الجامعة السورية الخاصة
SYRIAN PRIVATE UNIVERSITY

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Liver /internal medicine 2

- **References :**
- 1-Davidson English 2014
- 2- Davidson :Arabic from MOHE
  3- Position Paper WHO on viral hepatitis
- 4- lectures on SPU site
  5- extra reading added
- Languish : English
  Exam: MCQ
- May be added lectures by another professors

First lecture 2019-2020 liver (V.2)

- Liver disease
  -Introduction
  -Anatomy &physiology
  -Prevalence of liver disease
  -Jaundice
  -LFTs

2/12

-

LIVE === LIVER

- It was at one time considered the seat of live hence its name ,
- liver the thing we live with

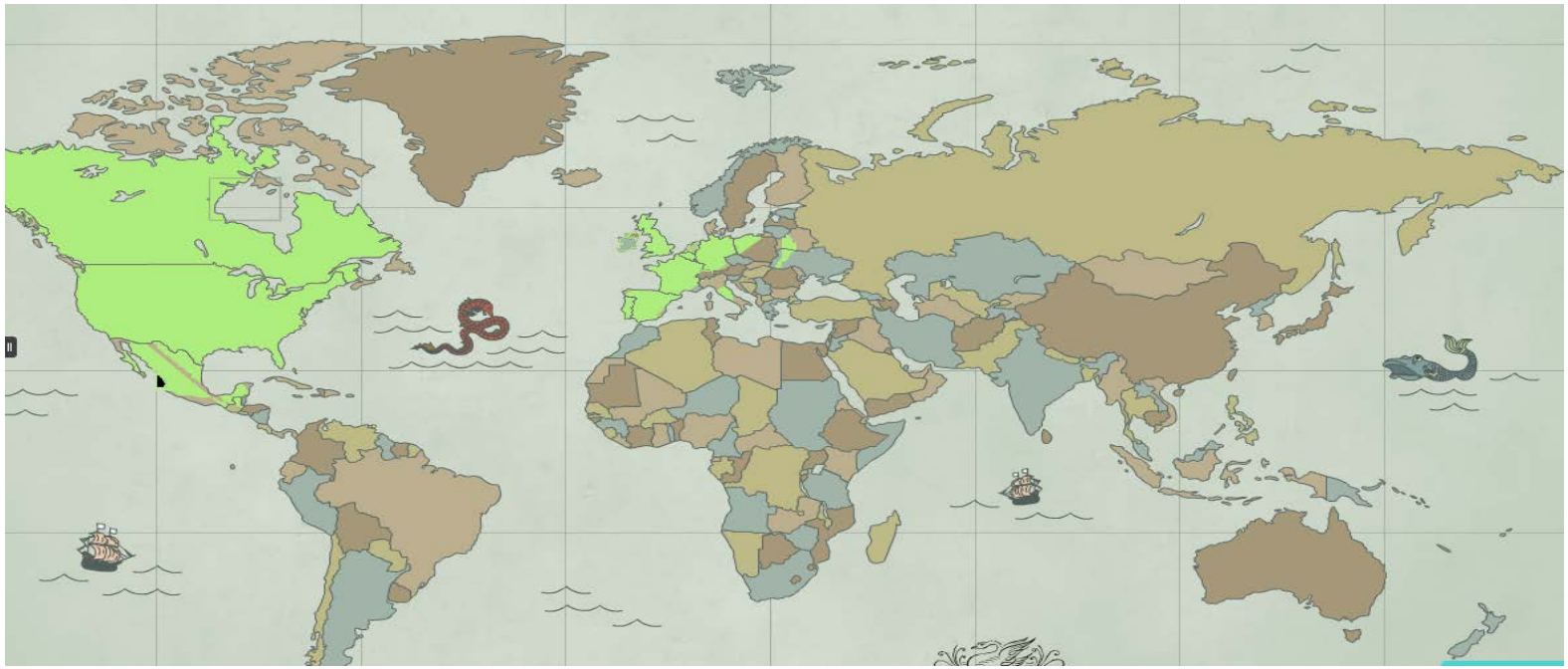
- Ambrose Bierce (1842-1914)

LIVER

- UNIQUE
- >500 vital function
- Holds one pint of blood supply at any given moment(13%)
- organ that can regenerate itself
- 1.2—1.5kg

WHO
Fact Sheet – N° 204 - 2016

منظمة الصحة العالمية



130–150 million people have chronic HCV.

(WHO) studies detect

21.3 million carriers in the Middle East

World Health Organization

May 2016

WHO adopted the first-ever global hepatitis strategy with a goal to eliminate viral hepatitis as a public health threat by 2030

World Health Organization

"Unlike most communicable diseases, the absolute burden between 1990 and 2013 increased"

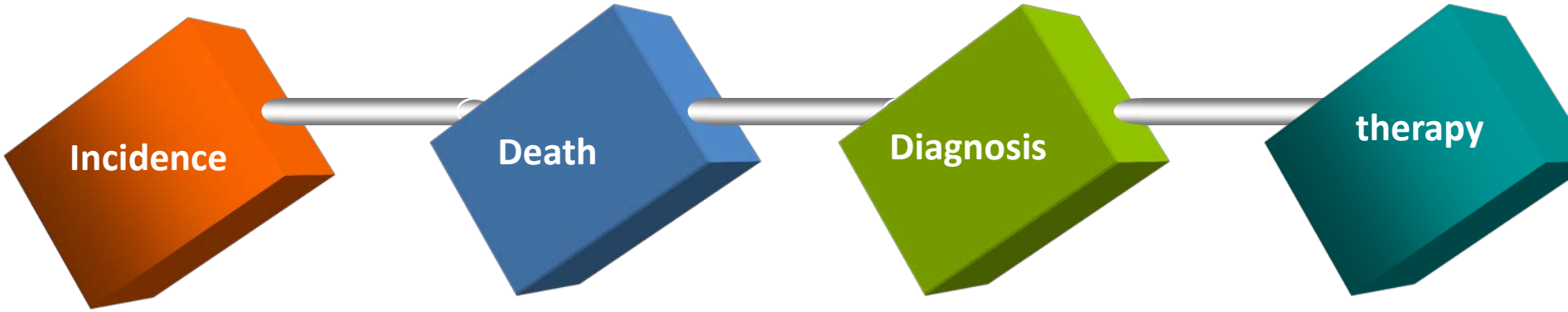
Stanaway and colleagues (2016) ,B&M review

World Health Organization

in North Africa and the Middle East, nearly one million deaths in 2013 due to viral hepatitis.

Stanaway and colleagues (2016)

WHO Goals

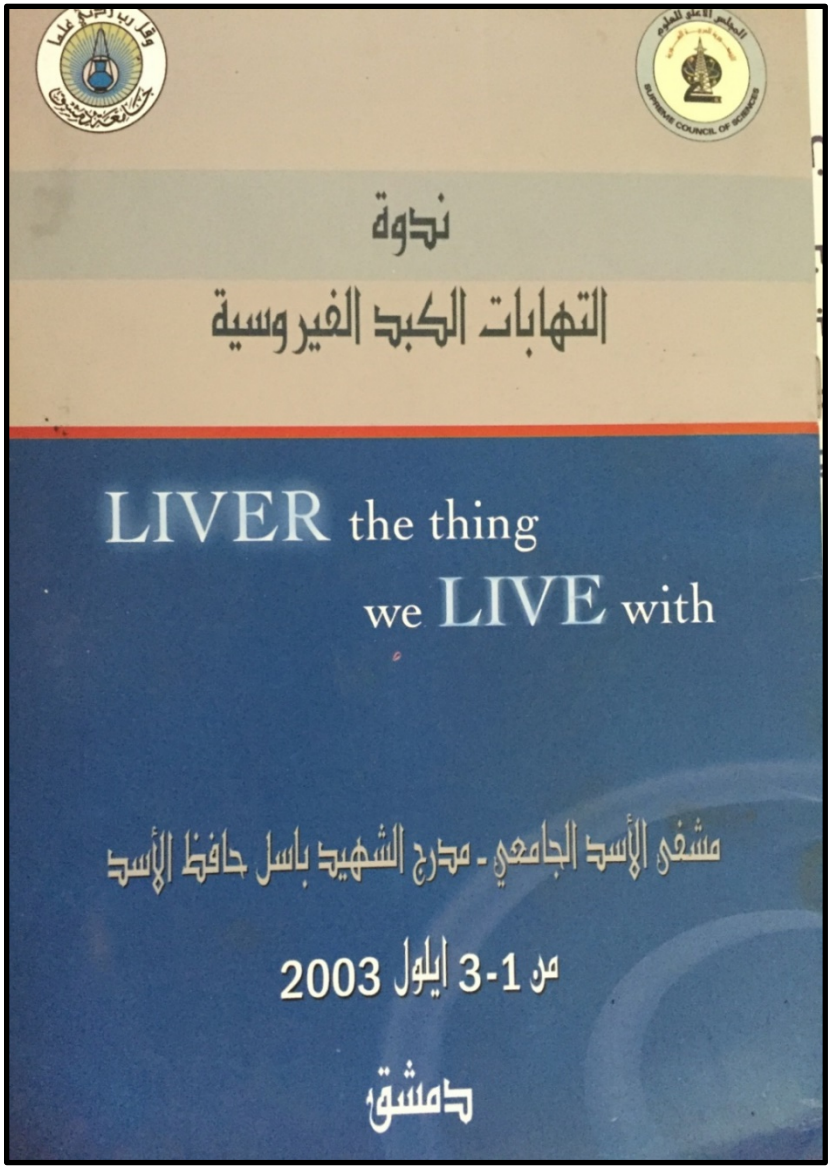


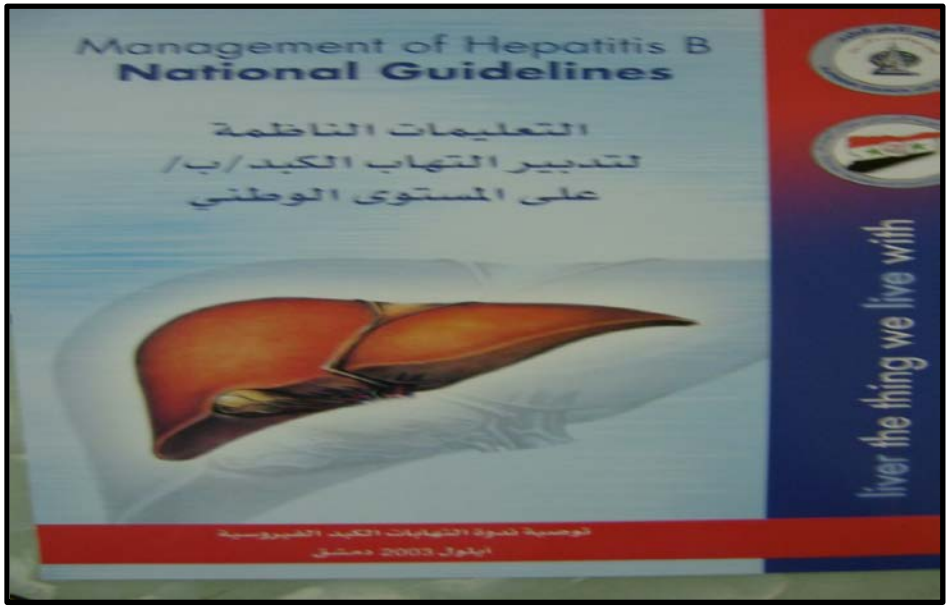
- **lower occurrence of new infection**
- %30 2020
- 2030 %80

