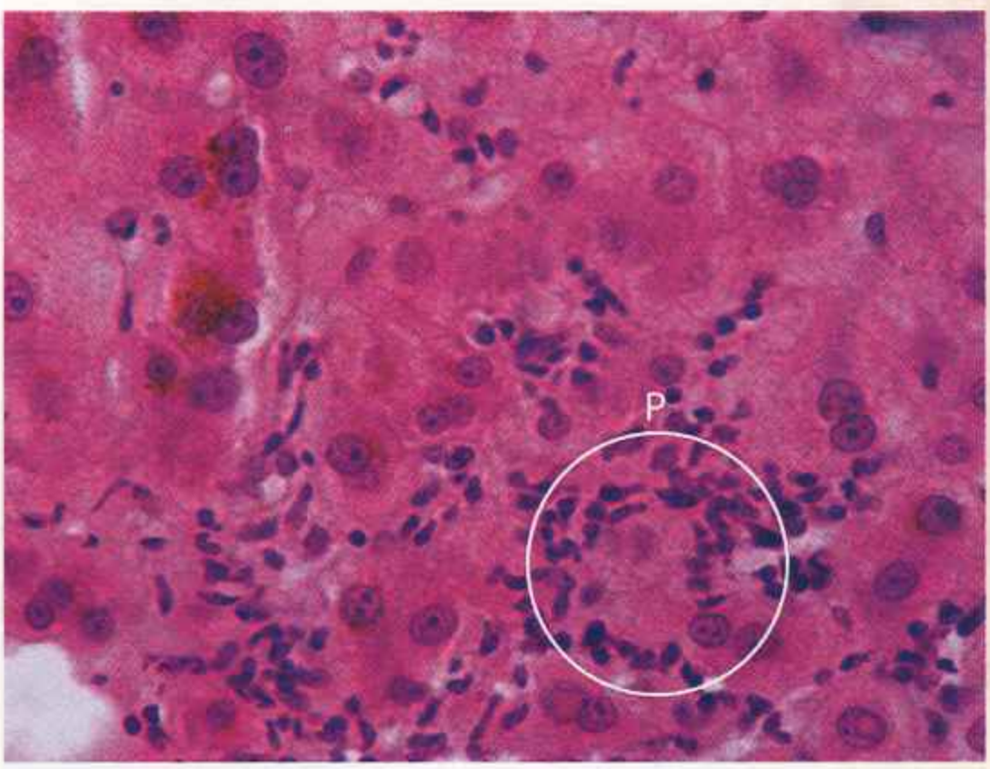


Fig. 15 Liver biopsy: chronic HBV hepatitis with HDV superinfection. This type of hepatitis leads to severe panacinar activity (inflammation-necrosis), and a more rapid progression to cirrhosis. Many of the hepatocytes are surrounded by lymphocytes (peripolesis [P]), one of the features of piecemeal necrosis. H&E stain.

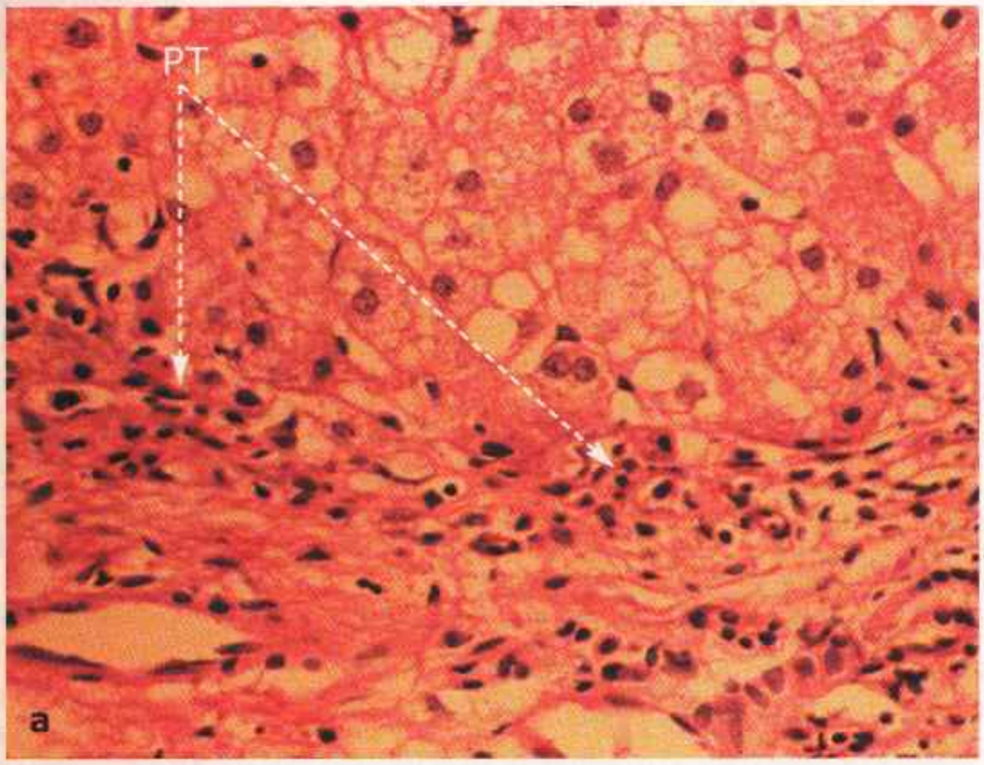




Fig. 16 Liver biopsy: Wilson's disease.
(a) Mild portal tract inflammation and periportal piecemeal necrosis (PT); the hepatocytes show microvesicular steatosis. H&E stain.
(b) Copper accumulation in the periportal hepatocytes is revealed by Shikata's orcein stain (A).

Liver cirrhosis

Cirrhosis is primarily alcohol-related, with the hepatic viruses (HCV and HBV) being the second cause; 10% of the patients have both conditions. The prevalence of different causes my be different in different countries. Alcoholic liver disease (ALD) may be observed in chronic alcohol abusers (> 80 g m/day). The three types of liver damage frequently encountered as a result of alcohol ingestion are: fatty liver (10-90%), alcoholic hepatitis (6-30%) and cirrhosis (15-58%).
An alcoholic patient may have one, two or all of these conditions simultaneously. The effects of chronic alcohol ingestion observed at liver histology are ballooning hepatocytes, megamitochondria, fatty liver, net fibrosis, Mallory' bodies and cirrhosis. Alcoholic cirrhosis is often insidious and accompanied by non-specific symptoms. Signs of liver failure, such as variceal bleeding, hepatic encephalopathy, ascites, infection or malnutrition, often become evident as the disease progress. The treatment of ALD is based on complete abstinence from alcohol and a low-salt diet with 1 g/kg/d of proteins. Liver transplantation has become a major option in cirrhotic patients who have achieved sobriety for at least one year. Other causes of cirrhosis are primary biliary cirrhosis (PBC), sclerosing cholangitis, drugs, and some hereditary diseases (Wilson's disease, genetic hemochromatosis, alpha-1 antitrypsin deficiency, and cystic fibrosis). Hemochromatosis is an autosomal recessive disorder of iron metabolism that leads to excessive iron deposition in the liver and several other organs (pancreas, heart, gonads and the upper gastrointestinal tract). Diagnosis is now

possible without liver biopsy, because a mutated MCH class I-like gene has recently been described that can be identified in 83% of homozygous patients. The treatment goal in the case of hereditary hemochromatosis is to initiate phlebotomy before the development of hepatic fibrosis or cirrhosis. Wilson's disease is an autosomal recessive disorder of copper metabolism that is characterized by an excessive accumulation of copper in various tissues (liver, brain, eye, skeleton, kidney). All cases of neurologic Wilson's disease have Kayser-Fleischer rings. In most patients, serum ceruplasmin concentration, 24-hour urinary copper excretion, hepatic histology, and quantitative copper studies may suggest the diagnosis. Treatment is based on oral D-penicillamine (600-1800 mg/d), which reduces excess copper store.

The therapy for of all types of cirrhosis consists of preventing and treating portal hypertensive bleeding, ascites, spontaneous bacterial peritonitis, and metabolic disorders, or liver transplantation.

Variceal bleeding. In order to prevent the first episode of gastrointestinal bleeding, the non-selective beta adrenergic blockers, propranolol, nadol or timolol are the only indicated treatments. There are various options for preventing recurrent variceal bleeding, including beta-blockers, endoscopic ligation or sclerotherapy, combination theraphy (beta-blockers and sclerotherapy), TIPS (transjugular intrahepatic portosystemic shunt), surgical portosystemic shunts, and liver transplantation.

Treatment of ascites (see ascites).

Prophylaxis and treatment of spontaneous bacterial peritonitis (SBP). SBP is diagnosed when

abdominal paracentesis leads to a positive ascitic fluid culture and ascitic fluid PMN count of > 250 cells/mm3. Most episodes are caused by E. coli, Streptococci or Klebsiella. SBP is a very severe complication, and the direct or indirect mortality rate is still high (25-40%). Antibiotic treatment (cefotaxime, ceftriaxone) must be empirically initiated before identifying the in-vitro susceptibility of the microorganism.
The prevention of SBP or its recurrence may be attempted by chronically using norfloxacin 400 mg/day.

The last but not the least chance for cirrhosis treatment, which is now available in almost all countries, is based on liver transplantation.
The diseases for which liver transplantation has been performed in adults can be divided into three broad categories: advanced chronic liver disease, fulminant hepatic failure and unresectable hepatic malignancy, although this last is a controversial and decreasing indication. In most transplant centers, chronic hepatitis C and alcoholic liver disease are the leading indications for liver transplantation, followed by chronic hepatitis B. The reasonable criteria for listing a chronic liver disease patient for liver transplantation should be clinical decompensation, particularly ascites or variceal bleeding, or a combined clinical and biochemical deterioration that meets the criteria for Child-Pugh class B or C. The listing criterion for transplantation for acute liver failure is severe acute liver failure. The usually accepted contraindications to liver transplantation include compensated cirrhosis, HIV seropositivity, extrahepatic malignancy, active untreated sepsis, active alcoholism or substance abuse, significant co-morbid conditions, and some precluding anatomic abnormalities.

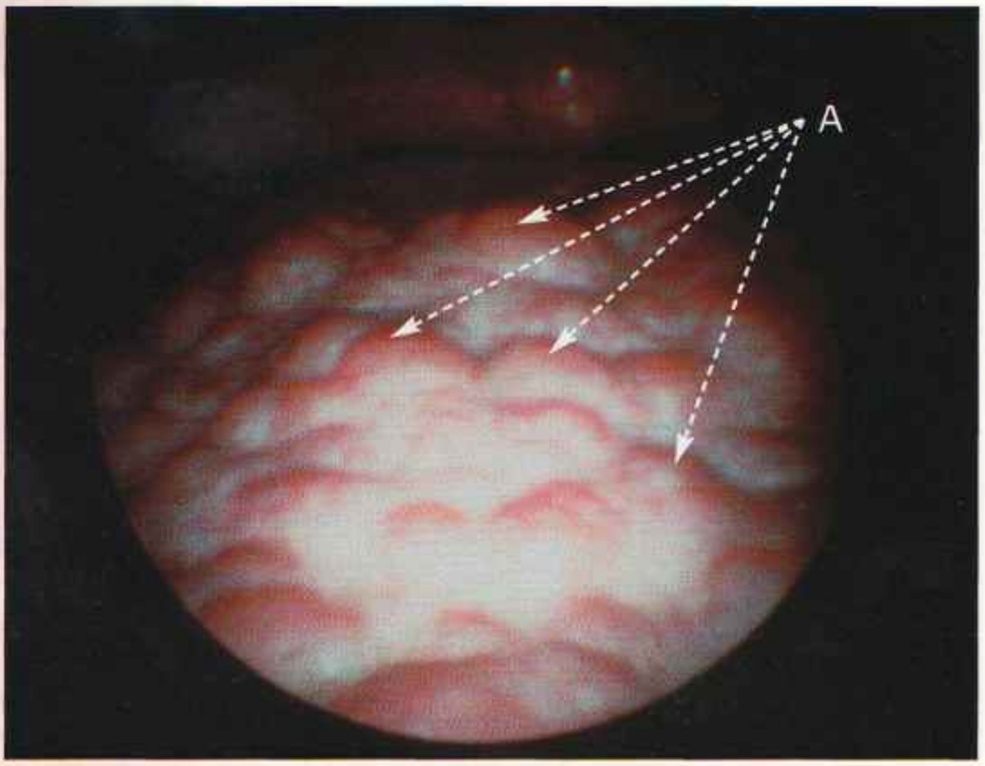


Fig. 17 Laparoscopy: alcoholic cirrhosis. Nodules are evident (A) and partially enclosed by the thickened Glisson's capsule (white areas).

