Evaluation of patients with elevated liver function test (LFT)

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How extensive should you be?

Elevated LFT in a 62 year old woman with arthrosis/osteoporosis, type 2 diabetes, hypertension and hyperlipidemia.

Extensive medication list.

Overweight. No liver stigmata.

Focused investigation?

28-year old woman with slight, pressing discomfort in her right upper abdomen. Previously healthy. On oral contraception since 3 years.

Bil 22, ASAT 0.8, ALAT 1.0, GT 1.2, ALP 2.6, INR 1.0

When should we use imaging?

1. Is the entire liver affected?

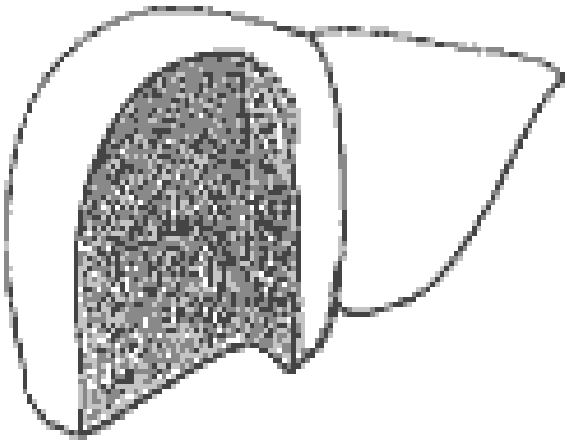
2. Are focal changes present?

3. Are the bile-ducts affected?

Liver imaging methods

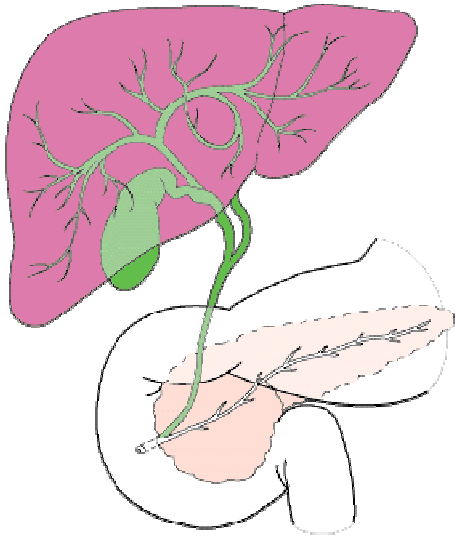
- Ultrasound
- MR incl. MRCP
- ERC
- PTC
- CT

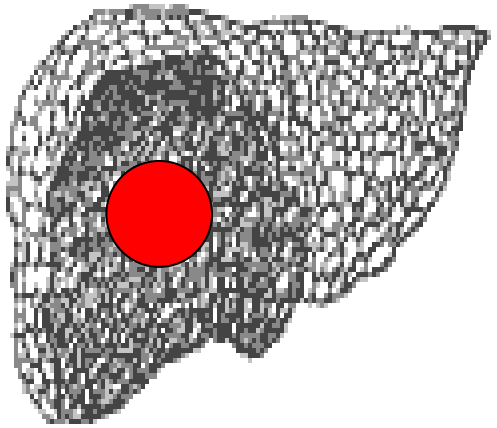
Which method should you choose?