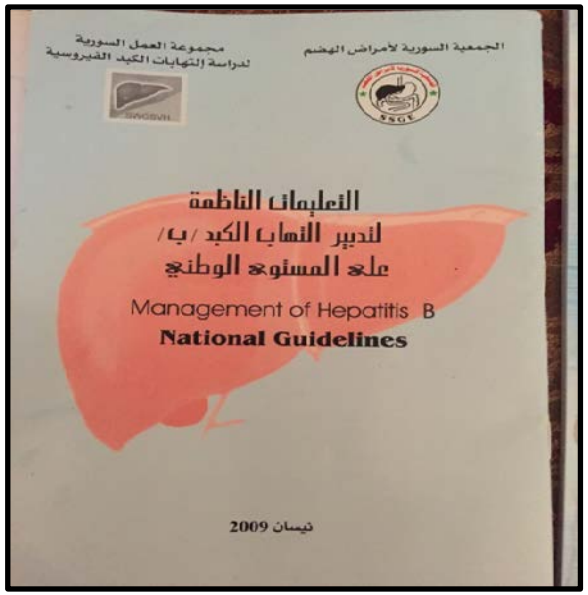
- **%10 2020** lower by
- **65%**
- **2030**

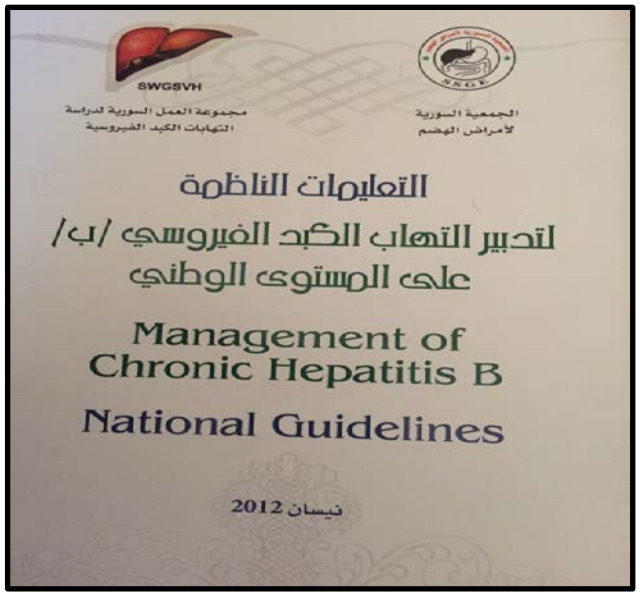
90 % of Pts Know about their illness

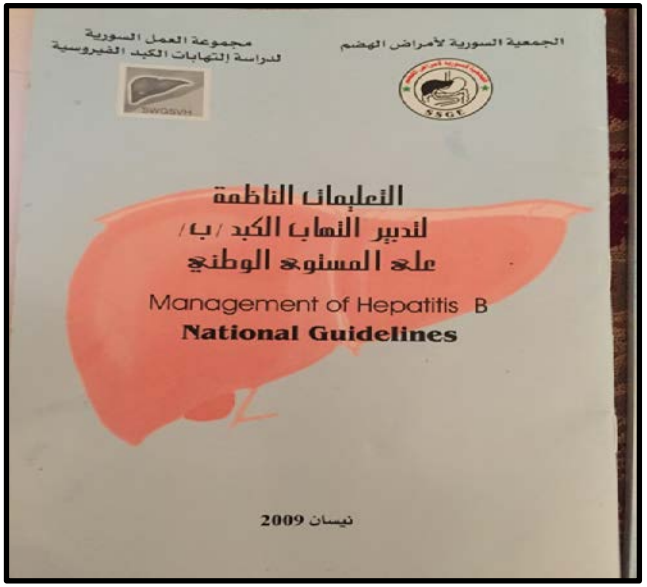
%80: 2030


ندوة
التهابات الكبد الفيروسية
LIVER the thing
we LIVE with
مشفى الأسد الجامعي - مدرج الشهيد باسل حافظ الأسد
من 1-3 أيلول 2003
دمشق


Management of Hepatitis B
National Guidelines
التعليمات الناظمة
لتدبير التهاب الكبد/ب/
على المستوى الوطني
liver the thing we live with


مجموعة العمل السورية لدراسة التهابات الكبد الفيروسية
الجمعية السورية لأمراض الهضم
التعليمات الناظمة
لتدبير التهاب الكبد /ب/
على المستوى الوطني
Management of Hepatitis B
National Guidelines
نيسان 2009


SWGSVH
مجموعة العمل السورية لدراسة التهابات الكبد الفيروسية
الجمعية السورية لأمراض الهضم
التعليمات الناظمة
لتدبير التهاب الكبد الفيروسي /ب/
على المستوى الوطني
Management of
Chronic Hepatitis B
National Guidelines
نيسان 2012


مجموعة العمل السورية لدراسة التهابات الكبد الفيروسية
الجمعية السورية لأمراض الهضم
التعليمات الناظمة
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SWGSVH
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التعليمات الناظمة
لتدبير التهاب الكبد الفيروسي /ب/
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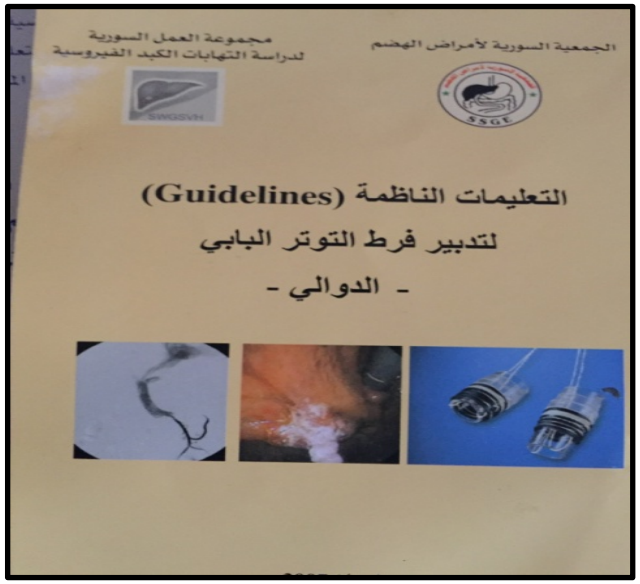
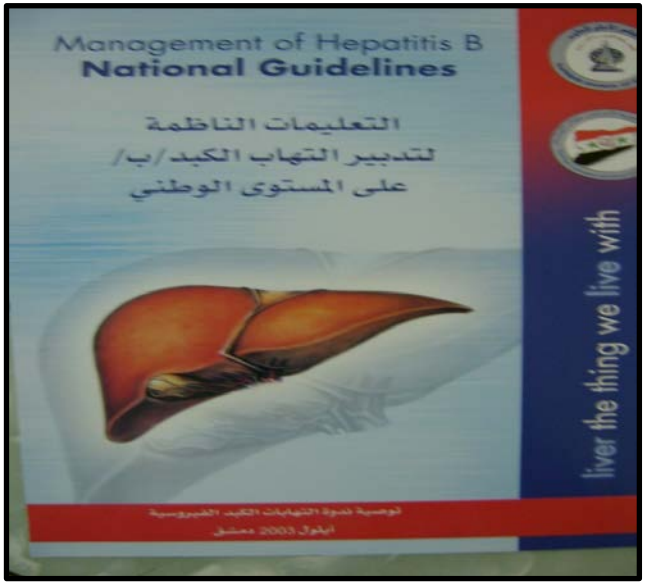

مجموعة العمل السورية لدراسة التهابات الكبد الفيروسية
الجمعية السورية لأمراض الهضم
التعليمات الناظمة (Guidelines)
لتدبير فرط التوتر البابي
- الدوالي -


Management of Hepatitis B
National Guidelines
التعليمات الناظمة
لتدبير التهاب الكبد/ب/
على المستوى الوطني
liver the thing we live with

Prevalence of Hepatitis B /C in >1milion blood donors

	1996	1997	1998	1999	2000	2001	2002
HBsAg	7.01	%5	4.4 %	3.94	3.85	3.6	%3.6
HCV	2.53	1.8	1.7	1.74	1.19	0.74	%0.4

إدارة نقل الدم
2003

Medicine can be notoriously insular


quality of data
quality of interpretation
Quality of evidence

Functional reserve

- Enormous functional reserve
  Surgical removal of 60% of the liver of a normal person produces minimal and transient hepatic impairment
- Regeneration restores most of the liver mass within 4 to 6 weeks.