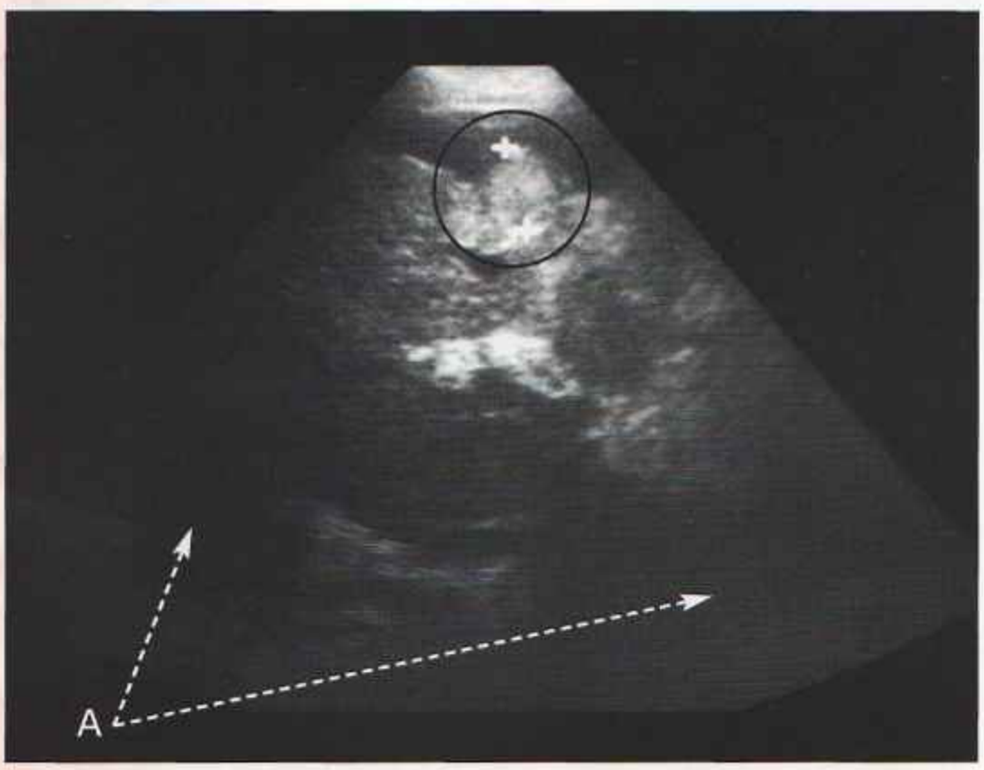
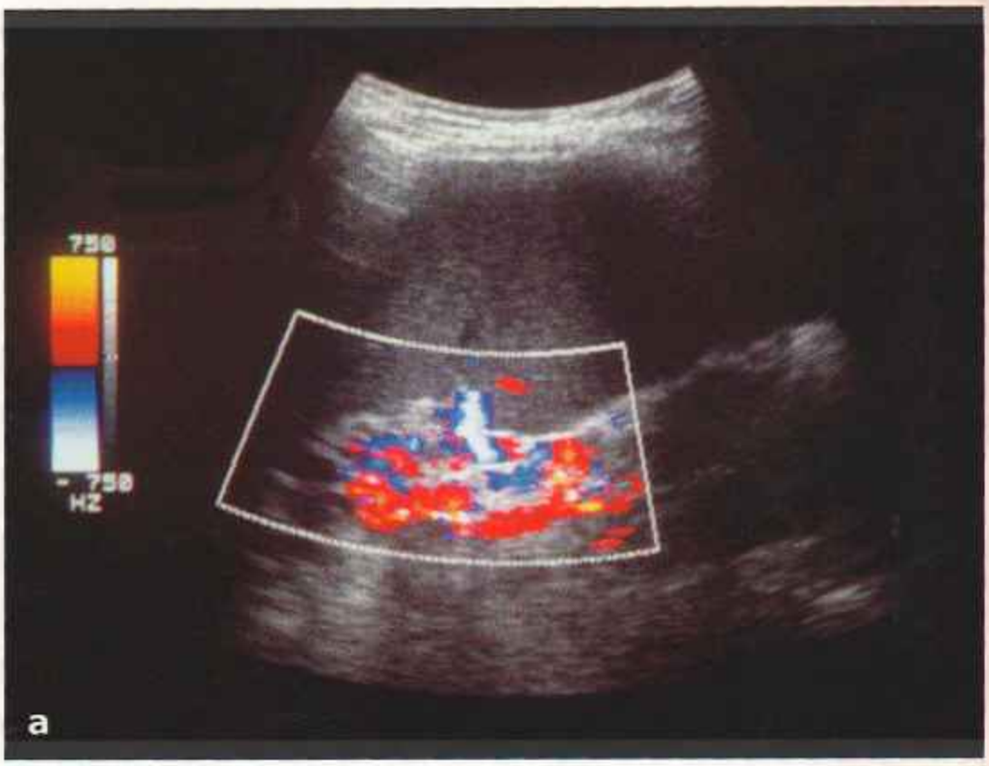


Fig. 18 Liver US: macronodular cirrhosis. The liver surface is grossly irregular; one large nodule is evident between the two crosses (top). Ascites is also present (A).



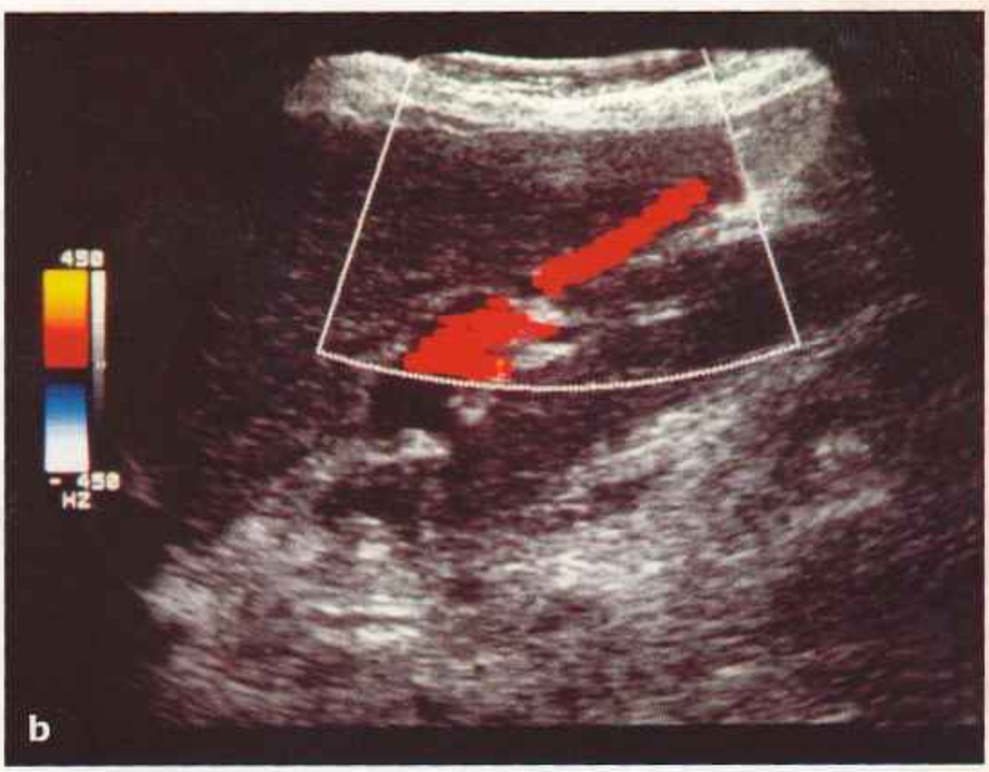


Fig. 19 Colour doppler ultrasonography: liver cirrhosis and portal hypertension with gastric varices.
(a) The flow in the gastric fundus varices is easy seen as red and blue images;
(b) Patent umbilical vein; dilated red collateral vessels radiate from the umbilicus ('caput medusae')

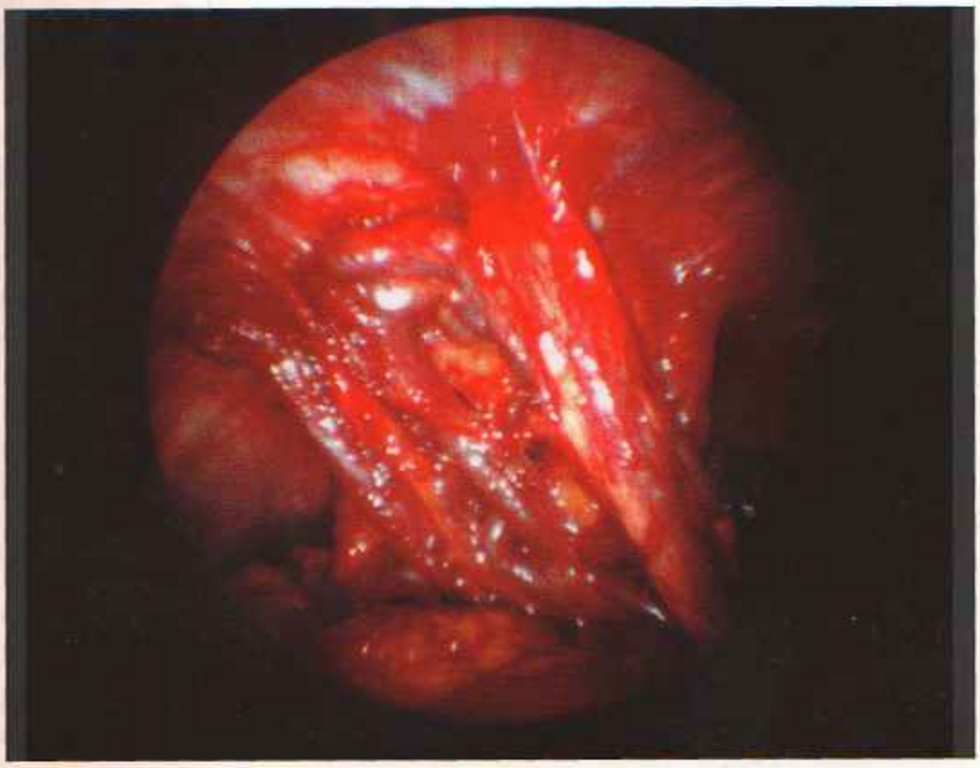


Fig. 20 Laparoscopy: liver cirrhosis and severe portal hypertension. Many enlarged collateral venous vessels can be seen.