Parenchyma

Bile ducts



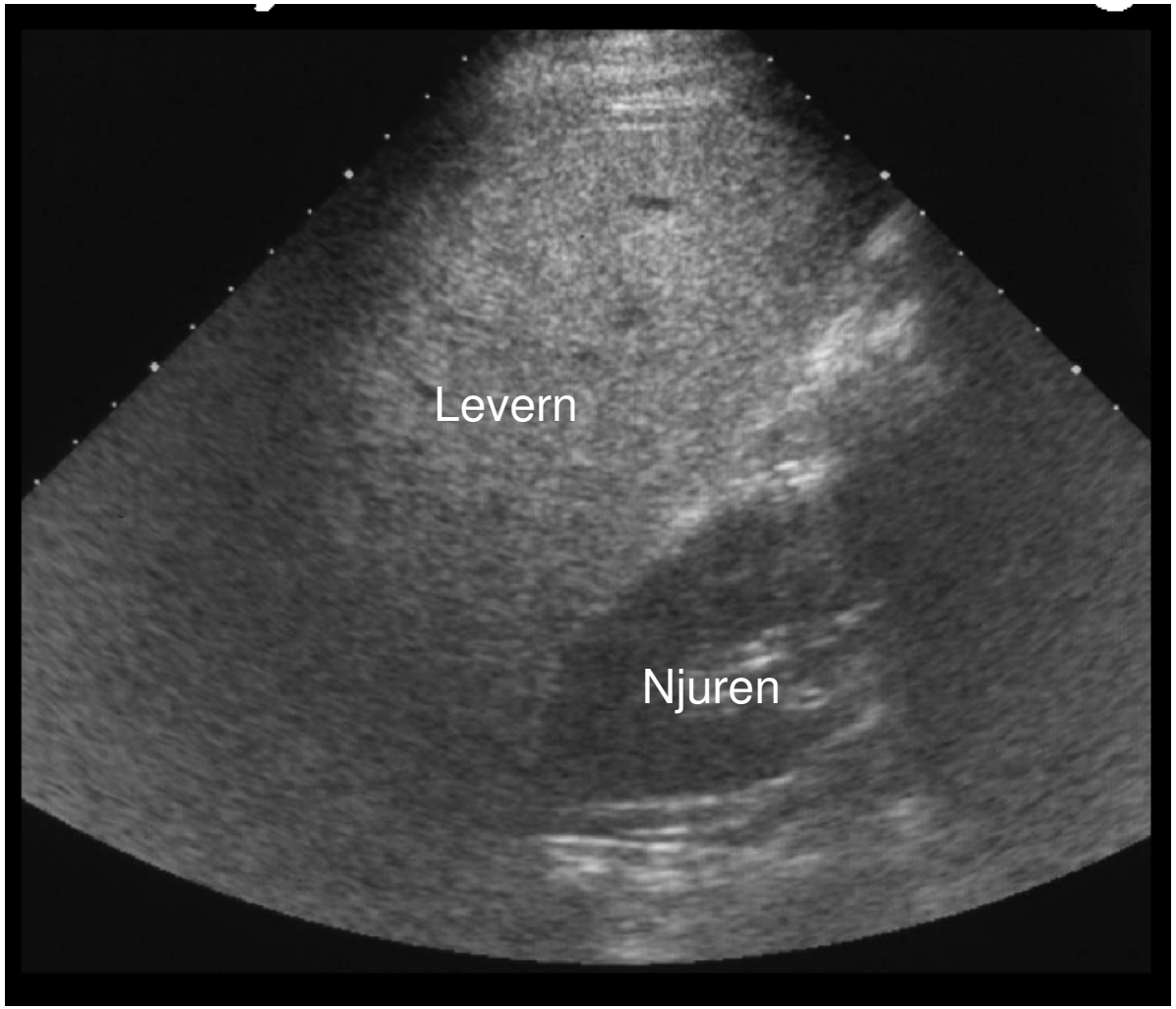


Focal changes

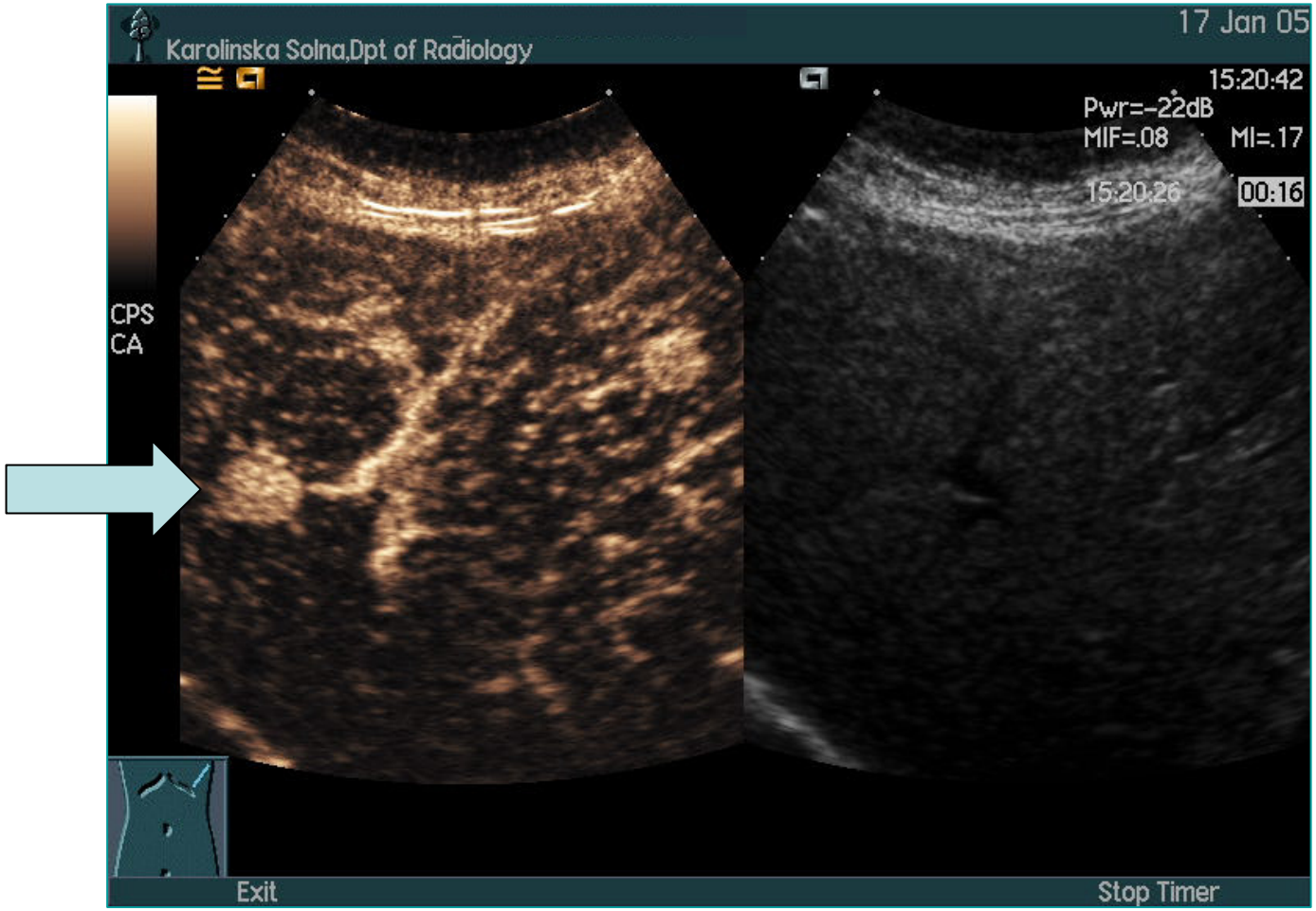
Ultra sound

Echogenicity

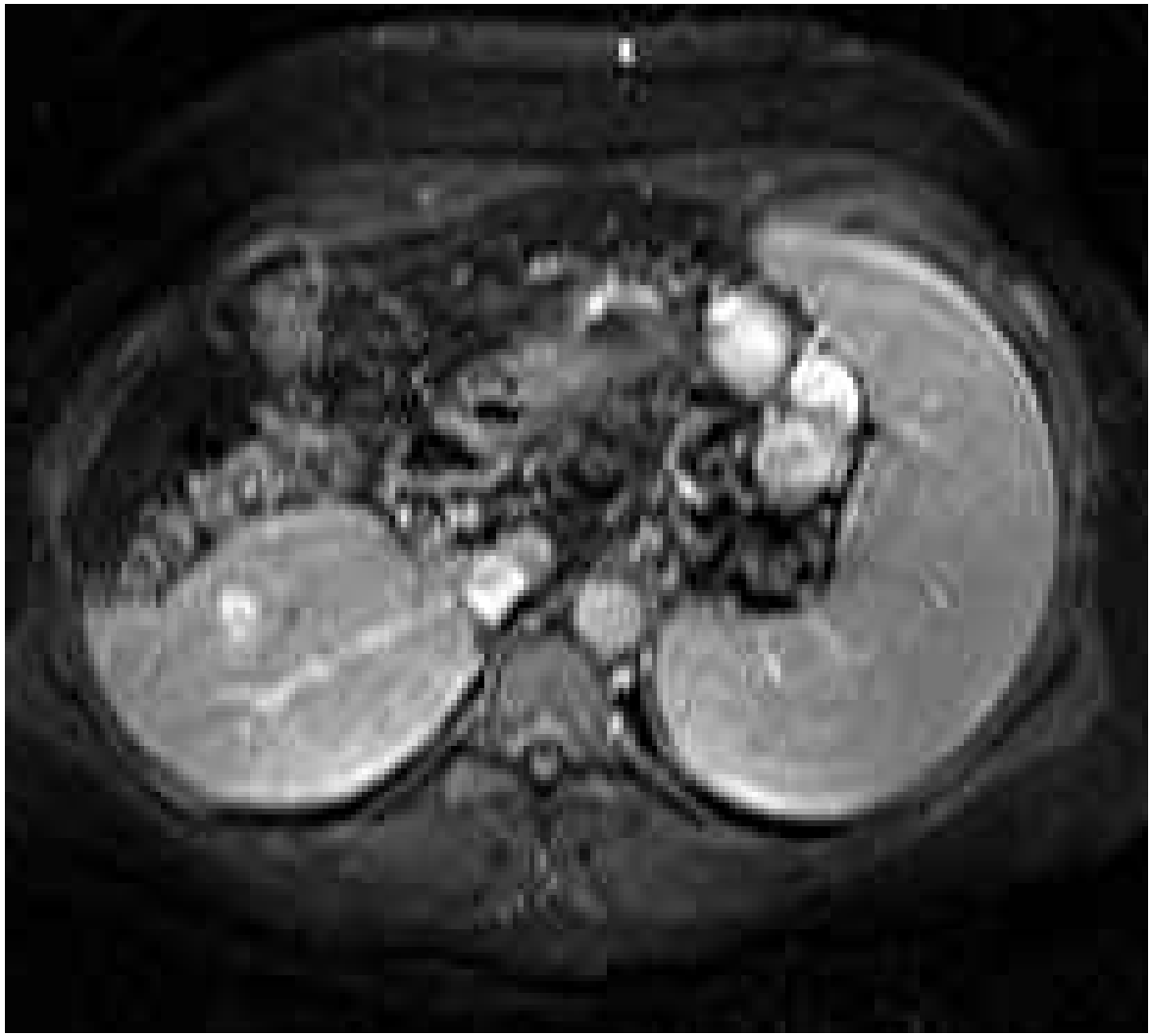
Penetrance



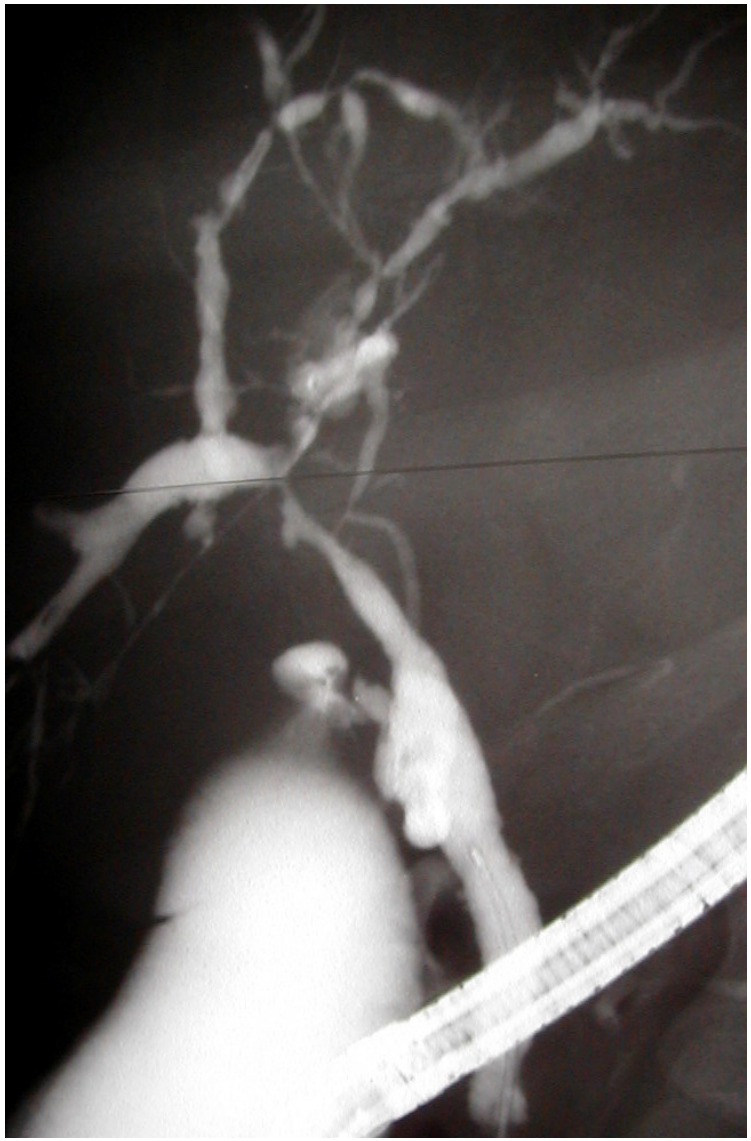
Contrast enhanced ultra sound in a woman with cirrhosis



CT and MR



MRC, primary sclerosing cholangitis



Which diseases are most likely in patients with elevated LFT?

Parenchyma

Only transaminases and GGT

Fatty liver alcohol
obesity

Chronic viral hepatitis

Haemochromatosis

AAT-deficiency

Autoimmune hepatitis

Drug induced

Transaminases and GGT + ALP

PBC

Drug induced

Focal

Transaminases and ALP/GGT

Focal nodular hyperplasia

Adenoma

HCC

Metastases

(Hemangioma)