Regeneration

- *Regeneration.*
- Cell death or tissue resection (such as in living-donor transplantation) triggers hepatocyte replication, to compensate for the cell or tissue loss.
- ***It is a normal compensatory response to cell death***

It is common

-1/3 OF THE WORLD POPULATION EXPOSED TO VIRAL HEPATITIS B

-The global prevalence of HBV infection in the general population was estimated at 3.5% with about
257 million persons living with chronic HBV infection.
http://www.who.int/wer Position paper WHO2017

More than one million of Syrian population are infected by hepatitis B&C

Winning over ----

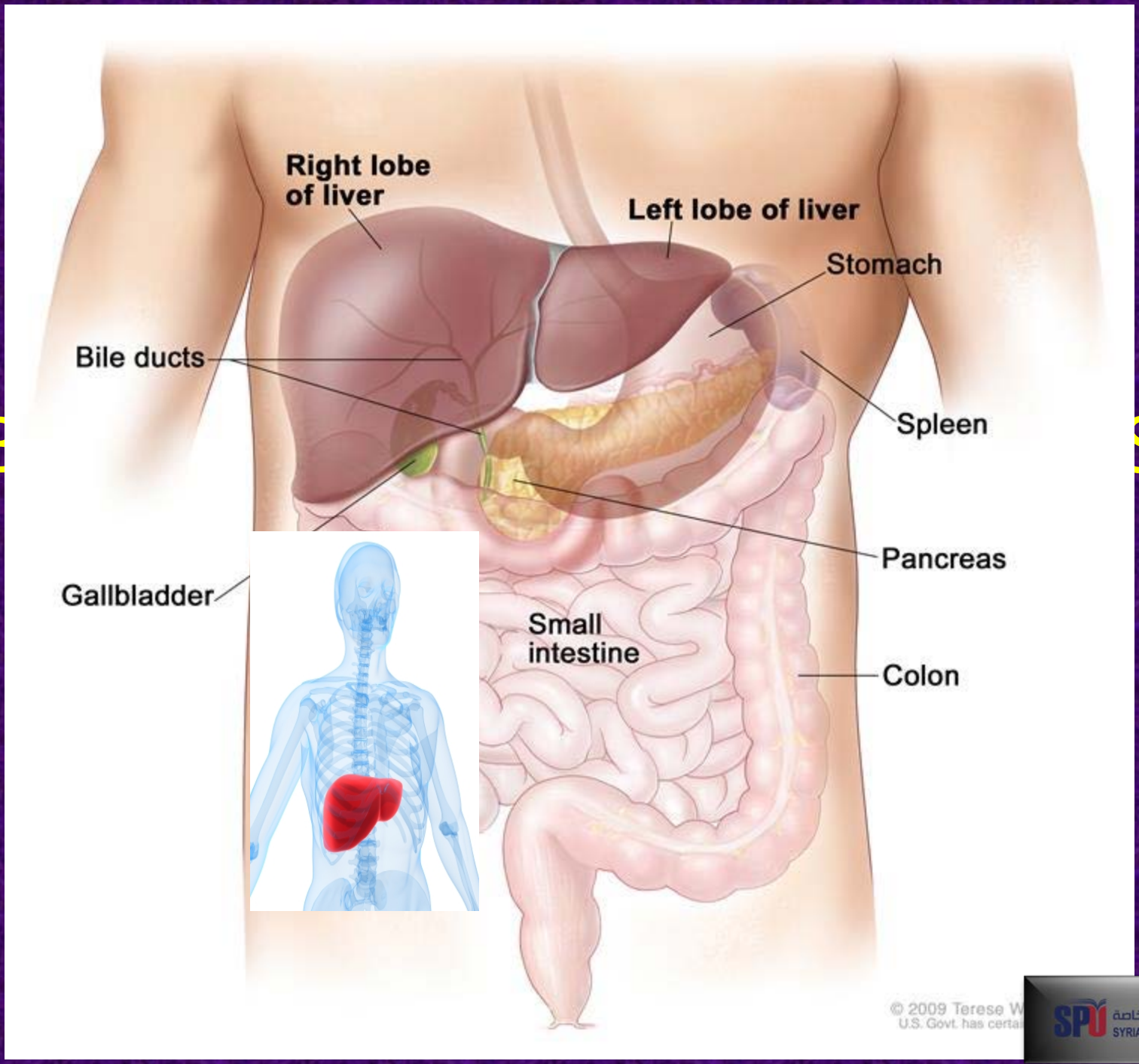
Therapeutic endoscopy

largely replaced surgery for

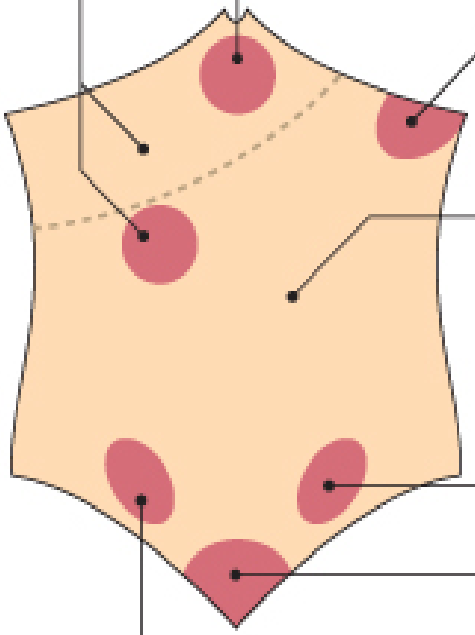
-Gastrointestinal bleeding

-Tumor palliation

-Biliary diseases.


Right lobe of liver
Left lobe of liver
Stomach
Bile ducts
Spleen
Pancreas
Gallbladder
Small intestine
Colon

4 ABDOMINAL EXAMINATION: POSSIBLE FINDINGS



Hepatomegaly
Palpable gallbladder

(Ch. 23)

Epigastric mass

Gastric cancer
Pancreatic cancer
Aortic aneurysm

Left upper quadrant mass

?Spleen	*?Kidney*
Edge	Rounded
Can't get above it	Can get above it
Moves towards right iliac fossa	Moves down
Dull percussion note	Resonant to percussion
Notch	Ballotable

Tender to palpation

?Peritonitis	*?Obstruction*
Guarding and rebound	Distended
Absent bowel sounds	Tinkling bowel sounds
Rigidity	Visible peristalsis

Left iliac fossa mass

Sigmoid colon cancer
Constipation
Diverticular mass

Generalised distension

Fat (obesity)
Fluid (ascites)
Flatus (obstruction/ileus)
Faeces (constipation)
Fetus (pregnancy)

Right iliac fossa mass

Caecal carcinoma
Crohn's disease
Appendix abscess

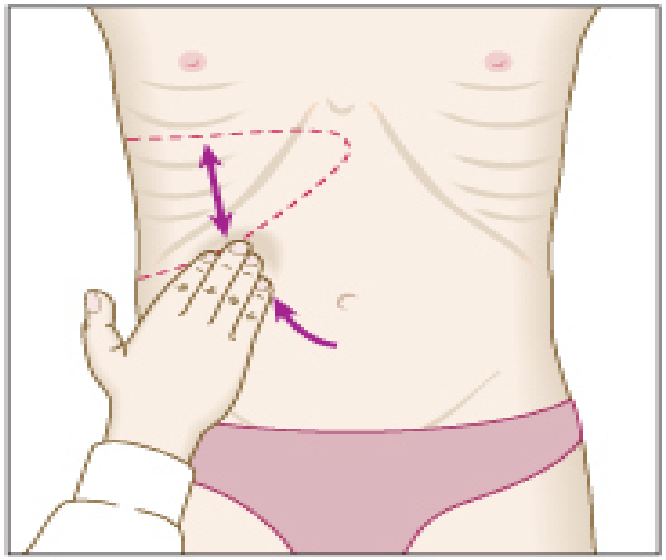
Suprapubic mass

Bladder
Pregnancy
Fibroids/carcinoma

5 PALPATION OF THE ABDOMEN

Liver

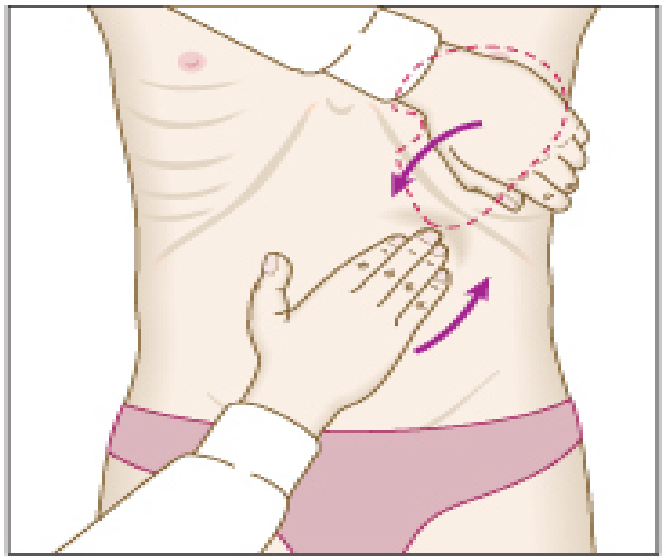
- Start in the right iliac fossa.
- Progress up the abdomen 2 cm with each breath (through open mouth)
- Confirm the lower border of the liver by percussion (see 6).