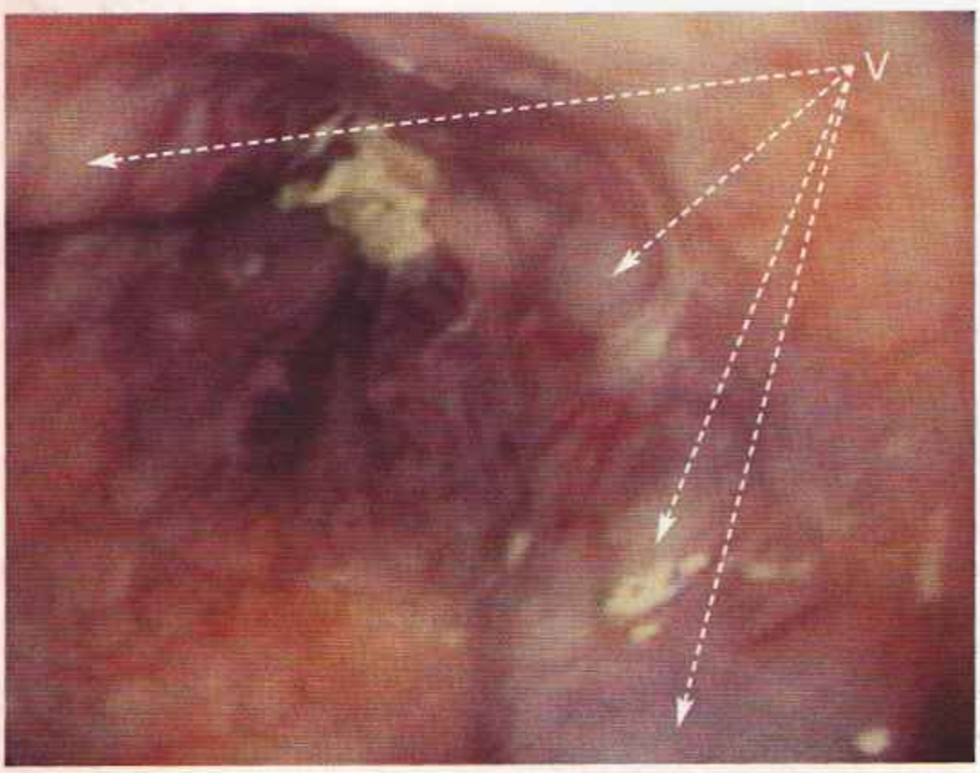
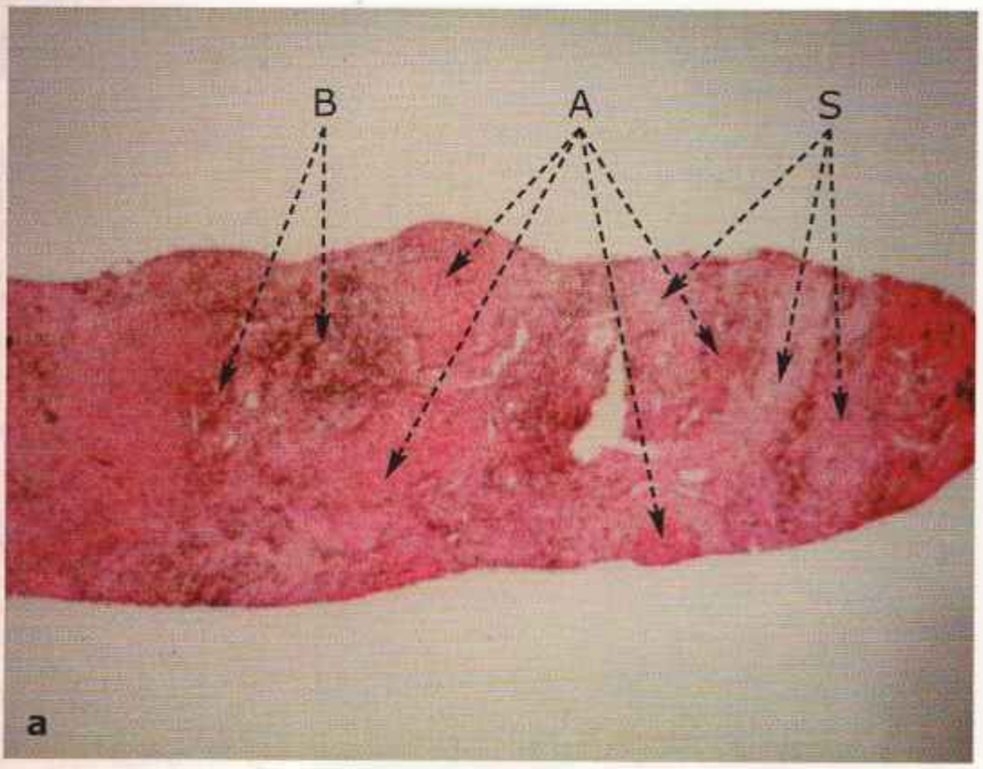


Fig. 21 Upper endoscopy: portal hypertension. Large esophageal blue varices (V) with red signs. Rupture of the varices occurs when portal pressure exceeds 12 mmHg.





Fig. 22 Colonoscopy: portal hypertension.
(a) In some patients, portal hypertension leads to anorectal or colonic varices (blue dilated veins) which may bleed.
(b) Normal rectum.



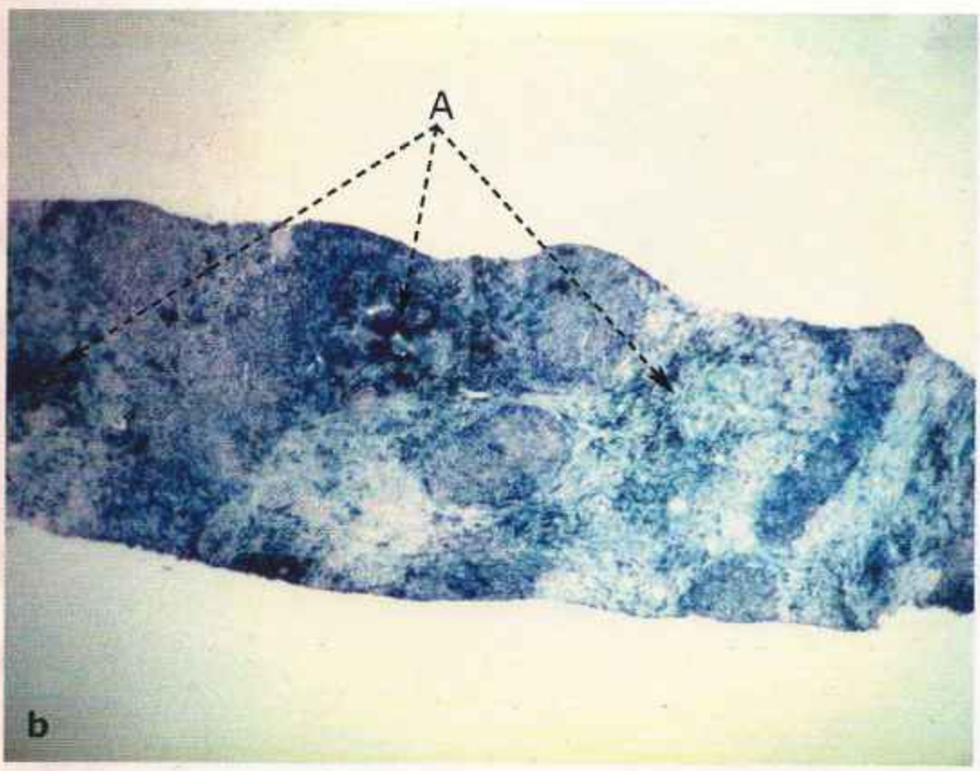


Fig. 23 Liver biopsy: cirrhosis due to genetic hemochromatosis.
(a) Connective tissue septa (S) surround the parenchymal nodules (A); a heavy brown deposition is also evident in the connective cells and hepatocytes (B), H&E stain.
(b) Using Perls' stain, the brown material becomes dark green (A), thus confirming that it is iron.

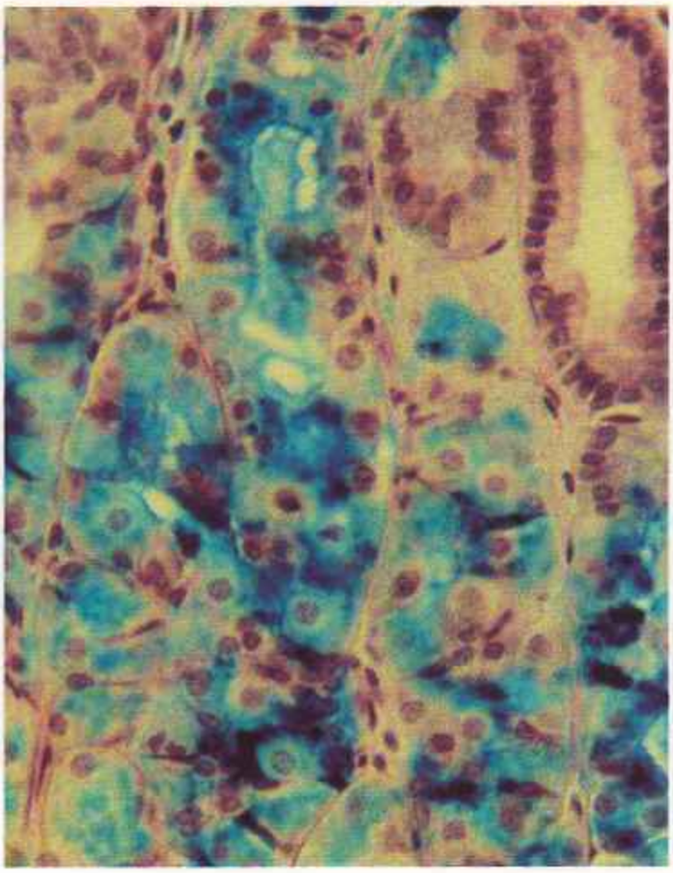


Fig. 24 Gastric biopsy: genetic hemochromatosis (same patient as in Fig 23). Perls' stain shows diffuse iron storage inside the fundus gland cells.

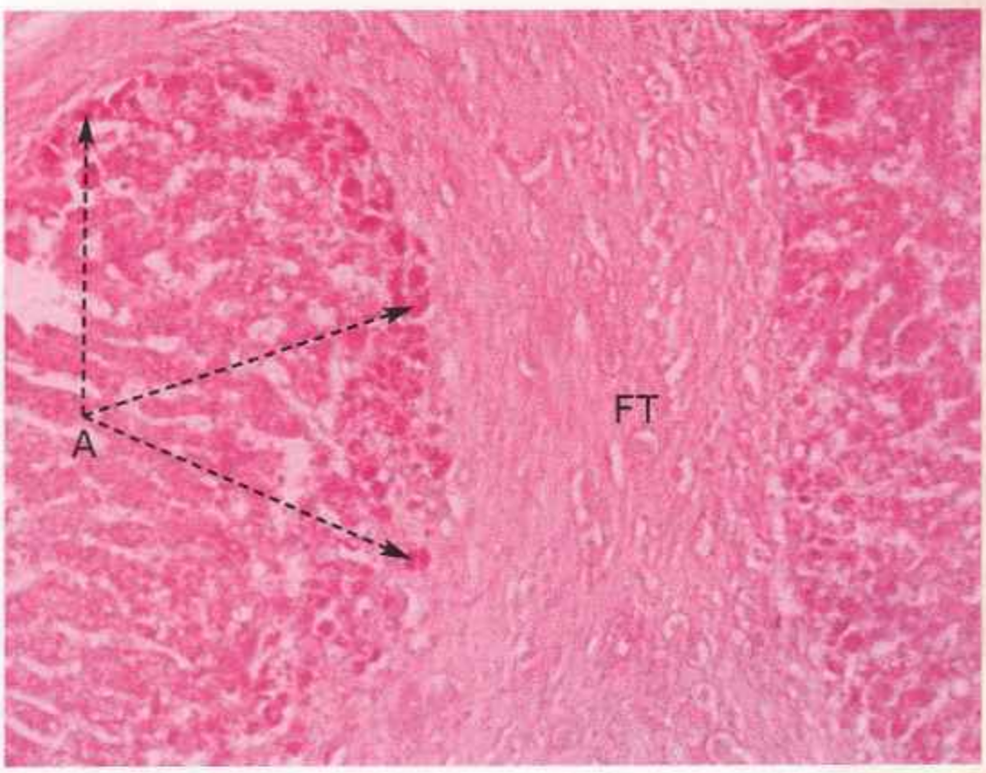


Fig. 25 Liver biopsy: cirrhosis due to homozygous alpha-1 antitrypsin deficiency. Intensely PAS-positive alpha-1 eosinophilic inclusions (A) are present in many of the hepatocytes of cirrhotic nodules; the nodules are separated by fibrous tissue forming septa (FT). PAS stain.