Bile ducts

Transaminases and ALP/GGT

Bile duct stone

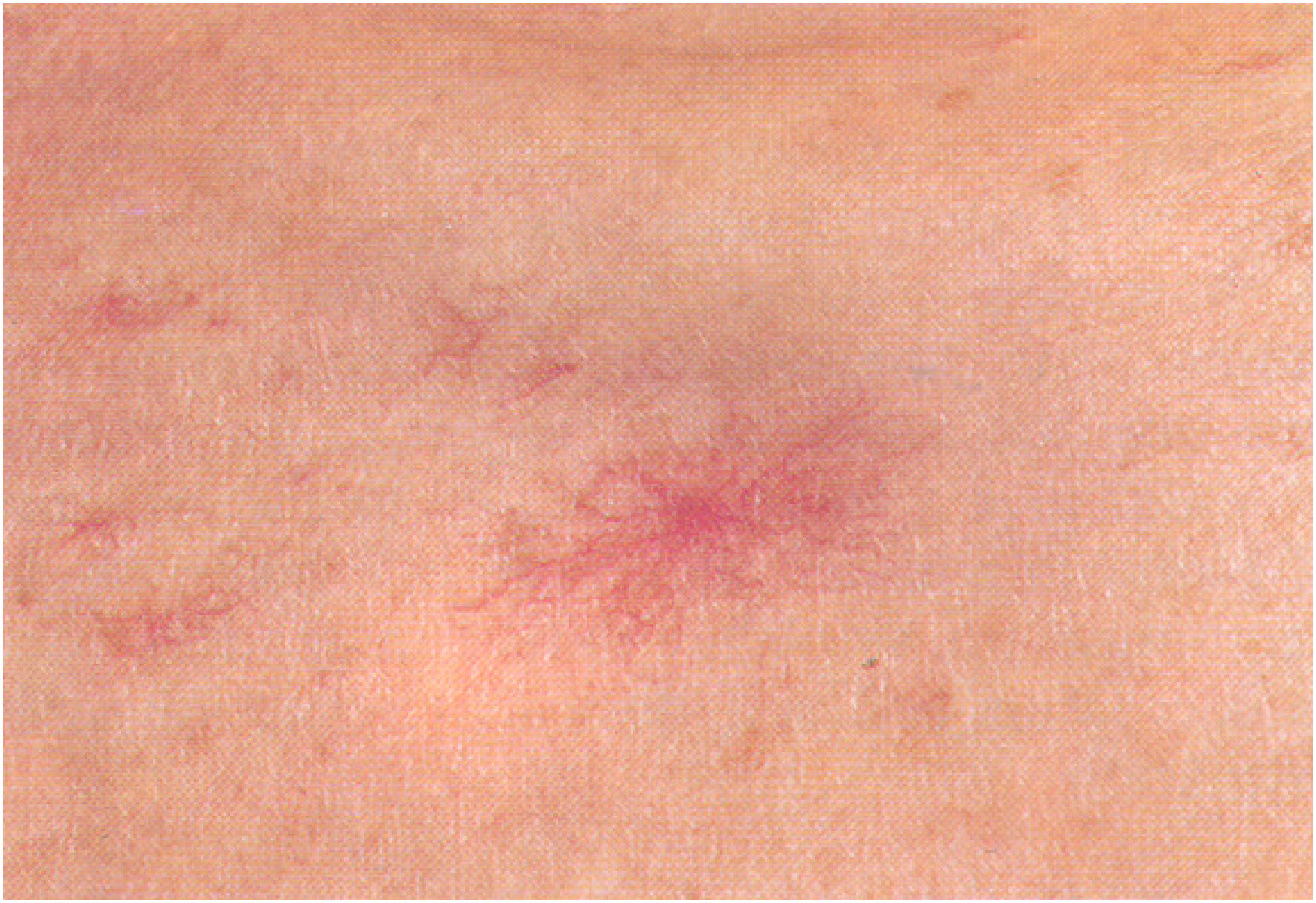
Cholangiocarcinoma

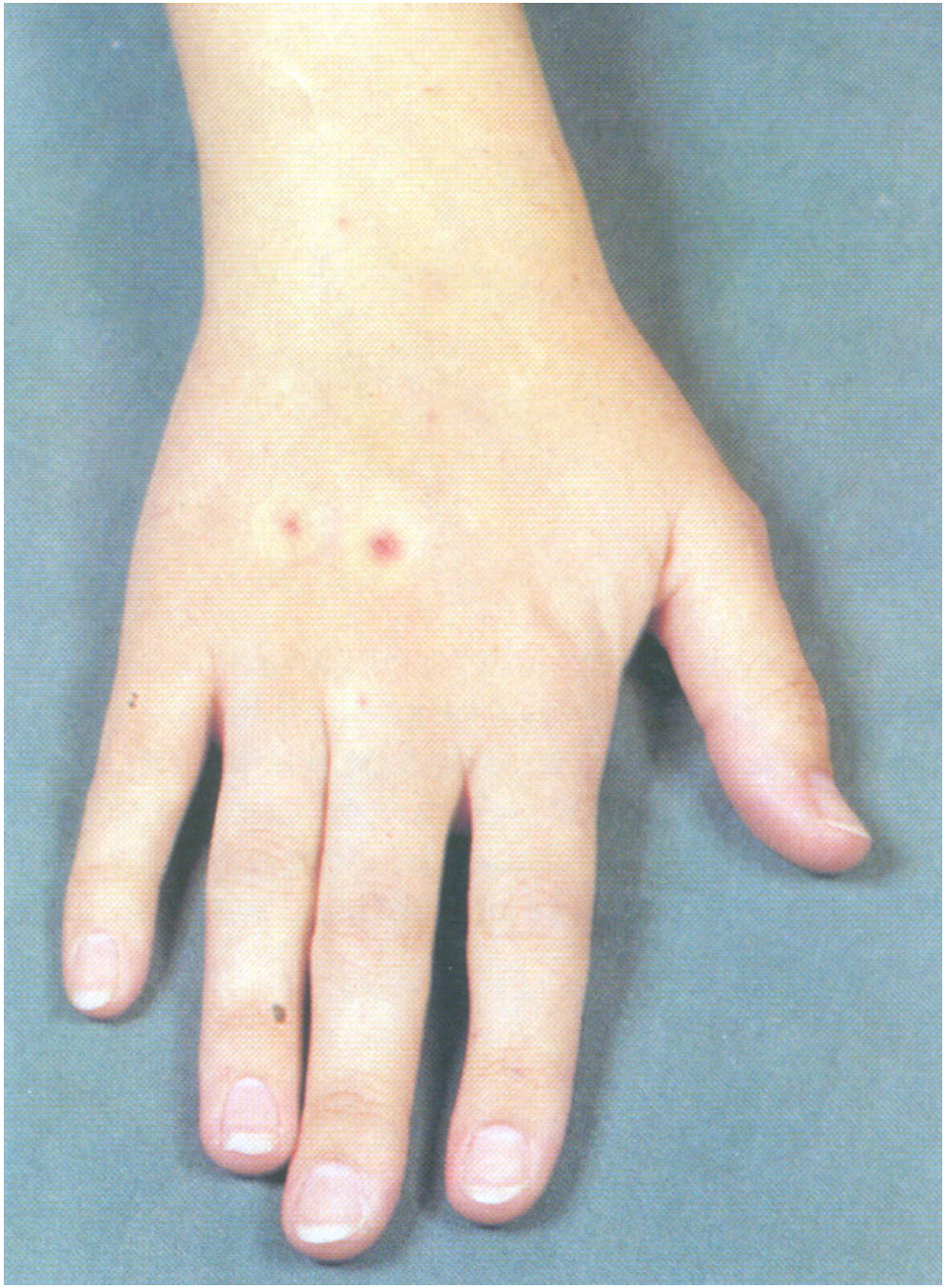
Pancreatic cancer

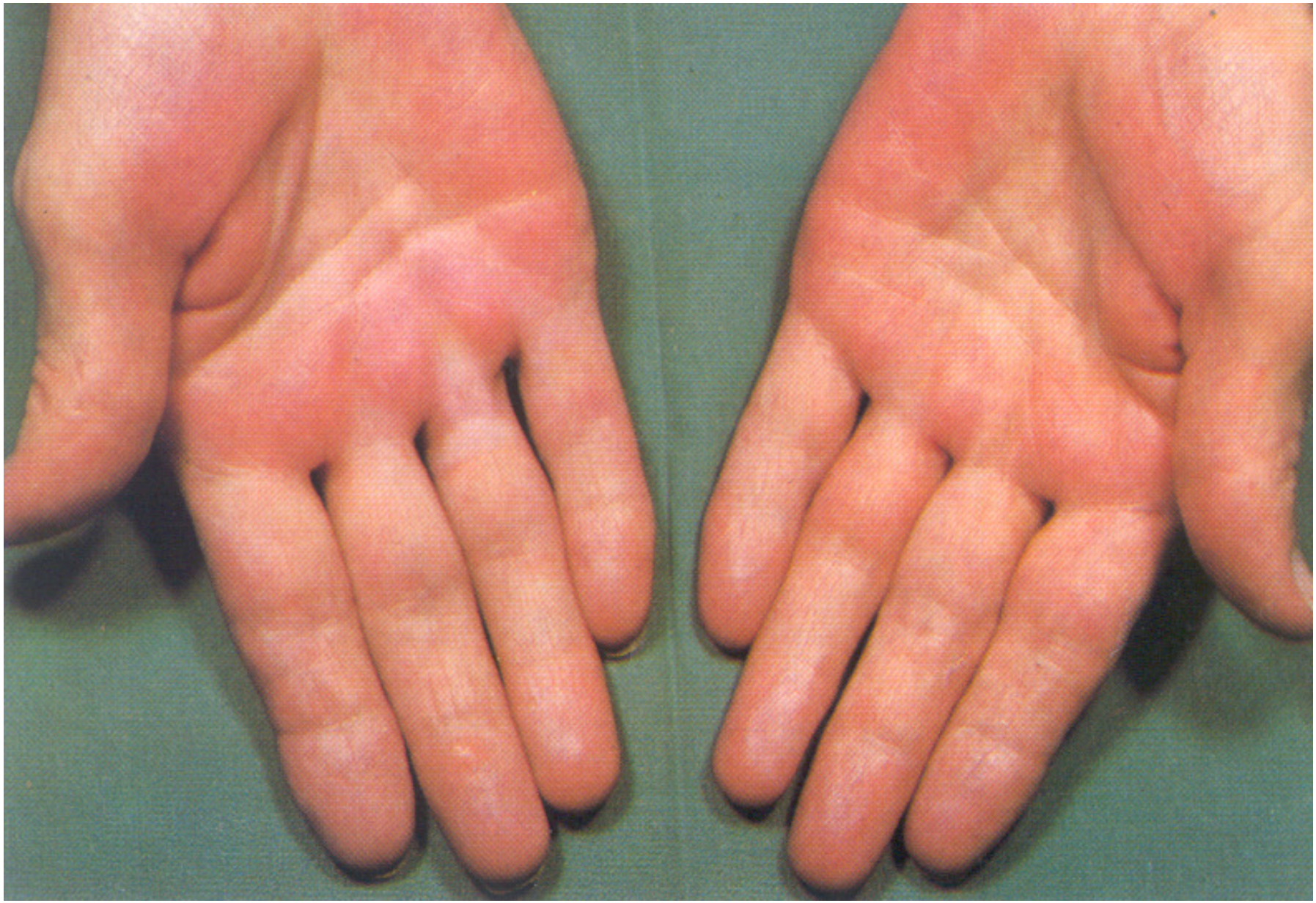
PSC

Diagnosis of chronic liver disease

- Elevated LFT (80%)
- Spiders, palmar erythema
- Icterus
- Decompensation (oedema, ascites, encefalopathi, variceal bleeding, infection)
- General symptoms (pain, cholangitis, itching, arthralgia, fatigue, anorexia)







Clinical evaluation of a patient with suspected/known chronic liver disease

- Etiology?
- Prognosis (cirrhosis? portal ht?)
- Acute and long-term management

Accidentally detected elevated LFT

Normal range: Mean ±2SD i.e. 2.5% of healthy individuals have some elevated LFT.

20 tests – 65% have at least one elevated test!

Intra-individual variation

Retesting of accidentally detected elevated LFT within 3 weeks will give normal results in 30% of patients.

(Lazo M, Ann Intern Med 2008)

How common?

Elevated ALT in 99/19877 recruits to US Air Force.
Specific explanation in 12/99

(Kundrotas, LW Dig Dis Sci 1993)

249 blood donors with elevated ALT - alcohol 11-48%, steathosis 22-56%, HCV 17-20%, diverse 4-8%, no specific diagnosis 2-4%.

(Hultcrantz R, Scand J Gastroenterol 1986)
(Katkow WN, Ann Intern Med 1991)