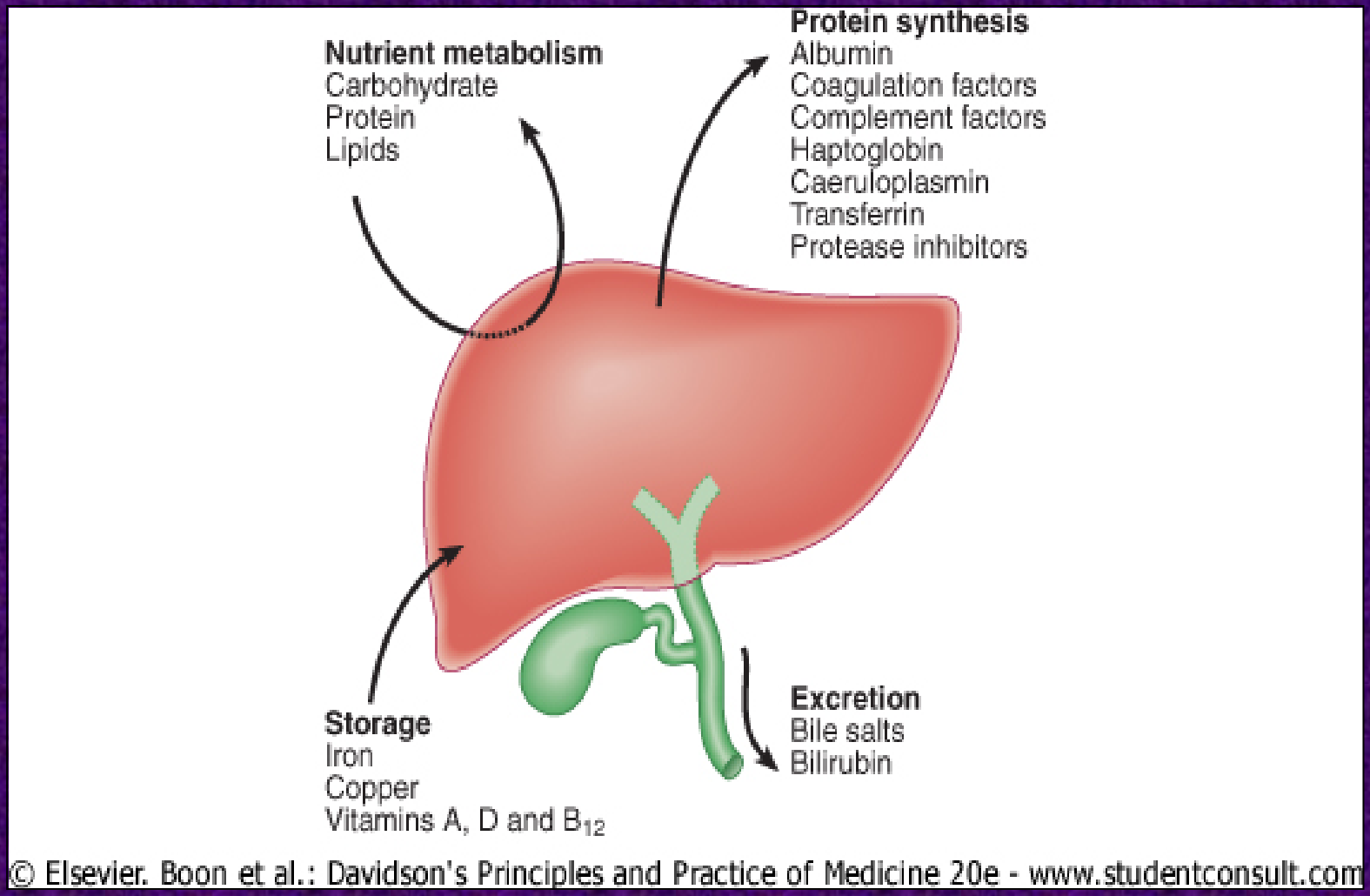
- Detect if smooth or irregular, tender or non-tender; ascertain shape.
- Identify the upper border by percussion (see 6).

Spleen

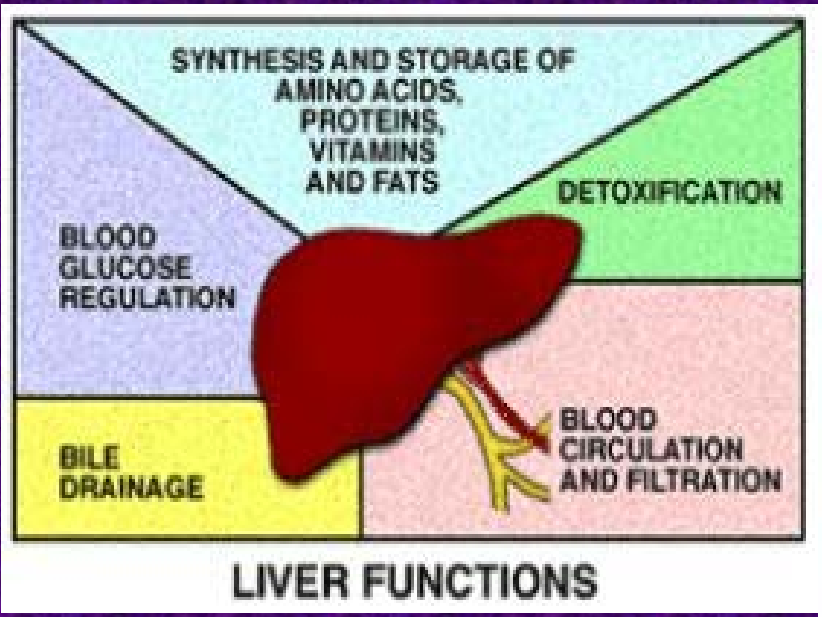
- Start again in the right iliac fossa.
- Progress towards the left upper quadrant at 2 cm intervals.
- Place the left hand around the lower lateral ribs as the costal margin is approached.



- Note the characteristics of the spleen
  - Notch
  - Superficial
  - Dull to percussion
  - Cannot get between ribs and spleen
  - Moves well with respiratio