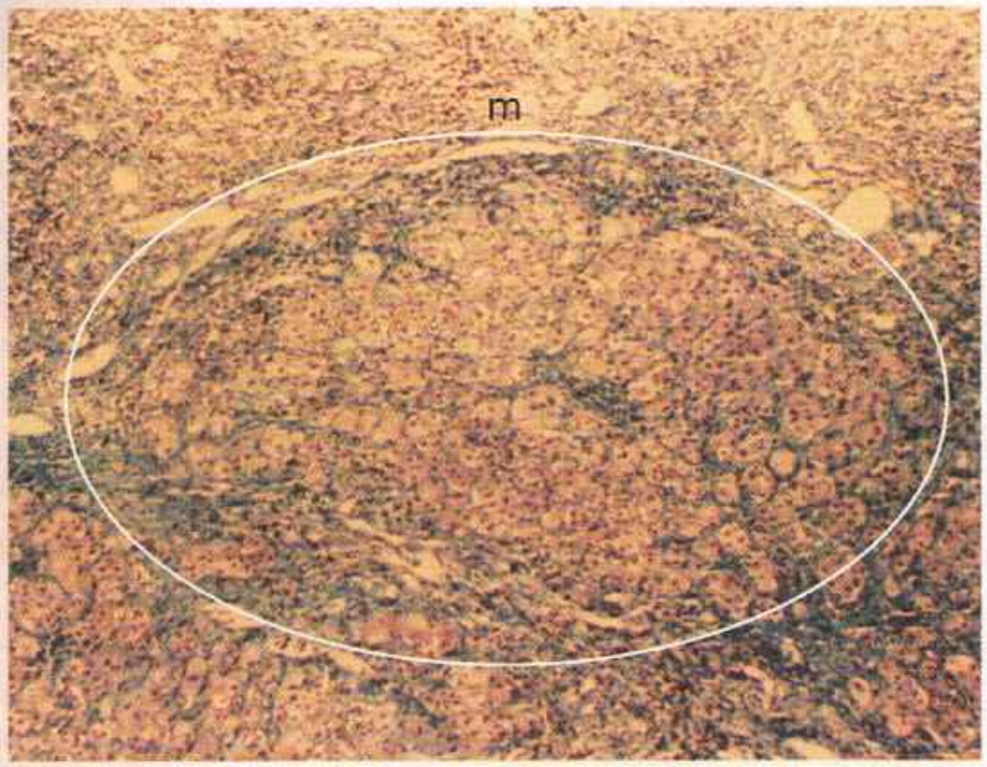


Fig. 26 Liver biopsy: micronodular cirrhosis (m) due to chronic HCV infection. Dense and diffuse lymphocytic infiltrate is associated with bile-duct lesions of the hepatitic type. Chromotrope-aniline blue stain.

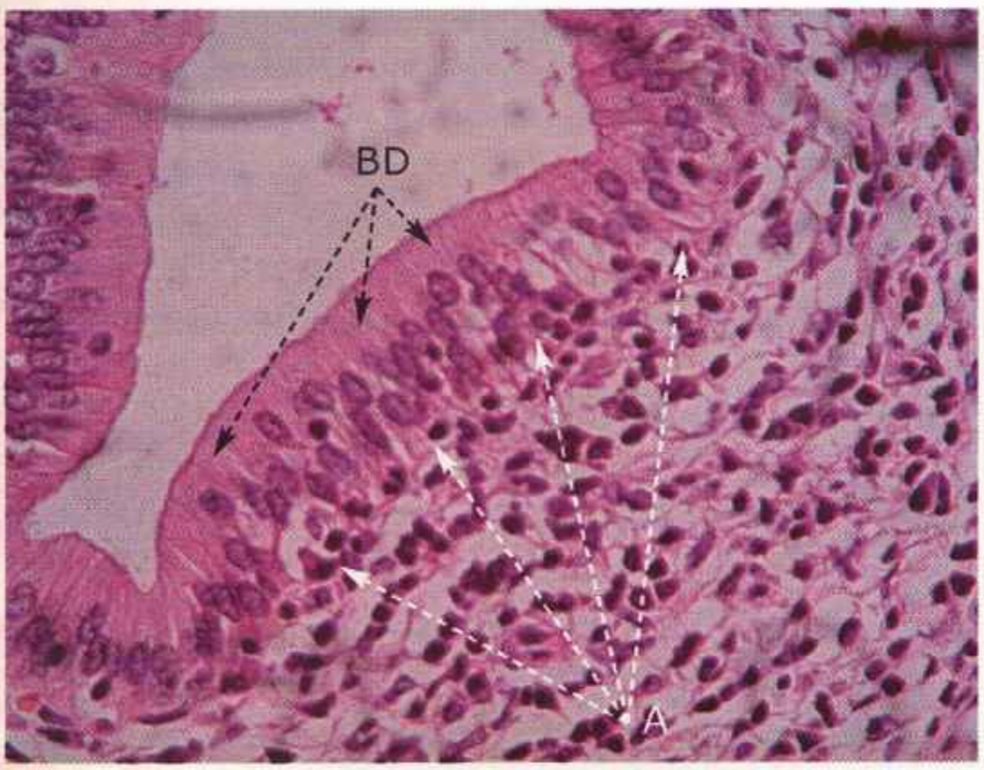


Fig. 27 Liver biopsy: primary biliary cirrhosis. Bile duct (BD) at high magnification. Typical early lesions: the inflammatory cell infiltrate extends from the portal tract into the hyperplastic biliary epithelium, and the basement membrane is focally disrupted (A). H&E stain.

Ascites

This may occur as a result of various conditions, including neoplasms, tuberculosis, pancreatitis and protein deficiency, and is commonly associated with cirrhosis.
The pathophysiology of ascite formation in cirrhosis is complex and involves the combined effects of intrahepatic portal hypertension, volume overload, and mechanical factors. In cirrhotic states, ascites is a sign of decompensated disease and is associated with a poor prognosis.
The mortality rate is up to 60% within two years of the first episode, as against 12% in patients without ascites. The effect of ascites on prognosis also depends on the associated development of spontaneous bacterial peritonitis (25% of patients over a two-year period) and hepatorenal syndrome, both of which further shorten survival. The 1-year cumulative probability of survival in patient with ascites decreases from about 66% to only 38% in the case of an episode of spontaneous bacterial peritonitis. Nearly all patients with hepatorenal syndrome die within 10 weeks of its onset because it is usually irreversible.
Ascites is a condition for listing a patient for liver transplantation, but can also be managed by regulating total body water content in various ways: bed rest, sodium dietary restriction (50 mmol/d), diuretic therapy (spironolactone, furosemide), or therapeutic paracentesis associated with intravenous albumin infusion.
In cases of refractory ascites, temporary or constant reinfusion procedures (peritoneovenous shunt) and liver transplantation are therapeutic options.

TOXIC AND DRUG-INDUCED LIVER DISEASE

Liver injury is frequently due to the introduction of pharmacologic and chemical agents. Up to 40% of "hepatitis" patients aged more than 50 years have a drug-induced disease. It has been estimated that drugs account for up to 25% of the cases of fulminant hepatic failure and they have also been incriminated as a frequent cause of acute cholestatic jaundice (they are the cause of about 5% of all cases of hospitalized jaundice). Hepatotoxicity due to drugs and other chemicals has two major mechanisms: it may be the predictable consequence of the intrinsic toxicity of an agent taken in a dose sufficient to cause liver damage (direct hepatotoxicity), or it may occur as an unpredictable reaction to a therapeutic dose of a drug due to an individual metabolic aberration or immunological hypersensitivity (idiosyncrasy). Twenty percent of the patients who are hypersensitive to drugs also show extrahepatic manifestations of hypersensitivity, such as rash, fever, leucocytosis and eosinophilia. The response to a challenge dose is delayed by days or weeks in the metabolic form of idiosyncrasy, but is prompt after one or two doses in the hypersensivity form. Examples of drugs in the metabolic category are sulindac and the sulfonamides; examples of drugs in the hypersensitive category are diclofenac and amiodarone.

Hepatic injury induced by drugs, enviromental pollutants, herbal products or food additives may be of two main types: cytotoxic (from steatosis to the diffuse death of

hepatocytes), cholestatic (jaundice with relatively little parenchymal injury), or mixed cytotoxic and cholestatic. The toxic injury may be acute or chronic (Tables 3, 4). The acute morphological lesions observed at light microscopy are necrosis, steatosis or obstructive cholestasis and chronic lesions are chronic hepatitis, fibrosis and cirrhosis. Any patient presenting jaundice, pruritus or altered biochemical liver tests, should be questioned about chemical and drug exposure. The diagnosis of drug-induced hepatic disease is easy if the injury follow the injection or ingestion of a well-known toxin, is often presumptive because the relationship between the use of a drug and subsequent liver disease may be impossible to demonstrate, a rechallenge may be dangerous or the lesions at liver biopsy may not be characteristic.

Table 3. *Drugs causing chronic cholestasis or chronic hepatitis*

Cholestasis	*Chronic Hepatitis*
Ampicillin	Acetaminophen
Barbiturate	Aspirin
Chlorpromazine	Diclofenac
Cimetidine	Fenofibrate
Floxacillin	Isoniazid
Methyltestosterone	Methyldopa
Thiabendazole	Nitrofurantoin
Tolbutamide	Papaverine
Troleandromycin	Sulfonamide

Table 4. *Categories of drugs and type of acute hepatic injury*

Categories	Cytotoxic and mixed	Cholestatic and mixed	Cytotoxic or cholestatic
• Anaesthetics	Halothane	----------	----------
• Neuro-psychotropics	Tricyclics	Chlorpromazine	Diazepam
• Anticonvulsants	Phentoin	----------	Phenobarbital
• Analgesics NSAIDs, other compounds	Acetaminophen Chlorzoxazone	Benoxaprofen Diflunisal	Allopurinol Gold
	Diclofenac Ibuprofen Phenylbutazone Indomethacin Salicylates	Penicillamine Propoxyphene	Naproxen Piroxicam Sulindac
• Antimicrobials	Amphotericin B Clindamycin Metronidazole Rifampin Ampicillin Sulfonamides Tetracyclines	Amoxicillin Erythromycin Cloxacillin Dicloxacillin Zidovudine	Cephalosporins Nitrofurantidin Penicillin Oxacillin Sulfadoxine
• Cardiovascular	Amiodarone Diltiazem Methyldopa Nicotinic acid Nifedipine	Ajmaline Captopril Coumadin Thiazides Verapamil	Amrinone Disopyramide Enalapril
• Drugs used in endocrine disease	Ciclofenil Tamoxifen Diethylstilbestrol	Tolbutamide Danazol Anabolic steroids	Thiouracil
• Anti-neoplastic	Tamoxifen Fluoruracil Methotrexate	Busulfan Floxuridine	Azathioprine

Liver cysts

Congenital biliary cysts are the most frequent tumor-like lesions. The etiopathogenesis of solitary cysts remain undetermined but they may be of developmental origin. They occur at all ages, although the majority present in the fourth to sixth decades of life. The cysts are lined by bile duct epithelium, and may be solitary or multiple, the latter usually being an aspect of autosomal dominant polycystic kidney disease. Cysts of less than 10 cm rarely cause symptoms, which may otherwise include an upper abdominal mass with a sensation of fullness or discomfort, nausea, vomiting and jaundice. Diagnosis is generally by chance and made during US or CT. At US, simple cysts are seen as clearly-defined echo-free spaces with thin walls. Adenocarcinomas and squamous cell carcinomas may arise in solitary cysts of the liver.