Contribution of liver biopsy to diagnosis

354 patients with elevated LFT (ALT, GGT and/or ALP) >6 months, after exclusion of patients with clinical or serological evidence of liver disease

- Steathosis 66%
- Lever biopsy contributed to clinical decisions in18%

(Shelly MM, J Hepatol 2001)

Conclusion

- Etiological diagnosis is usually possible without biopsy.
- Most patients with unclear diagnosis after careful history, physical examination and analysis of biochemical and serological tests have alcoholic liver disease or steathosis.

Clinical management

- Hepatocellular pattern pre-dominant (ALT, AST)
- Cholestatic pre-dominance (GGT, ALP)

Principles

- Consider retesting once within 3 weeks.
- Avoid further extended check-ups.
  Clinical decision!
- Keep extra-hepatic explanations in mind.

Medical history

- Drugs!!
- Contact with blood
- Other known diseases
- Alcohol
- Specific symptoms

Other diseases

- Cardiovascular
- Pulmonary
- Inflammatory systemic disease
- Thyroid disease
- Myositis (AST, CK)
- Malabsorption, coeliac disease
- Metabolic syndrome
- Addison

Physical examination

Low sensitivity!

- Spiders, palmar erythema?
- Signs of extrahepatic disorders? (jugolar veins, BP, atrial fibrillation, joints, skin, thyroid dysfunction)
- Oedema, ascites?
- Hepatomegali, splenomegali?