Main liver Functions

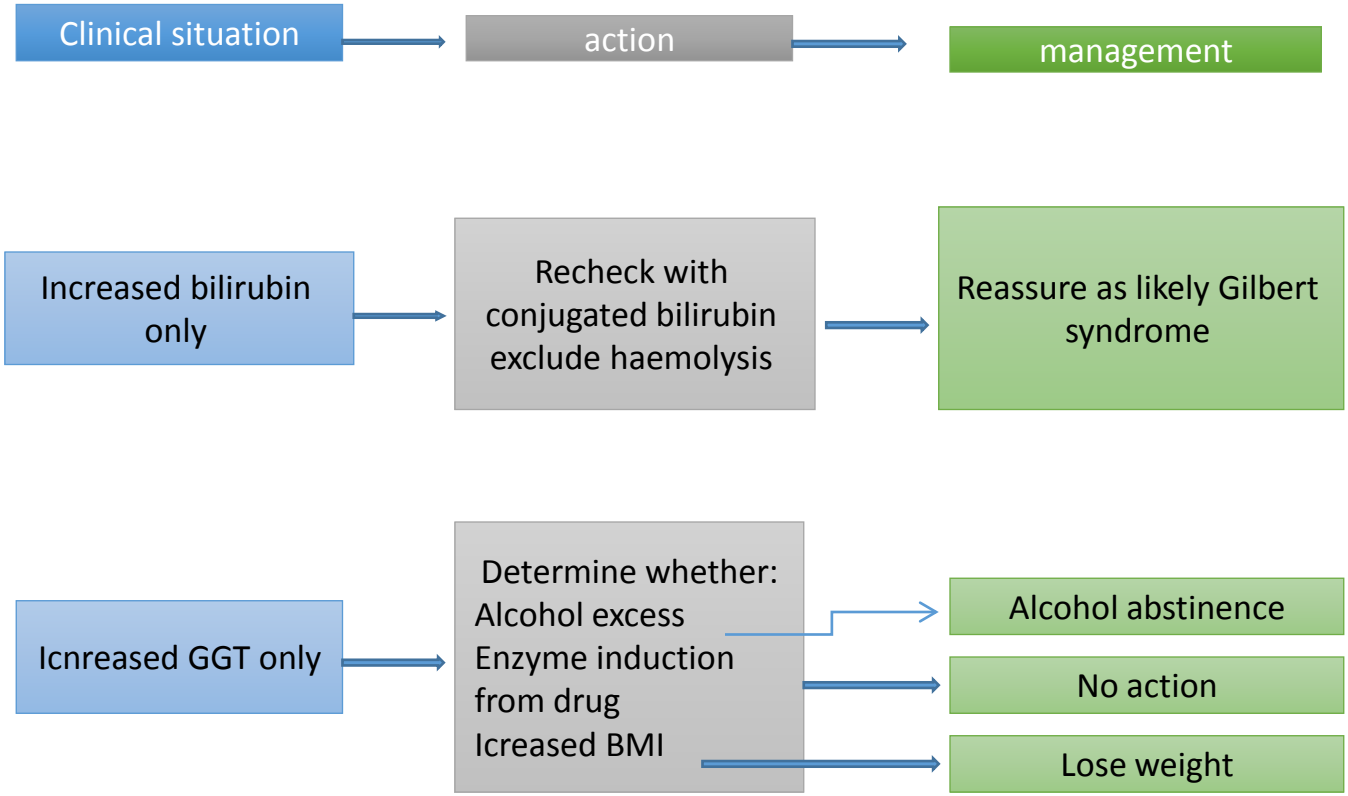


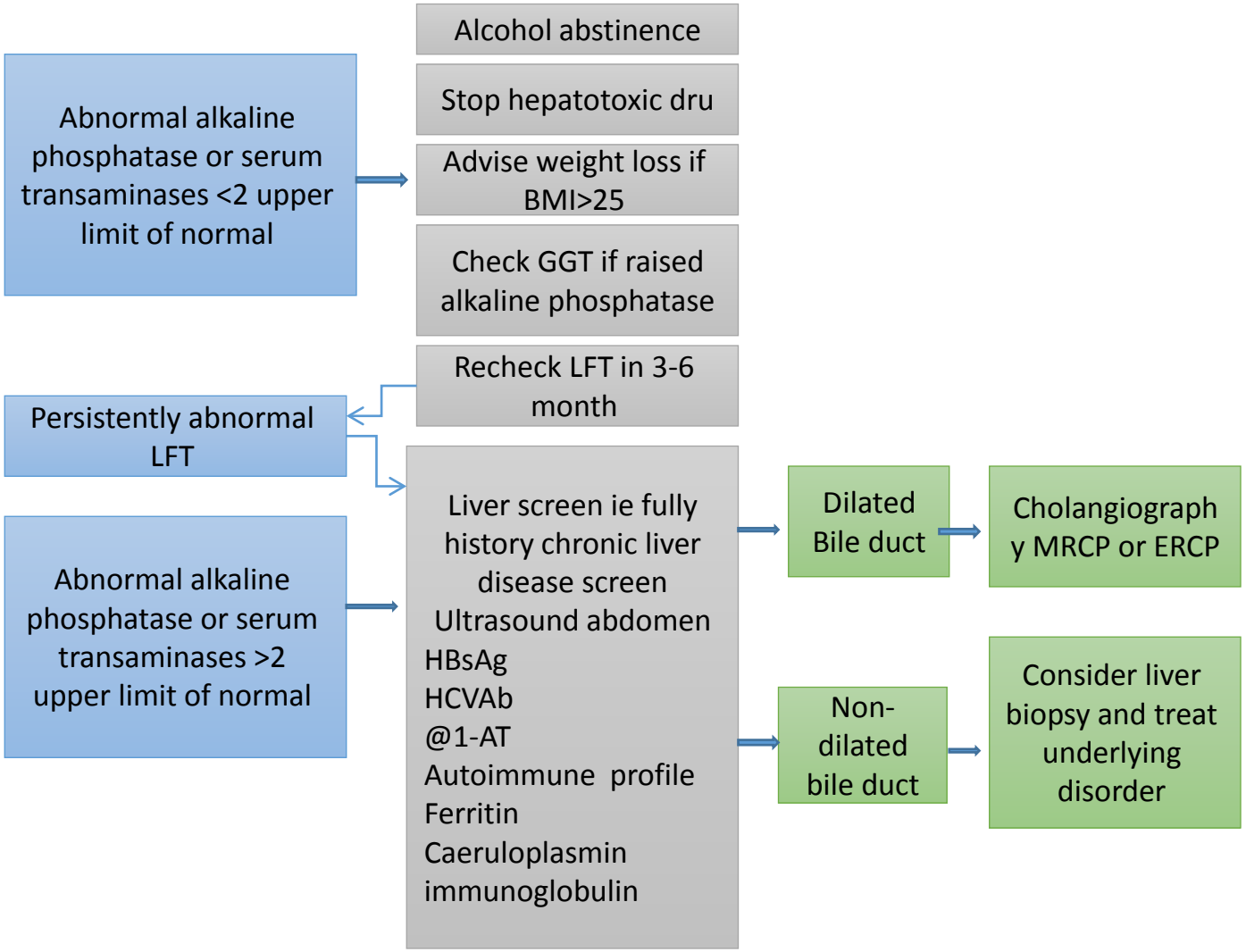
LIVER FUNCTIONS

What does the liver do?

500 VITAL FUNCTIONS

- Immunity against infection
- Regulates blood clotting
- Factory for proteins and cholesterol
- Clears blood of drugs, Chemicals, alcohol
- Excretes wastes via bile
- Converts excess glucose to starch for storage
- Excretes bile for fat digestion


Clinical situation
action
management
Increased bilirubin only
Recheck with conjugated bilirubin exclude haemolysis
Reassure as likely Gilbert syndrome
Icnreased GGT only
Determine whether:
Alcohol excess
Enzyme induction from drug
Icreased BMI
Alcohol abstinence
No action
Lose weight


Abnormal alkaline phosphatase or serum transaminases <2 upper limit of normal
Alcohol abstinence
Stop hepatotoxic dru
Advise weight loss if BMI>25
Check GGT if raised alkaline phosphatase
Recheck LFT in 3-6 month
Persistently abnormal LFT
Abnormal alkaline phosphatase or serum transaminases >2 upper limit of normal
Liver screen ie fully history chronic liver disease screen
Ultrasound abdomen
HBsAg
HCVAb
@1-AT
Autoimmune profile
Ferritin
Caeruloplasmin
immunoglobulin
Dilated Bile duct
Cholangiography MRCP or ERCP
Non-dilated bile duct
Consider liver biopsy and treat underlying disorder

1. Metabolism&Production

A. Amino acids are either used for the production of plasma proteins…:

1.Albumin 8-14 mg/day is necessary for maintaining vascular oncotic pressure and transporting small molecules eg. bilirubin

2.Clotting factors (II,VII,IX,X) which are in tern modified be vitamin K-dependent enzymes (Vit K is also stored in the liver)

3.Complement factors

4.Haptoglobulin (bind to the free hemoglobin in the blood)

5.Transferrin (iron carrier in the blood)

6.Protease inhibitors: eg. alpha1-antitrypsin

… The remaining Amino Acids are broken down to urea

B. ½ of the absorbed Glucose is:

1. stored in the liver as Glycogen or converted to glycerol & fatty acids (thus preventing hyperglycemia).
2. During fasting gluconeogenesis occurs to prevent hypoglycemia.

C. Liver metabolize lipids: producing very low-density lipoproteins & also metabolize low and high density lipoprotiens.

D. Bilirubin metabolism: conjugation bilirubun into bilirubin mono or di –glucuronide by the enzyme UDP-glucoronyl transferase.

E. Drugs absorbed from the gut by the portal vein reach the liver to be metabolized, sometimes into other forms (some are even more effective), and after the drug does its action its mostly metabolized into inert compounds.

Storage

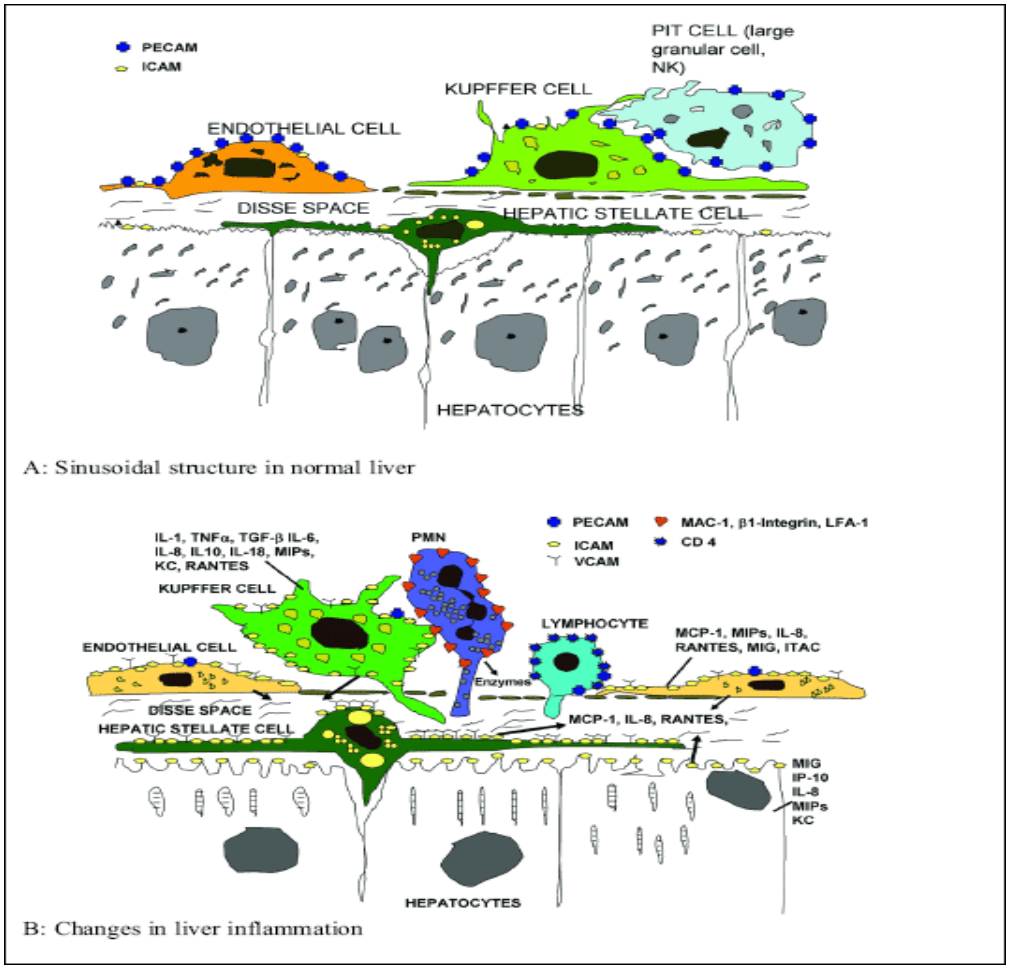
- 1. Vitamin A,D and B12 are stored in large amounts.
- 2. Vitamin K & folate in smaller amounts.
- 3. Iron within 2 compounds (ferritin&hemosiderin)
- 4.copper (also excreted in bile)

Excretion

- The main excreted product is the Bile which contains:

1. Bile acids (from cholesterol)
2. Bilirubin (conjugated)
3. phospholipids
4. cholesterol
5. copper
6. Drugs
7. Nutrient metabolism waste products

Immune regulation



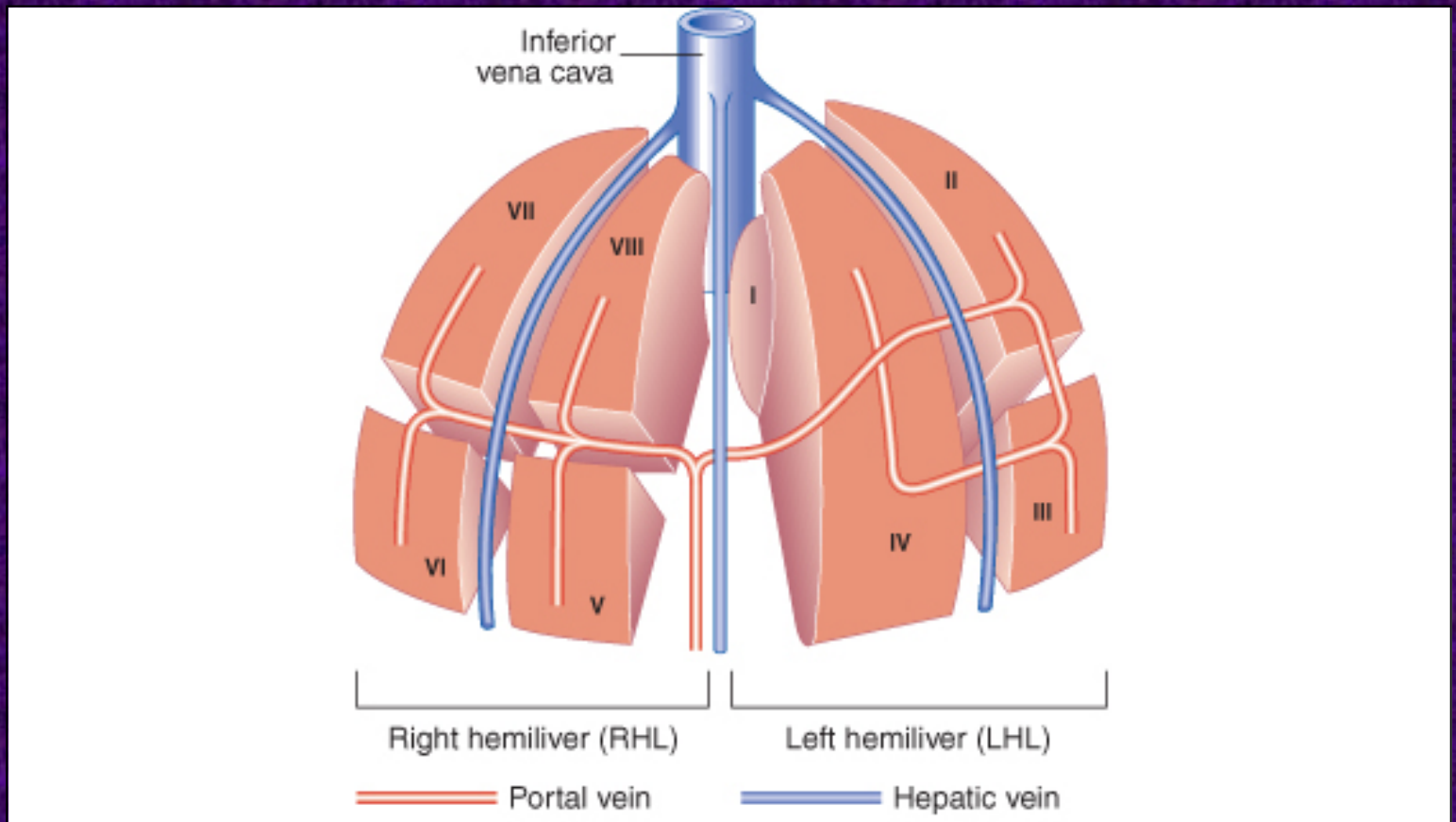
- 9% of normal liver is immune cells.