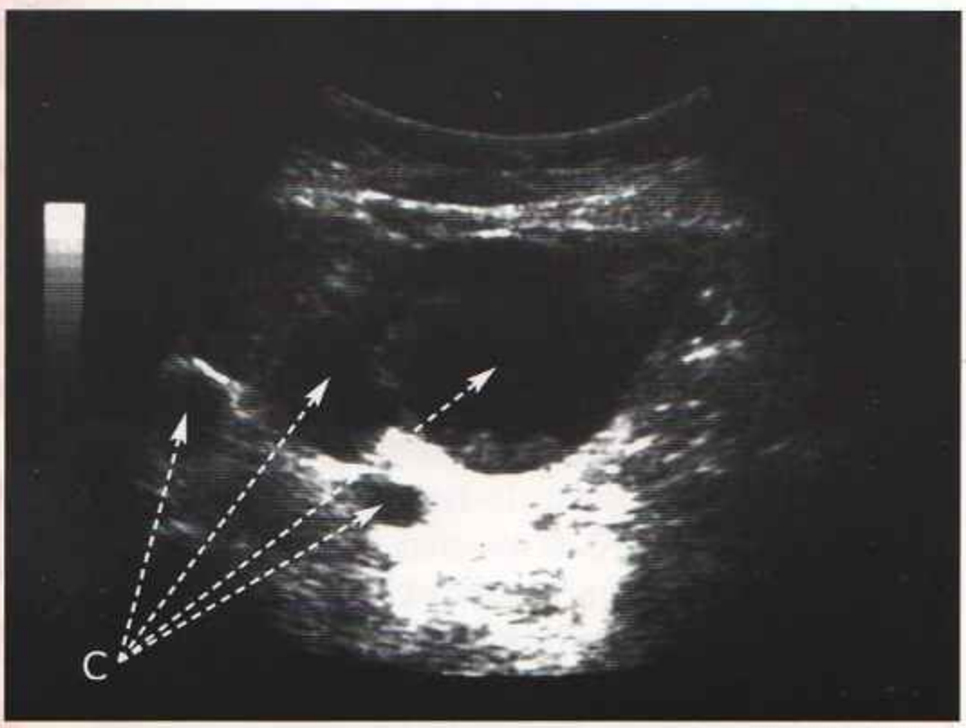


Fig. 30 Liver US: multiple cysts (C). Cysts appear as multiple anechoic and well-defined areas that also show acoustic enhancement.

Primary liver tumors

The term hepatoma used for any tumor arising in the liver has no histological meaning, and should be abandoned.

Tumors of the liver can be benign or malignant and are usually classified as hepatocellular, biliary, mesenchymal and mixed. The most frequent benign epithelial tumor is the hepatocellular adenoma, which consists of cells closely resembling normal hepatocytes. The tumor may be single or multiple and occurs in otherwise normal liver. It is mainly observed in young women and as an etiologic relationship to the use of oral contraceptives or anabolic steroids, and to familial diabetes mellitus. The most frequent malignant tumor is hepatocellular carcinoma (HCC), the incidence of which varies from 100 in South Africa, to 3 in Australia, India and Germany. The implicated etiologic factors are viral hepatitis (HBV, HDV, HCV), alcohol, thorotrast, aflatoxin exposure, porphiria cutanea tarda, genetic hemochromatosis and alpha-1 antitrypsin deficiency. It is commonly associated with cirrhosis but may rarely occur in its absence. The mean risk of developing HCC in patients affected by cirrhosis or chronic hepatitis is respectively about 12.5% and 3.8%. The greatest clinical problem concerning HCC is early diagnosis, which is now possible if patients at risk have their serum alpha foetoprotein levels monitored and undergo US every 3-6 months. The sensitivity of US in detecting an undetermined focal lesion is 95% and its specificity is 99%, and its sensitivity in detecting HCC (i.e. the neoplastic nature of the focal lesion) is only about 60%. The diagnostic sensitivity for HCC of US associated with a biopsy

of the lesion is 93% and the specificity is 100%. CT-scan is also used, and is more sensitive than US if performed after an injection of lipiodol (Lipiodol-CT). Lipiodol-CT allows an evaluation of the effect of antineoplastic drugs injected directly into the tumor (hepatic arterial embolization). Other therapeutic procedures for HCC are US or CT-guided PEI (percutaneous ethanol injection), which is indicated when the tumor size is less than 5 cm, or TACE (trans arterial chemo embolization) with lipiodol or doxorubicin. Whenever possible, the best procedure remains curative surgery. The 3-year survival rate is 13-26% with no treatment, 40-79% after surgery, and 41-71% after PEI.

Hemangioma (cavernous hemangioma) is the most common benign tumor of the liver, being observed in about 7% of autopsy series and about 4% of the subjects undergoing US. It consists of a large network of vascular endothelium-lined spaces filled with red blood cells. Hemangiomas are usually small (1-4 cm in diameter), but may occasionally be enormous. The higher frequency of hemangiomas in multiparous females suggests that they may be hormone-related.
Clinical manifestations are rare, and the tumor is discovered only by chance at US. If the CT or US findings are not characteristic, an angiogram or biopsy is necessary. If the lesion is characteristic, almost always, a follow-up US examination may be performed within 6-12 months; an unchanged lesion does not represent a clinical problem, but the lesions may very occasionally grow to sizes that need surgery or can burst. A few cases may undergo thrombosis, progressive fibrosis and calcification. Giant hemangiomas (> 10 cm in diameter) can be complicated by platelet sequestration and consumptive coagulopathy (Kasabach-Merritt syndrome).

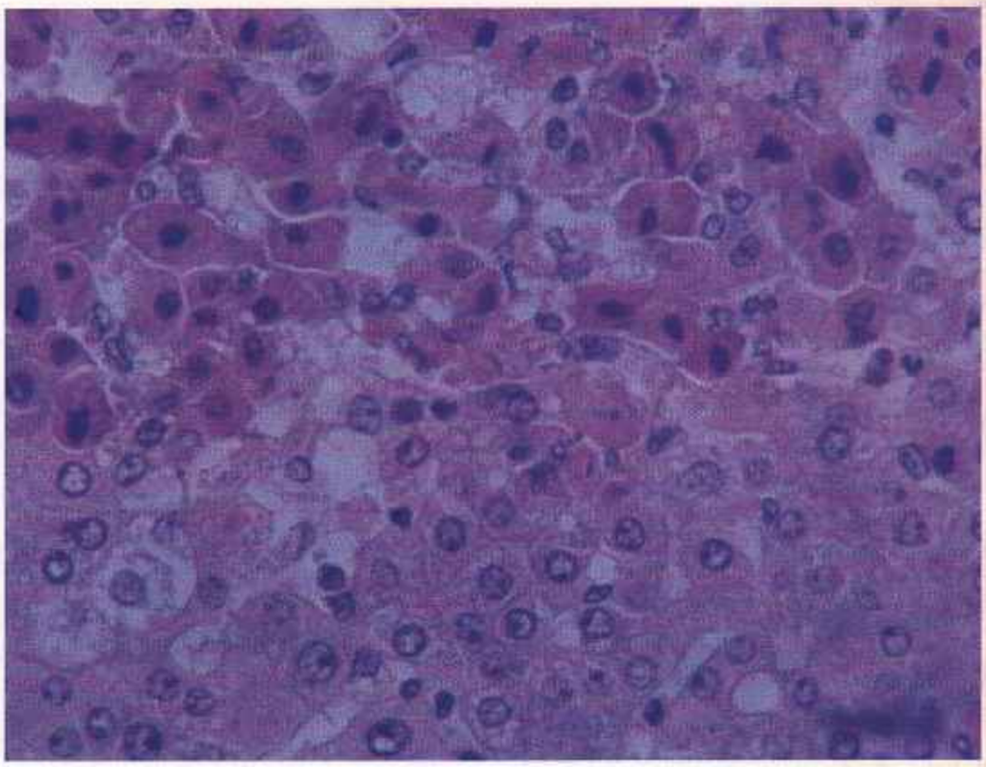


Fig. 31 Liver biopsy: hepatocellular adenoma. The Tumor cells (bottom) are larger and paler than the normal hepatocytes (top). H&E stain.

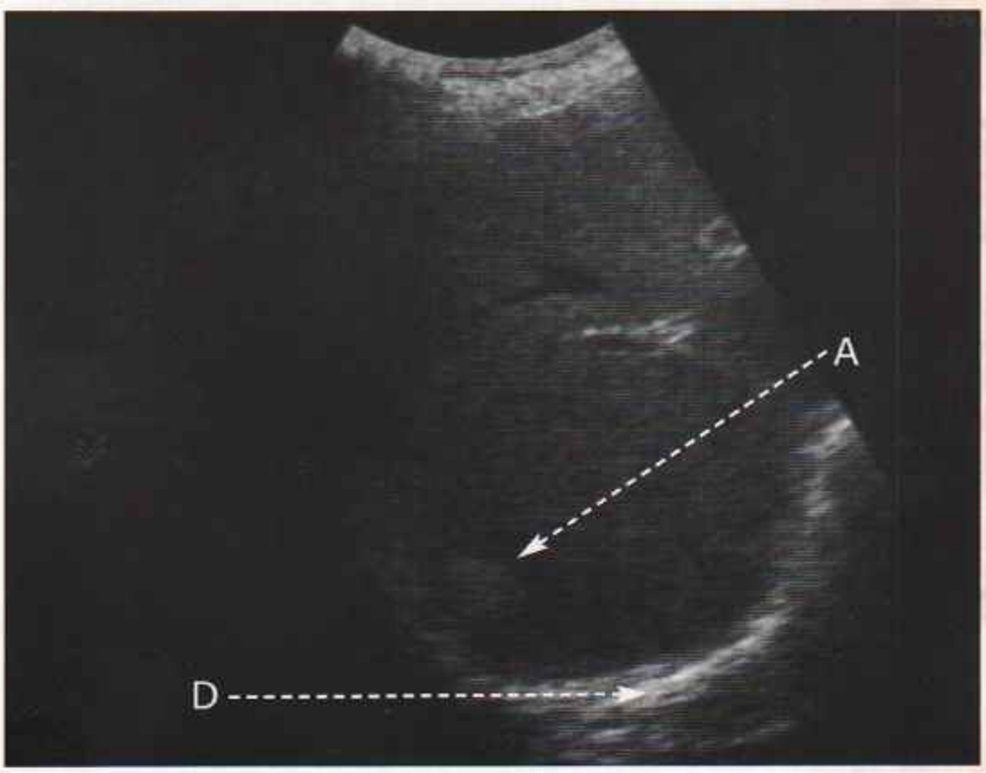


Fig. 32 Liver US: cavernous hemangioma. The round lesion of 15 mm in diameter (A) has a homogeneous echodense pattern that is sharply outlined, diaphragm (D).