Isolated elevation of bilirubin

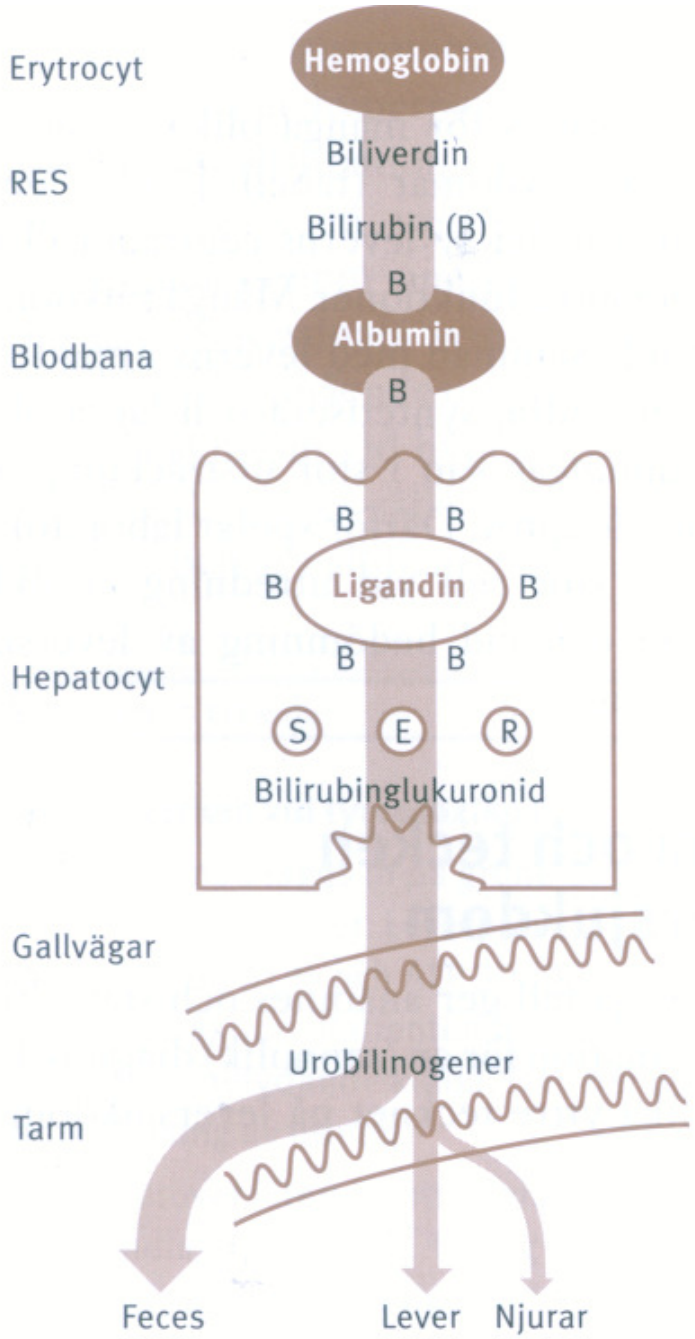
- Hemolysis
- Defect conjugation

  unconjugated — Gilbert (3-7%)

  (Crigler Najjar typ 2)

  UDP glucoronyl transferase

  (conjugated: Dubin-Johnson, Rotor)


Erytrocyt
Hemoglobin
RES
Biliverdin
Bilirubin (B)
B
Blodbana
Albumin
B
B B
B
Ligandin
B
B B
Hepatocyt
S
E
R
Bilirubinglukuronid
Gallvägar
Urobilinogener
Tarm
Feces
Lever
Njurar

Other isolated biochemical findings

GGT – usually not liver/bile ducts
(drugs, alcohol, obesity)

ALP – bone, growing teen-agers,
metastases, osteomalacia, Paget.

- Always interpret GGT and ALP together!
- ALP isoenzymes

Phosphatidylethanol in blood (HPLC)

- Estimates mean alcohol consumption during 2 weeks
- An abnormal phospholipid generated in cellmembranes *only* by ethanol
- Specificity as a marker of alcohol consumption 100%
- No false positive results
- Correlates with amounts of alcohol consumed over >7 days

Cholestatic predominance

- Must always be investigated!
- Intrahepatic/extrahepatic
- Ultrasound, (CT), MRCP, ERCP
- PBC – AMA, IgM
- PSC – IBD? MRCP
- Drugs

Hepatocellular predominance

Chronic viral hepatitis

HCV – antibodies, RNA

HBV – HBsAg, anti-HBsAg, Hb_cAg e-antigen, DNA

Hepatocellular predominance 2

Autoimmune hepatitis – IgG, ANA, SMA
(LKM, ANCA, SLA)