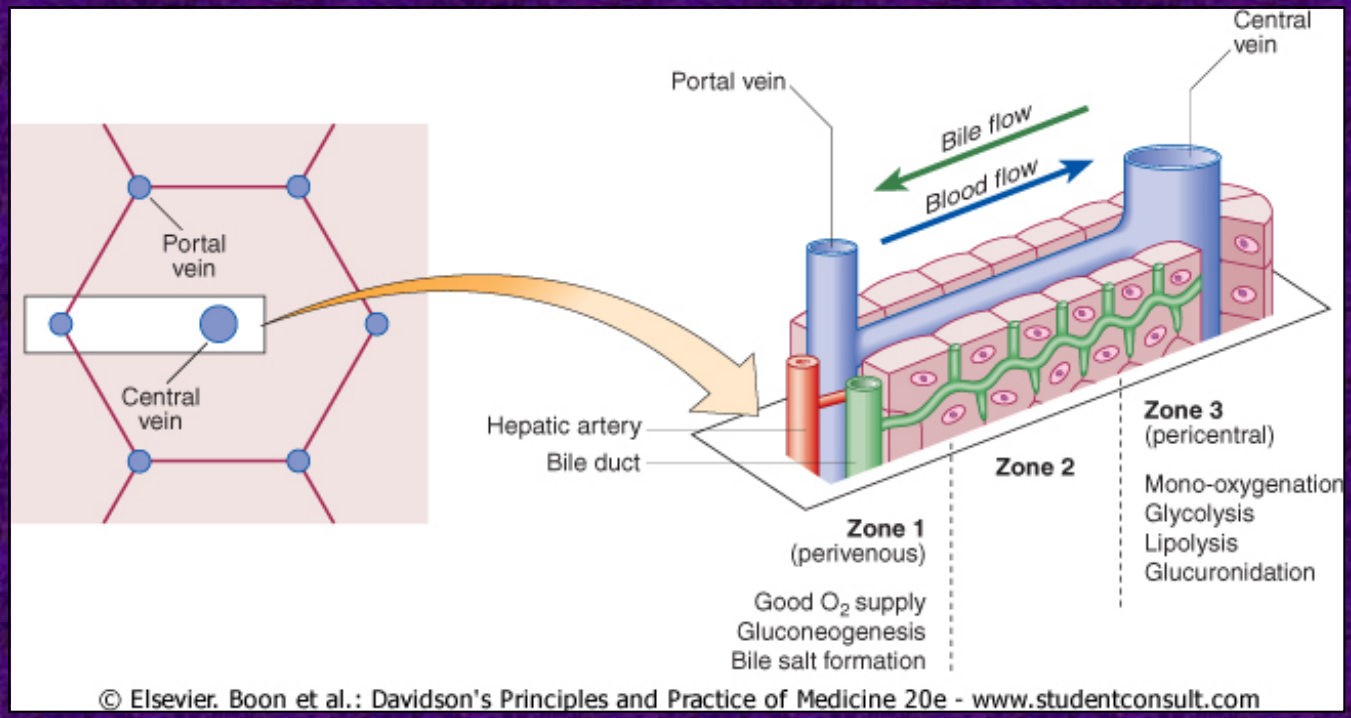
1.Cells for Innate immunity:

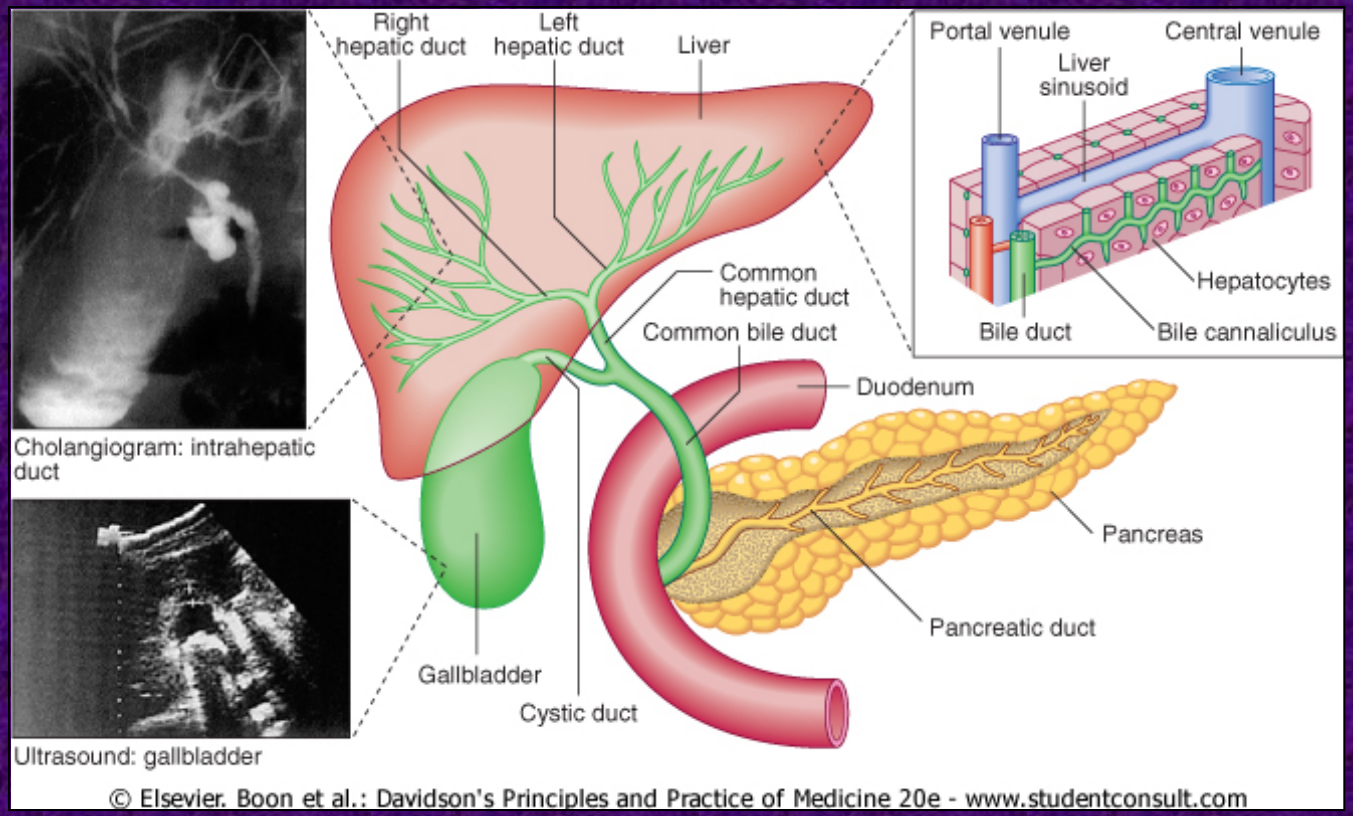
4% Kupffer cells(from blood monocytes)