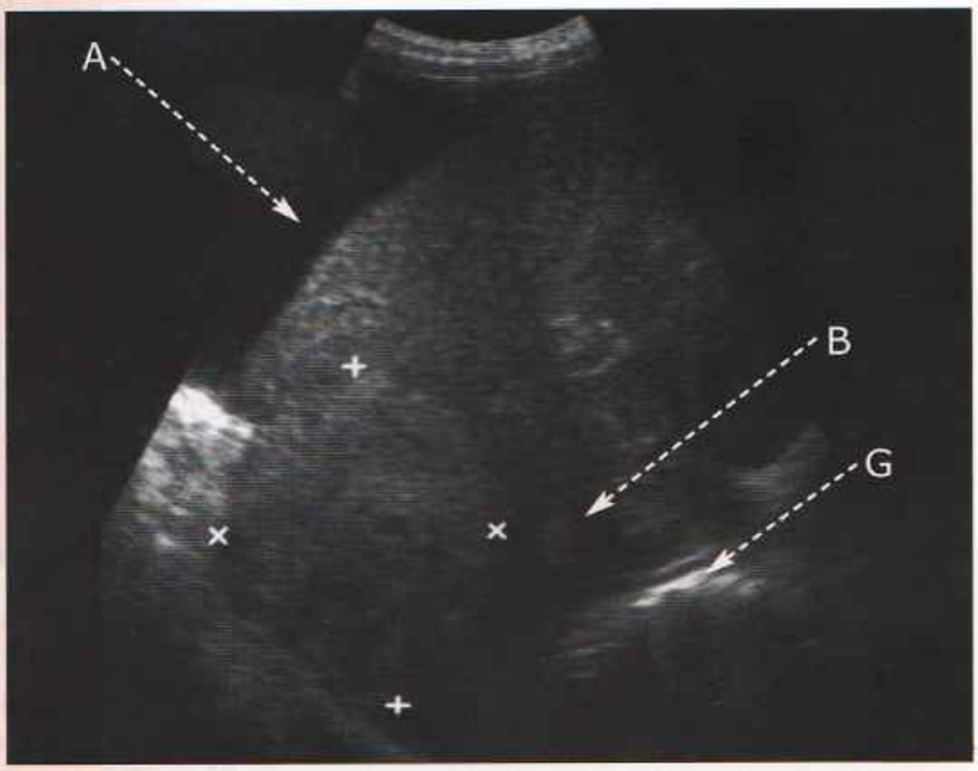
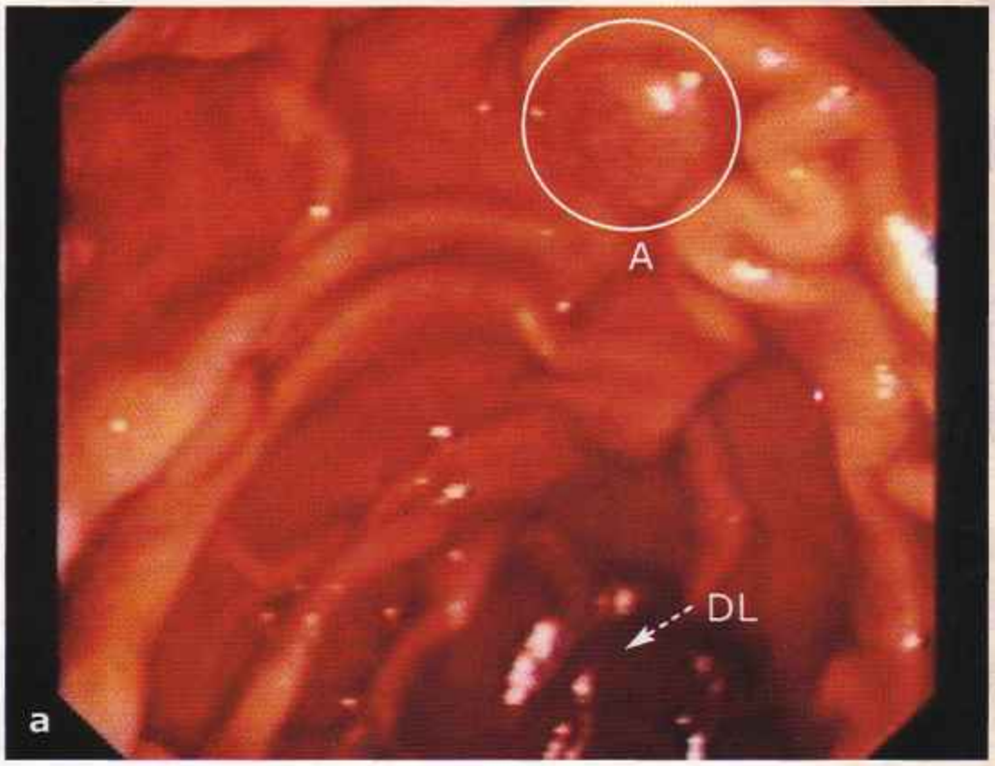


Fig. 33 Liver US: multifocal HCC and cirrhosis. The largest lesion (white crosses) is 97 mm in size and has irregular areas with a hypoechogenic pattern; there is another smaller neoplastic lesion (B), ascites (A), and gallstones (G).



Fig. 34 Liver lipiodol CT-scan. HCC in HCV-related cirrhosis. Ct check scan after a second chemoembolization: the fact that there is still selective uptake by the tumor (A) means that the neoplastic lesion has not been completely destroyed.



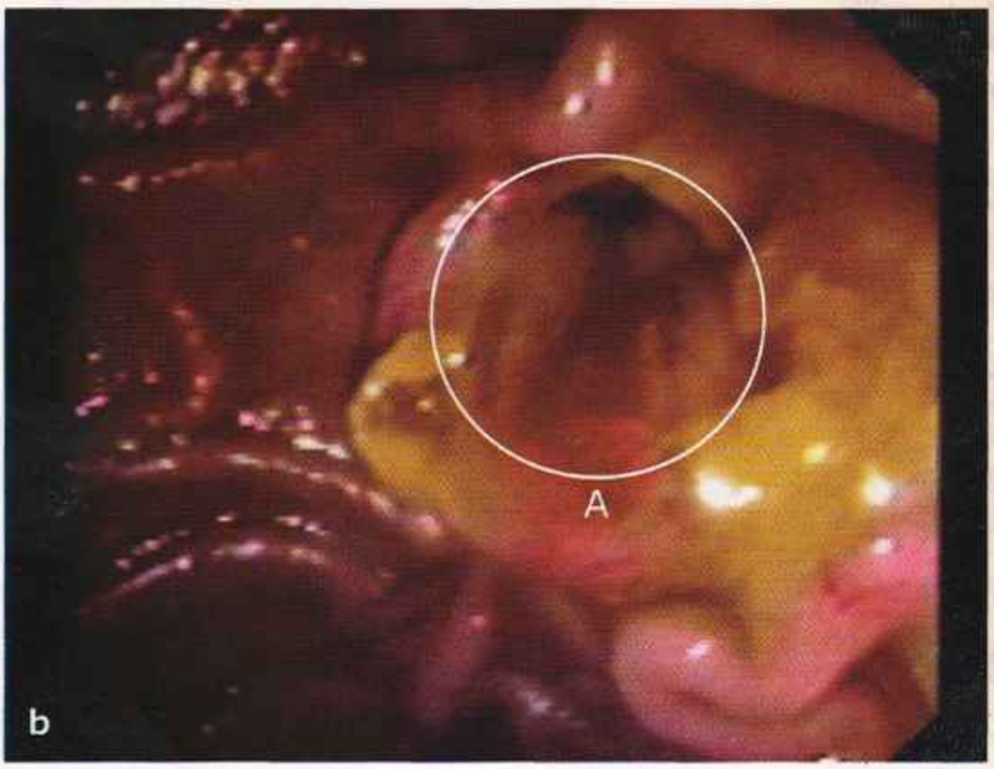


Fig. 43 Therapeutic ERCP: duct stone.
(a) Papilla of Vater (A) before sphincterotomy, duodenal lumen (DL).
(b) Papilla after sphincterotomy (A). ERCP can also be used for the balloon dilatation of strictures, the placement of stents and nasobiliary drains, and the management of patients with pancreatic problems.

POST-CHOLECYSTECTOMY SYNDROME

Gallstones are extremely common and cholecystectomy one of the most frequent surgical procedures although most gallstones are clinically asymptomatic. The number of cholecystectomies is also increasing because of the advent of the laparoscopic procedure, which is widely considered safe. However, many patients are not satisfied because of the lack of improvement, relapsing symptoms or the recurrence of new complaints presumably related to the operation. These "post-cholecystectomy syndromes" range from mild to severe symptoms and are clinically characterized by right upper quadrant pain or discomfort, altered bowel movements, flatulent dyspepsia, nausea, eructations, an intolerance to fatty foods, and jaundice. The two main problems are abdominal pain and altered bowel movements.

The diagnostic criteria of pain suggestive of a pancreobiliary origin are:

- Pain in the RUQ or epigastrium radiating to the shoulder or back
- Pain episodic (from a few minutes to several hours)
- The absence of other gastrointestinal symptoms
- No stones revealed by US/ERCP
- An interval of at least six months following the procedure.

The frequency of pain one year after cholecystectomy is 28 % for minor and 7% for moderate to severe symptoms. Eighty-six percent of the patients are female. The causes of pain at one year are biliary abscesses or stones (2%), ulcer or hernia wound pain (9%). The pain is

considered functional in 26% of the patients. Sphincter of Oddi dysfunction is often considered the cause of post-cholecystectomy pain, but does it exist? Most gastroenterologists would say yes, but it is over-diagnosed; on the basis of manometric criteria, it is present in less than 1% of the patients.

The second main post-cholecystectomy symptom is chronic diarrhea. Altered bowel movements after cholecystectomy are reported by about one-third of the patients, with women being more susceptible than men. Persistent diarrhea significantly affects the quality of life of 12% of the patients. The diarrhea is frequently post-prandial, or occurs early in the morning, is difficult to delay, and may appear some years after surgery. The malabsorption of bile salts is the pathogenetic mechanism, and the main diagnostic criteria is the response to cholestiramine. Other less frequent entities related to cholecystectomy are idiopathic recurrent pancreatitis and small bowel motility disorder.

In conclusion, be cautious about drawing causative relationships between symptoms and gallstones, and therefore be cautious about recommending cholecystectomy, particularly in women with signs of irritable bowel syndrome, because the procedure may worsen pre-existing symptoms.

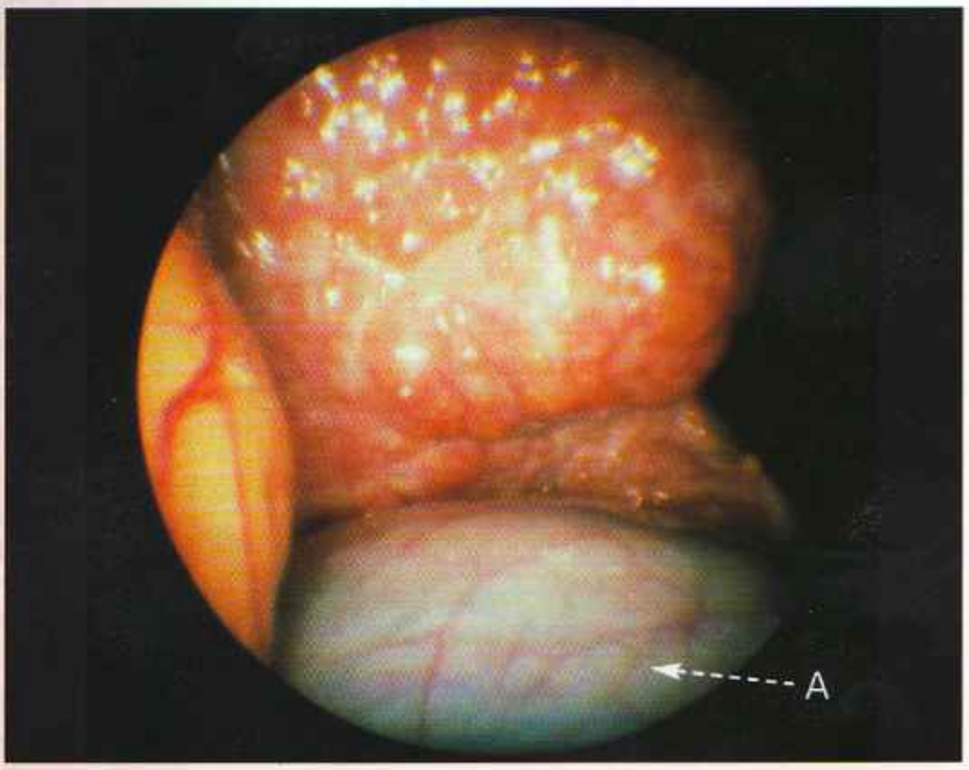


Fig. 44 Laparoscopic cholecystectomy: cirrhotic liver (top) and distended gallbladder (A). US had previously revealed gallstones and acute cholecystitis. After surgery, one more episode of jaundice.