Note! 20% will not be ANA or SMA positive

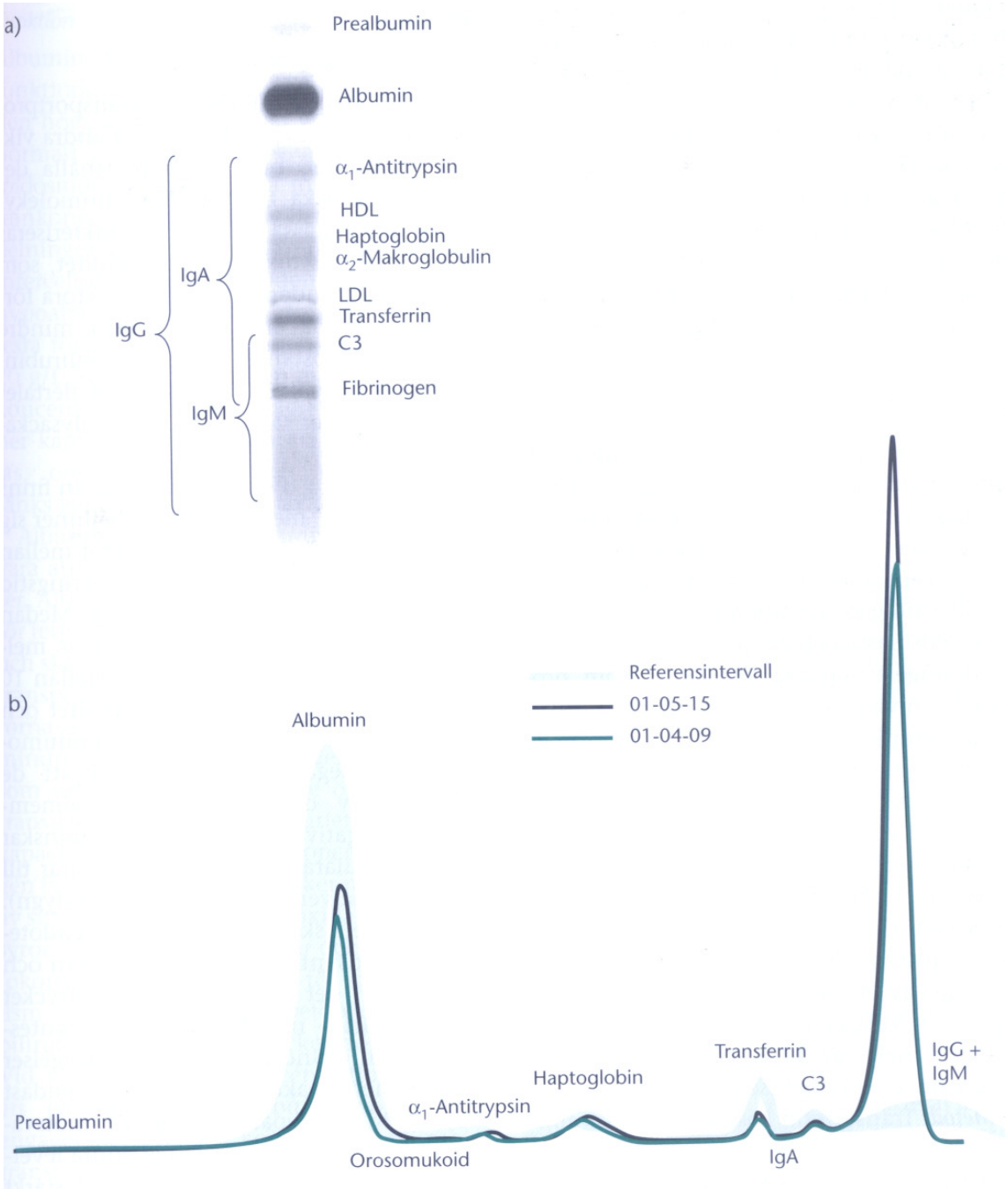
Hepatocellular predominance 3

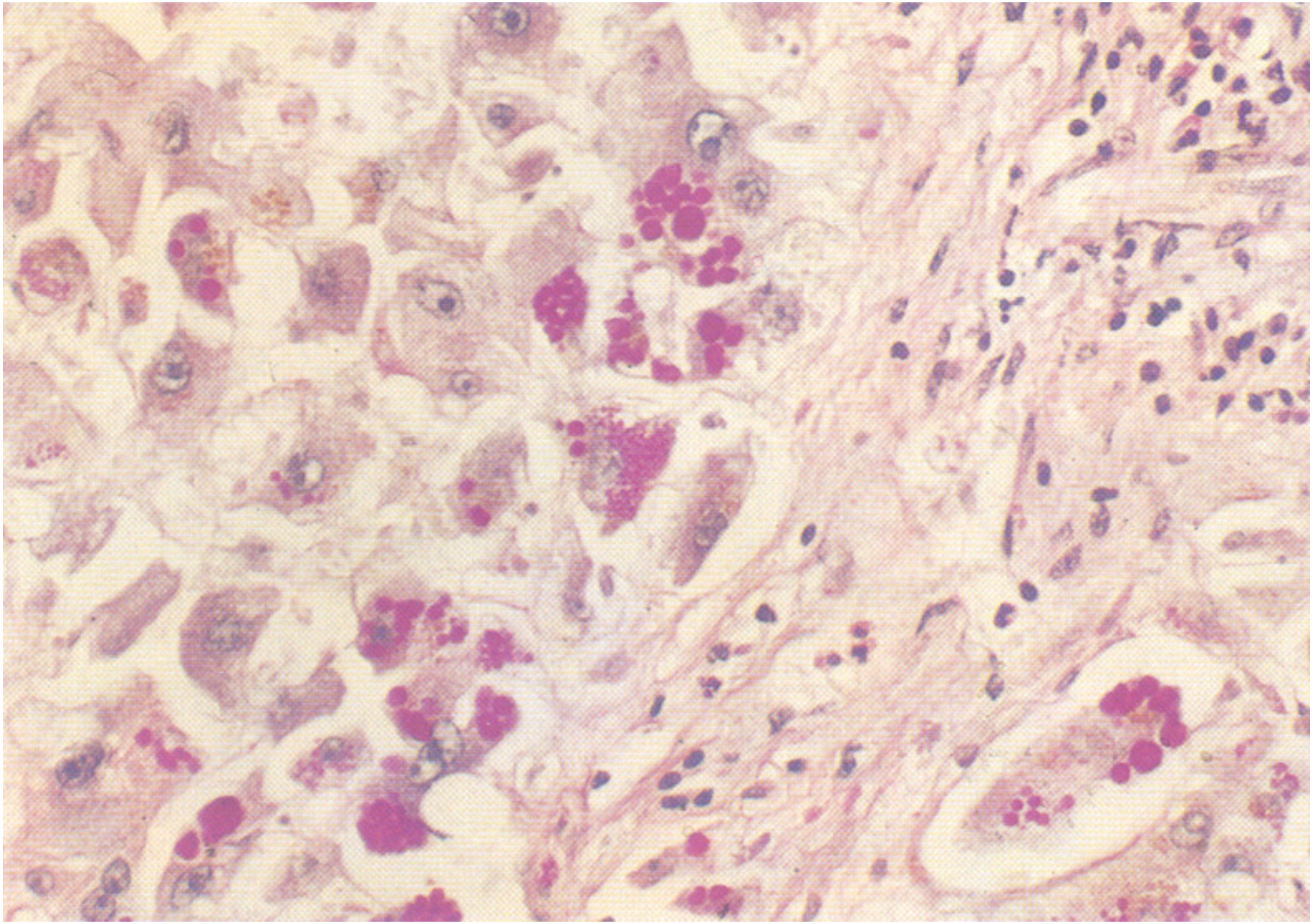
Steathosis – ALT (GGT)

NASH – increasing AST with fibrosis

Hepatocellular predominance – metabolic liver disease

- AAT-deficiency
  - Upper middle age
  - Plasma protein analysis
  - Isoelectric focusing
- Wilson
  - Unusual!
  - 5-25 years, up to 40 years
  - Low ceruloplasmin in 85%
  - tU-copper
  - Mutation analysis


a)
Prealbumin
Albumin
α1-Antitrypsin
HDL
Haptoglobin
α2-Makroglobulin
LDL
Transferrin
C3
Fibrinogen
IgA
IgG
IgM
b)
Referensintervall
01-05-15
01-04-09
Albumin
Prealbumin
α1-Antitrypsin
Orosomukoid
Haptoglobin
Transferrin
C3
IgA
IgG +
IgM