2.5% Macrophages & Natural killer cells

2. Cells for adaptive immunity: B&T lymphocytes

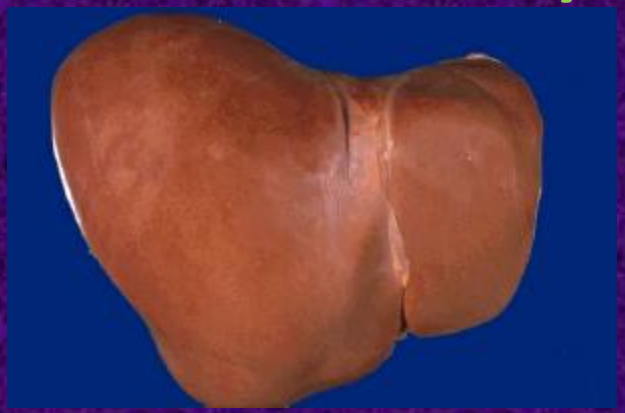




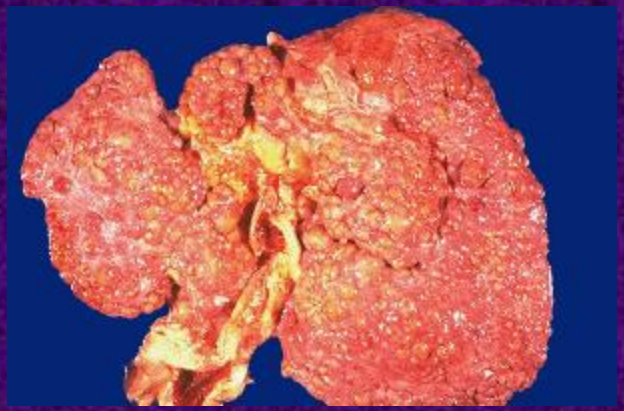


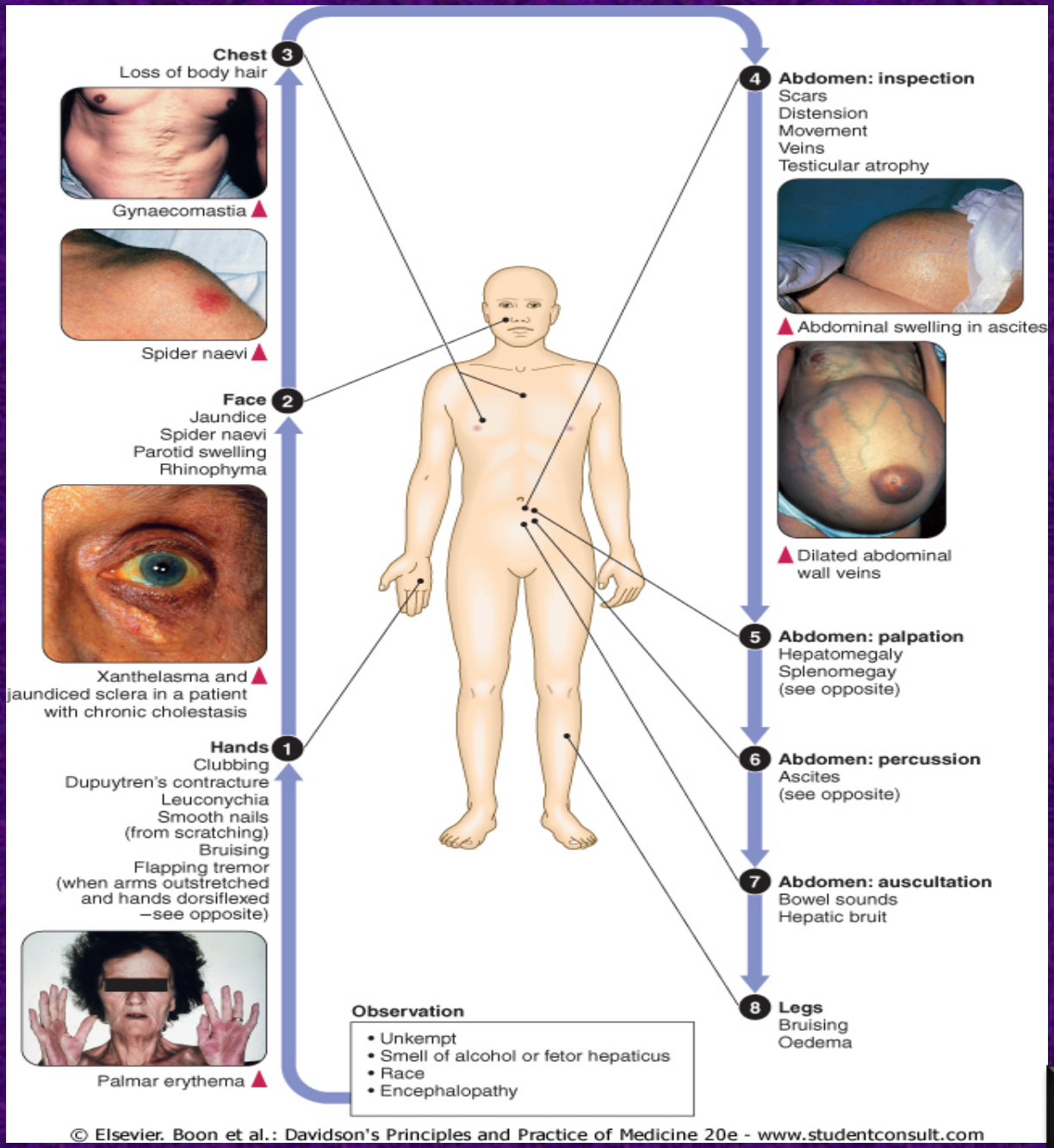
liver from to

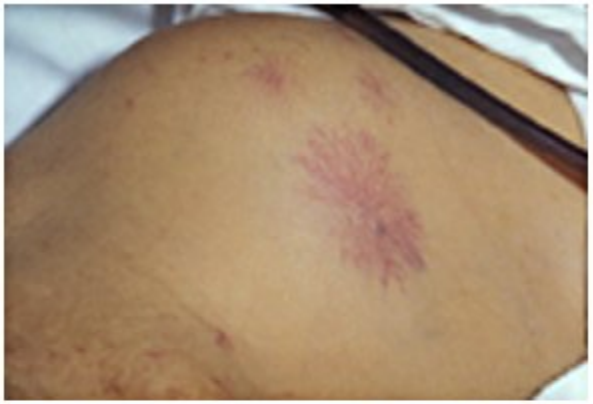
healthy

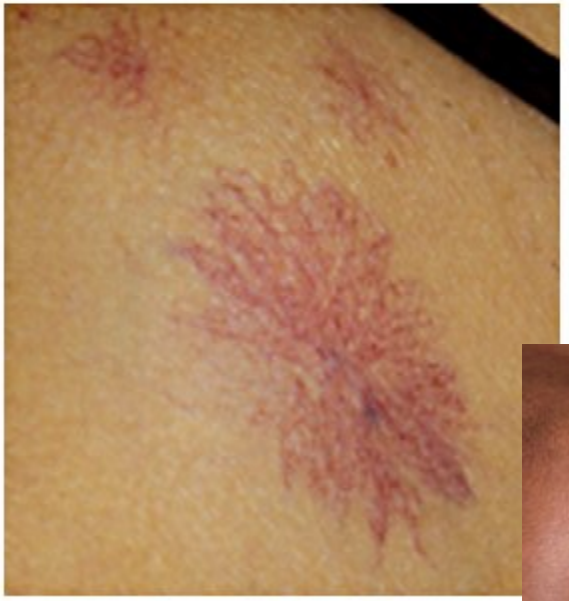


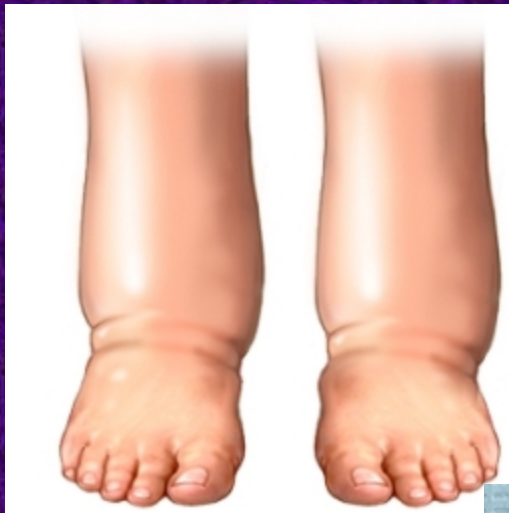
cirrhosis



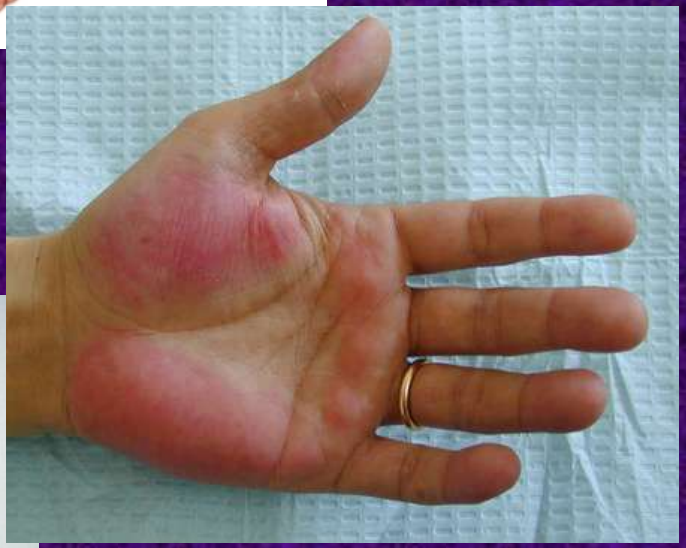








Edema (swelling) of the ankles and feet