Fig. 45 US, magnificated image: two stones inside the dilated common bile duct after right and left bile duct confluence.

Foodborne diseases

These diseases can be transmitted by foods, nutritional factors or other ingested substances, and caused by pathogenic agents (viruses, bacteria and fungi) or chemical agents such as drugs (see "Drug-induced liver disease"), alimentary toxins and toxicants. The injury is sometimes due to toxic substances normally present in foods, but may also be caused by bacteria or fungal toxins contaminating harmless foods. The diseases can be associated with significant morbidity and mortality, as well as hepatic injuries.

Various bacteria cause food poisoning as a result of their specific enterotoxins: Staphylococcus aureus, Bacilus cereus, Clostridium perfrigens, Vibrio cholerae, Enterotoxigenic Escherichia coli, Vibrio parahaemolyticus, and Shighelia spp.
The symptoms appear after a short incubation period of 1-16 hours (or may be more) and generally include diarrhea, nausea, vomiting, and abdominal pain; fever is rare, and the liver is usually spared. In most cases the diseases are self-limiting and no specific. Diagnosis or treatment is necessary, and rehydration may be enough. A typical food poisoning disease due to fungi follows the chronic ingestion of peanuts contaminated with Aspergillus flavus, which can cause acute hepatic damage, cirrhosis and HCC by means of the fungal aflotoxins.

In other cases, the food poisoning is not due to infective agents but to chemical compounds of 'nutritional' factors (herbal-plant products), and these cases often lead to hepatic damage.

The severity of the hepatotoxic effects depends not only on the toxic components but also on individual susceptibility due to metabolic or immunologic idiosyncrasy, or a concomitant immune system deficiency (AIDS, chemotherapy, organ transplantation). One well-known example of chemical toxicity follows the ingestion of the mushroom Amanita phalloides. Mushroom poisoning is clinically characterized by transient severe diarrhea followed by acute and fatal hepatic and renal failure; the liver shows severe steatosis and centrolobular necrosis.

A variety of endotoxins produced by the dinoflagellates of fish (tuna, dolphins and barracuda) or shellfish (molluscs) can cause poisoning syndromes, such as histamine fish poisoning (scombroid), ciguatera, paralytic or neurotoxic shellfish poisoning, tetrodoxin poisoning. The clinical picture depends on the type of toxins developed; vomiting, diarrhea and neurologic symptoms are present from five minutes to 3-6 hours after the ingestion of fish or shellfish. Liver injuries are rare in these cases, as already observed in the case of bacterial poisoning.

Plants of the genera Crotolaria, Heliotropium and Senecio (used to make bush tea) can lead to veno-occlusive disease (VOD) because of their pyrrolizidine alkaloids content. The clinical features and hepatic congestion of VOD are similar to those of Budd-Chiari syndrome, which is due to hepatic vein thrombosis.

Toxic epidemic syndrome is another model of food poisoning. This is a multisystem illness attributed to cooking oil adulterated with aniline-denaturated rapeseed oil. The liver damage (fatal in some patients) resemble that caused by cholestatic hepatitis and is similar to

chloropromazine-induced liver injury. Other herbal medications or diet supplements available from "natural food" stores can also lead to liver damage, especially Mate tea (health aid), Germander (assists weight loss), Chinese herb preparations (medicinal tea), Chaparral leaf (medicinal), Margosa oil (health aid).
The diagnosis may be difficult when the patients do not report taking a herbal preparation because they fear their physician's disapproval or believe the intake of "natural drugs" has nothing to do with "drug esposure".

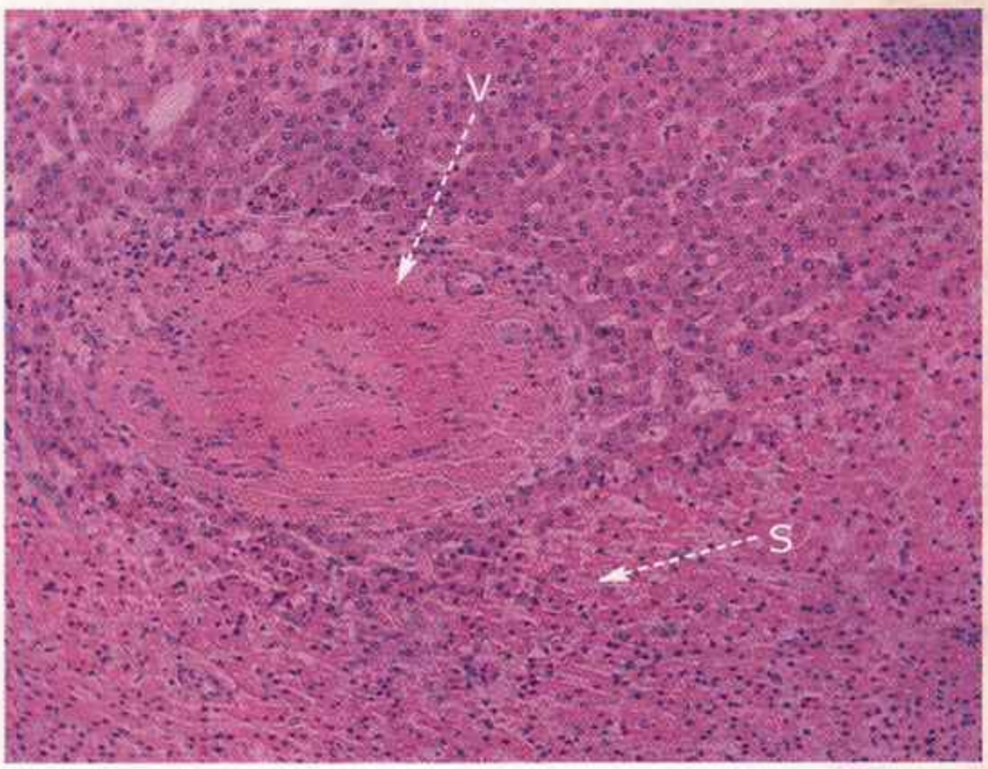


Fig 46 Liver biopsy: Veno-occlusive disease due to pirrolizidine-containing dietary supplement-Senecio. Hepatic vein thrombotic occlusion (V) by fibrous tissue (chronic lesion), with a few inflammatory cells scattered inside the fibrous tissue; the sinusoids (S) are congested. H&E stain.

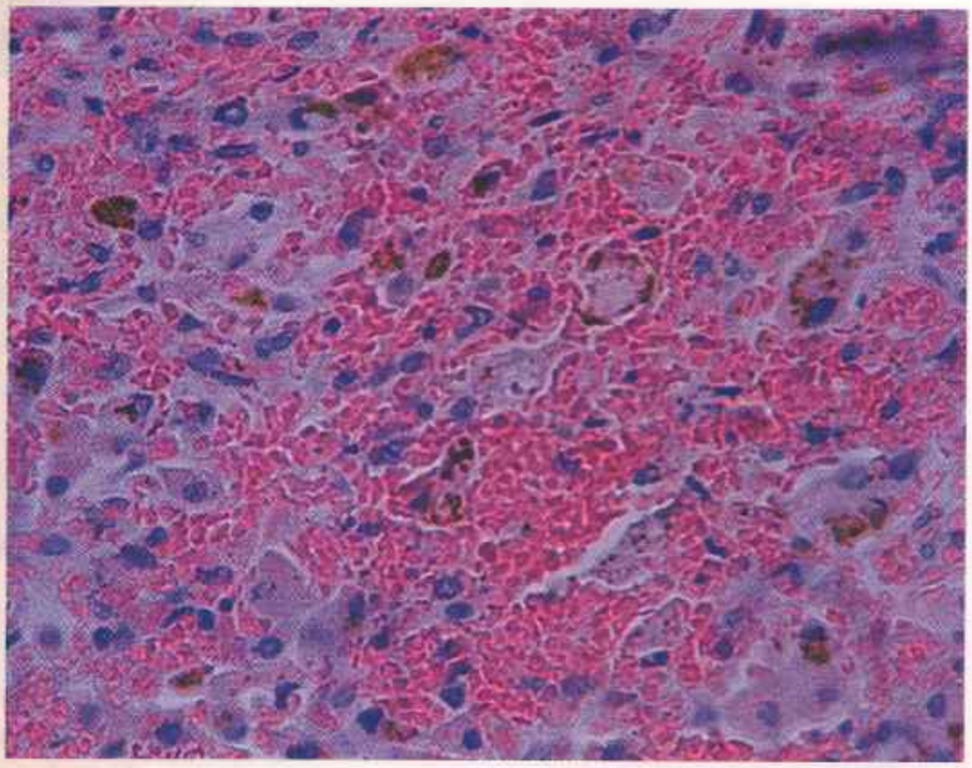


Fig. 47 Liver biopsy: acute injury (probably due to toxic food). Marked hemorrhage with perivenular necrosis (red area) and canalicular cholestasis (brown spots); no stromal inflammation. H&E stain.

BIBLIOGRAPHY

1) Sherlock S, Dooley J: *Diseases of the Liver and Biliary System, 10th ed., Oxford, Blackwell, 1997*

2) Zakim D, Boyer TD: *Hepatology: A Textbook of Liver Disease, 3d ed., Philadelphia, Saunders, 1996*

3) Arias IM et al: *The Liver: Biology and Pathophysiology, 3d ed., New York, Raven, 1994*

4) Schiff L, Schiff ER: *Diseases of the Liver, 7th ed.; Philadelphia, JB Lippincot, 1993*

5) Morgan DJ,Smailwood RA: *Drug-induced liver disease. Curr Opinion Gastroenterol 12: 2469 1996*

6) Mc Sween et al: *Pathology of the Liver, 3rd ed., London Churchill Livingstone, 1994*

7) Watson RR: *Liver pathology and Alcohol. New Jersey (USA), Umana Press, 1991*

8) Sieisinger & Fordtran's: *Gastrointestinal and Liver Disease, 6th ed., Philadelphia, Saunders, 1997*

9) Okuda K: *Hepatocellular carcinoma: Recent progress. Hepatology 15: 948, 1992*

10) Barak AL et al: *S-adenosylmethionine generation and prevention of alcoholic fatty liver by betaine. Alcohol. 11 (6): 501-3, 1994*

11) Conte D et al: *Stainable iron ingastric and duodenal mucosa of primary hemochromatosis patients and alcoholics. Am J Gastroenterol 1987; 82,3: 237-40*

12) Mandelli C et al: *Hepatic iron concentration in alcoholic and posthepatitic cirrhosis and haemochromatosis. Eur J Gastroenterol Hepatol 1991; 11: 835-40*

13) Zanella A et al: *Hepatitis C virus and liver histology in blood donors reactive to a single antigen by second-generation recombinant immunoblot assay. Hepatology 1995; 108: 913-7*

14) Conte D et al: *Nonalcoholic steatohepatitis. Report of five cases and review of the literature. Ital J Gastroenterol 1995;27: 363-365*

15) Bianchi PA, Velio P: *Neoplasie dell'intestino e cancerogenesi. In "Manuale delle malattie dell'apparato digerente". Unigastro 2ª edizione 1998-2000, Ed. UTET Torino 1998: 389-97*

16) Quatrini M et al: *Malattie dell'apparato digerente. In C Zanussi "Metodologia diagnostica in medicina interna", Ed. UTET Torino, 1999: 227-274*

JETEPAR®

PHARMACOLOGICAL MANAGEMENT OF THE IMPAIRMENT OF DETOXICATION

To be successful, the therapy of intoxication must first of all interrupt the vicious circle of the overload of toxic substances due to liver insufficiency and the further aggravation of liver insufficiency caused by the cumulation of toxic substances. The vicious circle of intoxication is quite easy to explain: liver insufficiency means no complete elimination of toxic substances with a chronic cumulation that creates a permanent impairment of liver function with a consequent deterioration of the remaining ones. In addition to this chronic liver damage, the metabolic general impairment at hepatic level involves other organs and functions such as the CNS, the gastrointestinal tract, the endocrine glands and the kidneys with a cumulative dangerous and negative effect (Fig. 1).