Haemochromatosis

Manifest liver disease in middle age – elderly

Heterozygotes in 10% of the population – no disease

HFE homozygotes (C282Y) 0.5%

Compound heterozygotes

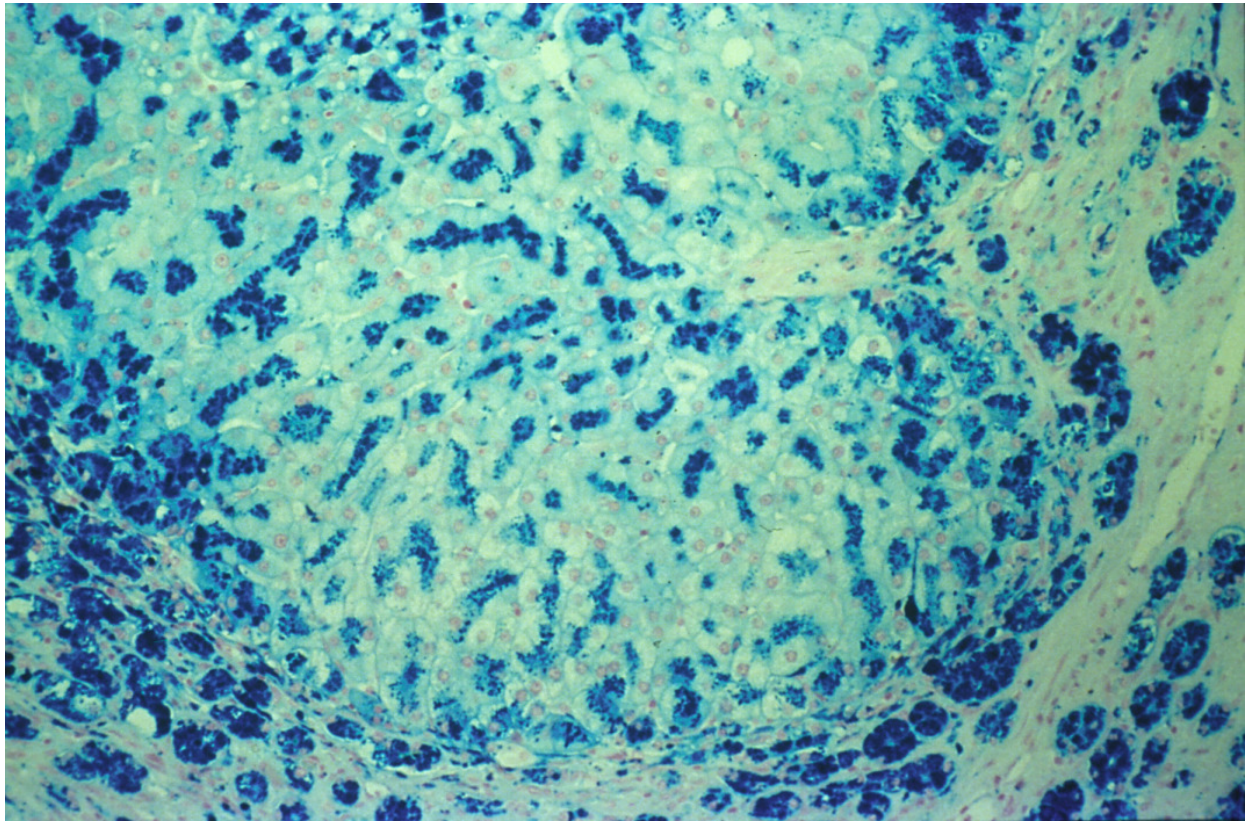
Low penetrance

Transferrin saturation >50% (>45% in females)

Ferritin (acute phase reactant! alcohol!)

Ferritin <1000 – no fibrosis

Haemchromatosis with fibrosis



Summary

Bilirubin	ANA, SMA, AMA
AST	HCV-antibodies
ALT	HBsAg
GGT	TSAT
ALP	Plasma protein analysis (AAT, ceruloplasmin, Ig)
PK/INR	

Always!!

Cardiovascular causes of liver disease

Acute, less often chronic liver disease

- Ischemic hepatitis (forward failure)
- Right heart failure
- Budd-Chiari
- Portal thrombosis
- Occlusion of a. hepatica

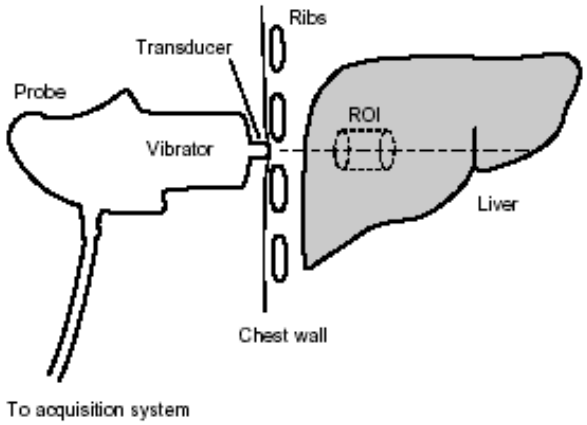
When should we perform a liver biopsy?

Etiology?

Fibrosis!

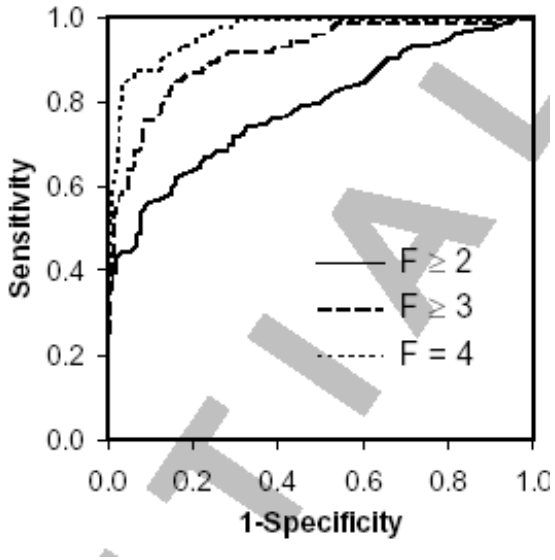
Prognosis?

Indication for treatment?



Liver stiffness, transient Elastography

FIBROSCAN



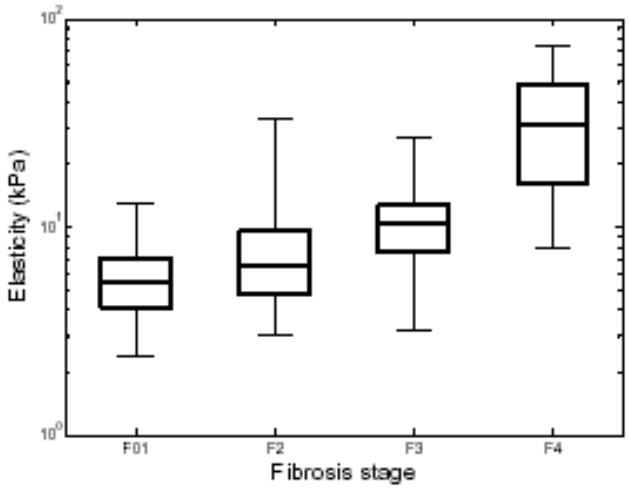


FIG. 3. Liver stiffness values for each fibrosis stage. The

How important is it to separate NASH from steathosis?

History/Physical exam/LFT

Biopsy

Fatty liver/NASH