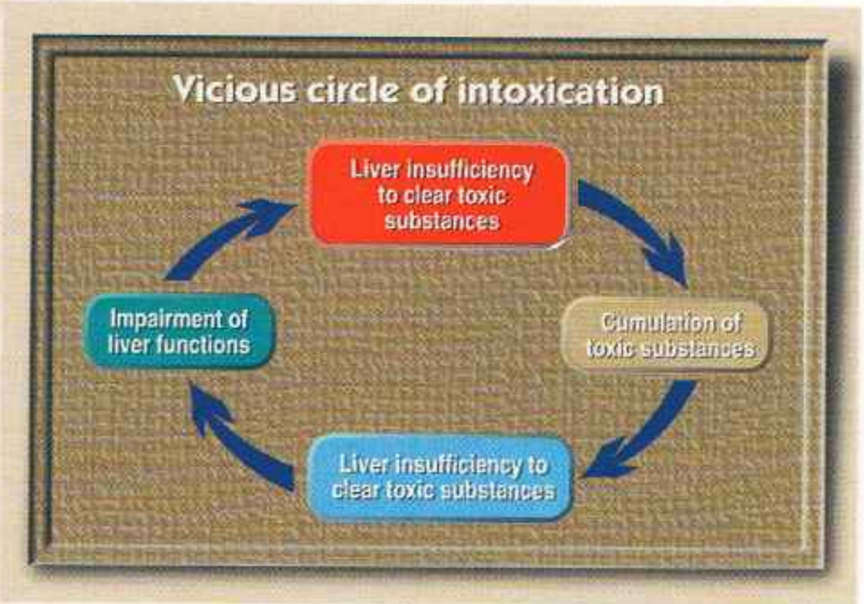


Fig. 1

JETEPAR AND HEPATIC FAILURE (12)

The above mentioned principles are combined in a single drug: JETEPAR (Fig. 3).

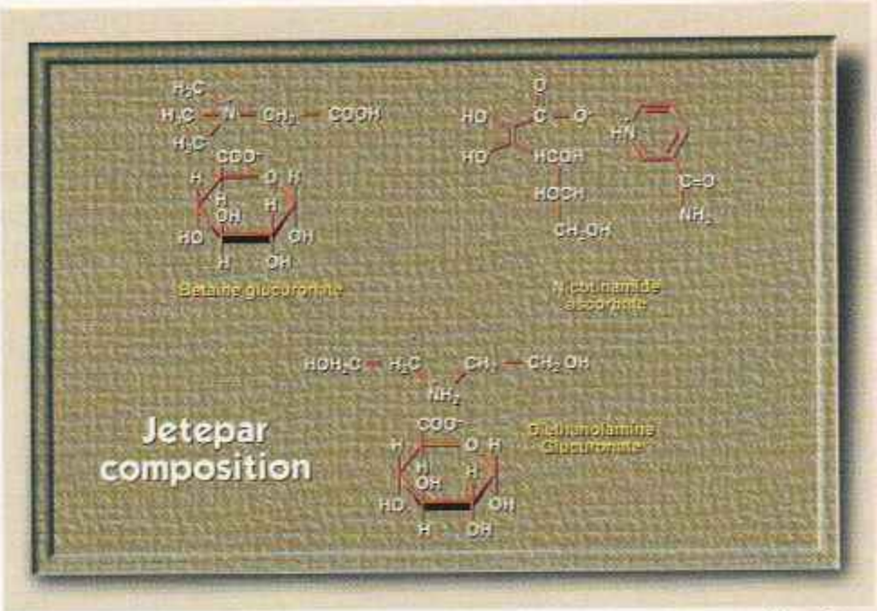


Fig. 3

Because of a complete mechanism of action, Jetepar provides:

- Improvement of hepatic functionality with nicotinamide ascorbate that catalyzes the detoxifying process in the liver;
- Protection of hepatocyte with betaine glucuronate that increases liver capacity to carry out toxic agents;
- Detoxifying activity with diethanolamine glucuronate that clears liver cells from fat.

Several animal studies have shown the efficacy of Jetepar in experimental liver damages and in exogenous intoxications demonstrating that JETEPAR is effective in improving detoxication processes when they are impaired by lesions of the liver due to obstruction of the biliary tract, hyperlipidic diet, poisoning by carbon tetrachloride, partial hepatotectomy. Many are the diseases provoking liver insufficiency and impairment of liver metabolism. Jetepar has been studied in clinical trials involving more than 600 patients suffering from various infective and not infective acute and chronic liver diseases (Fig. 4). Jetepar drives the detoxication reactions, stimulates the respiration of hepatocytes and restores the functions of the liver (Figg. 5, 6, 7).

Jetepar and published clinical experiences

Diagnosis	N° of patients
Acute hepatitis	119
Chronic hepatitis	192
Fatty liver	98
Liver cirrhosis	83
Cholestasis	17
Liver insufficiency	24
Misc. liver disord.	40
Uremia	50
Total	623

Fig. 4

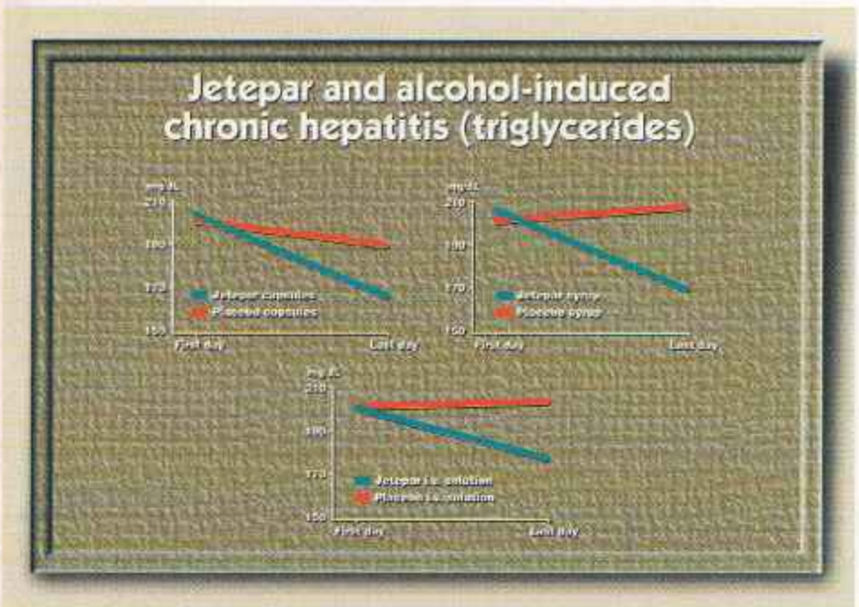


Fig. 5

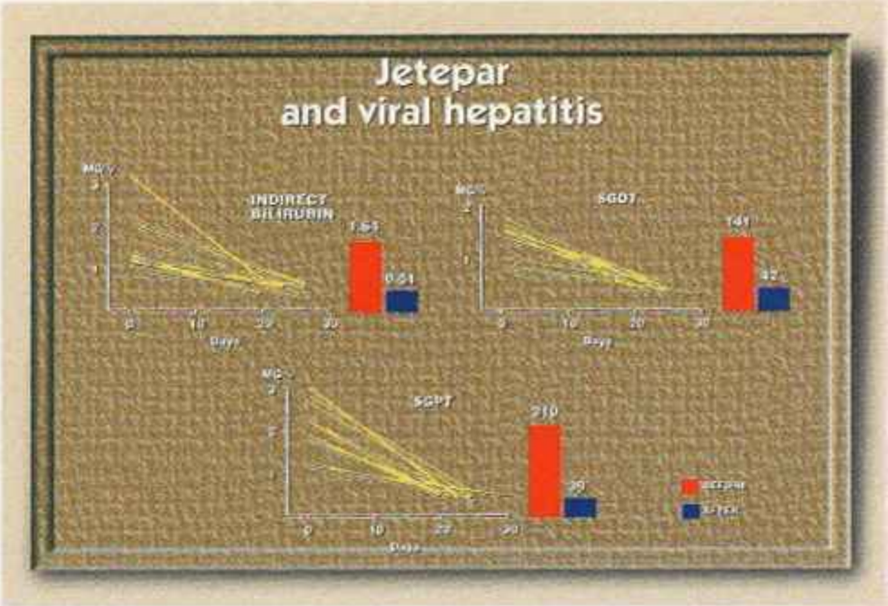


Fig. 6

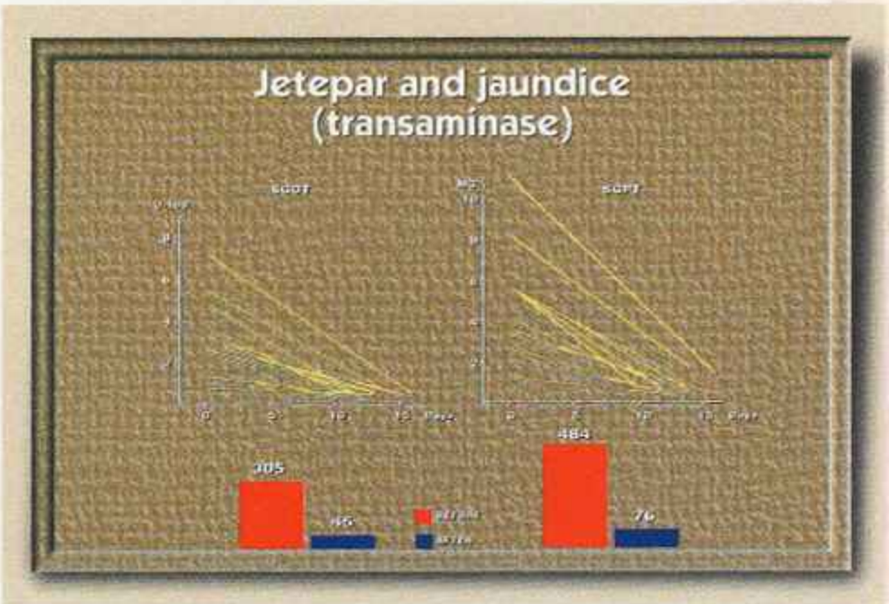


Fig. 7

Jetepar can be considered a complete treatment in any case of liver disfunction related to metabolic impairment because of its synergic mechanism of action and rational combination of active ingredients. Jetepar is safe, the patient's compliance is favoured by different routes of administration (i.v., i.m., capsules and syrup) and can be administered also to children.