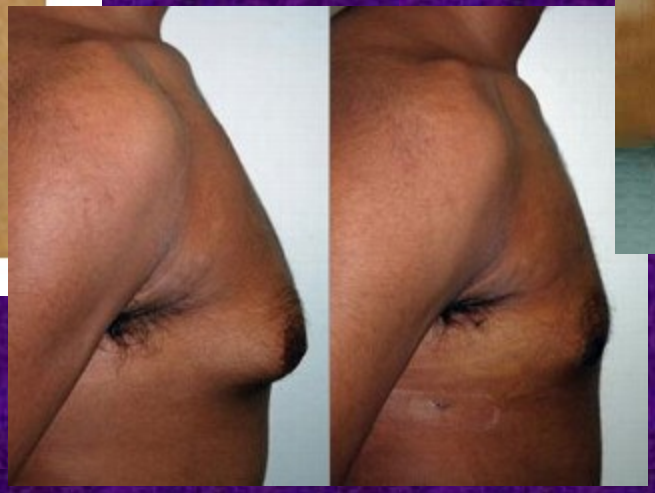
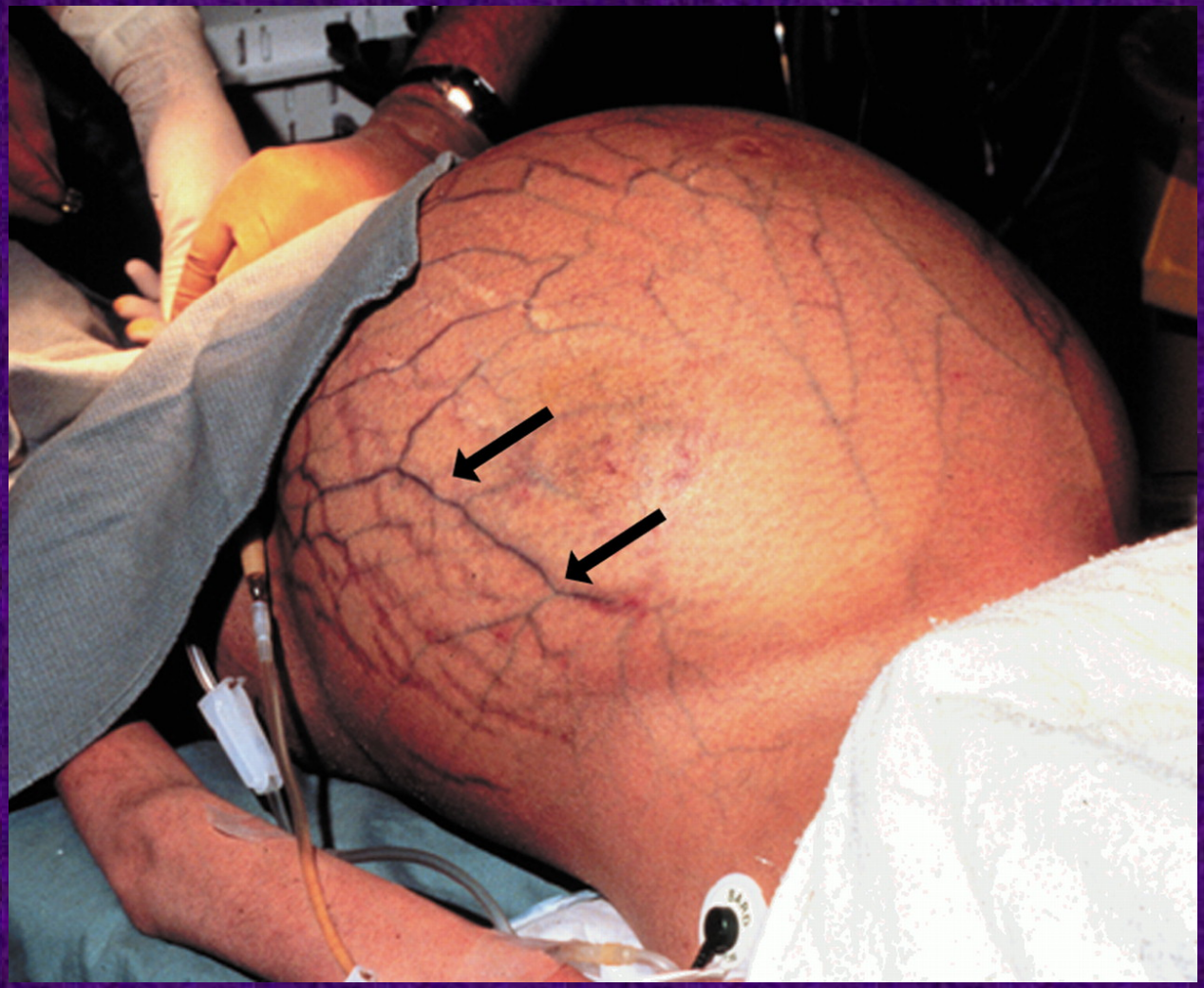
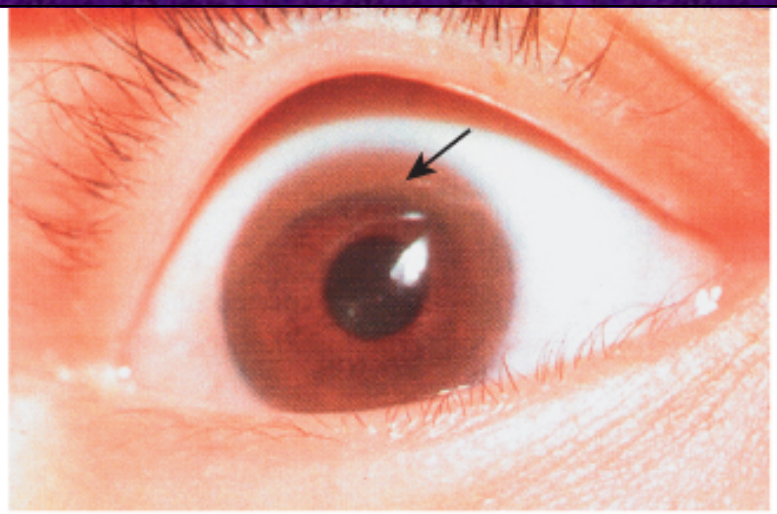


Figure 10. Photograph shows a caput medusae accentuated by a large amount of ascites in a patient being prepared for liver transplantation.

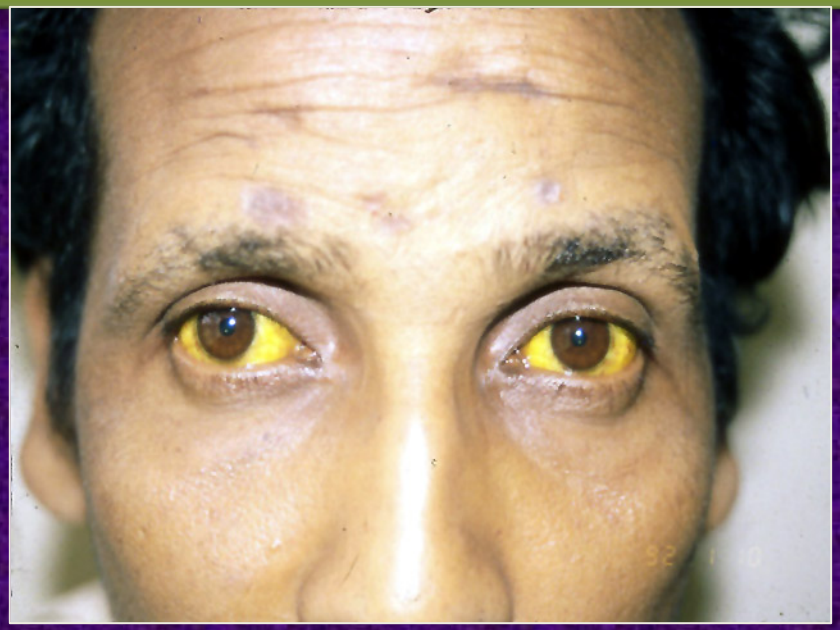


Henseler K P et al. Radiographics 2001;21:691-704

RadioGraphics



Jaundice

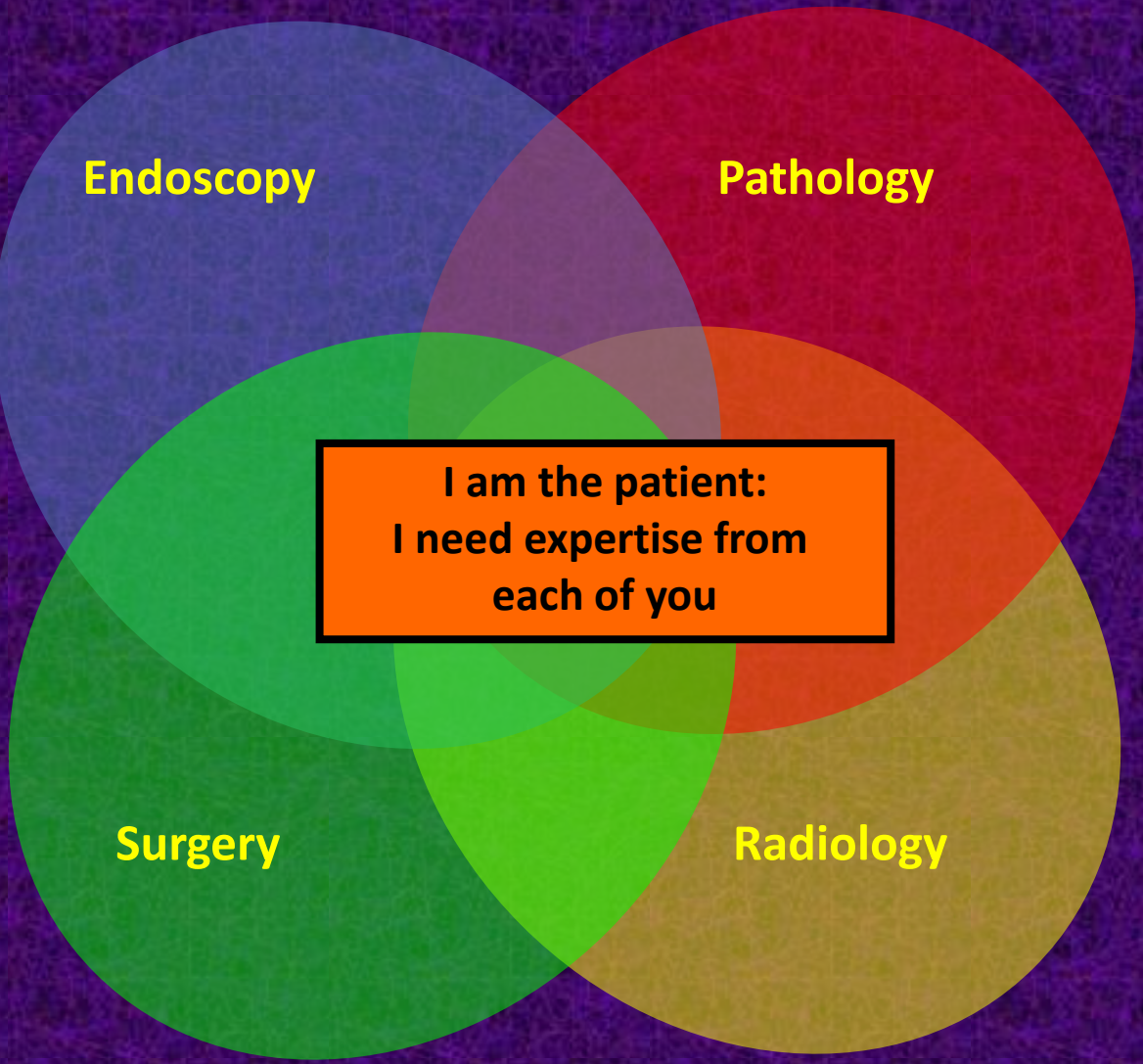


Jaundice is usually detectable clinically when the plasma bilirubin

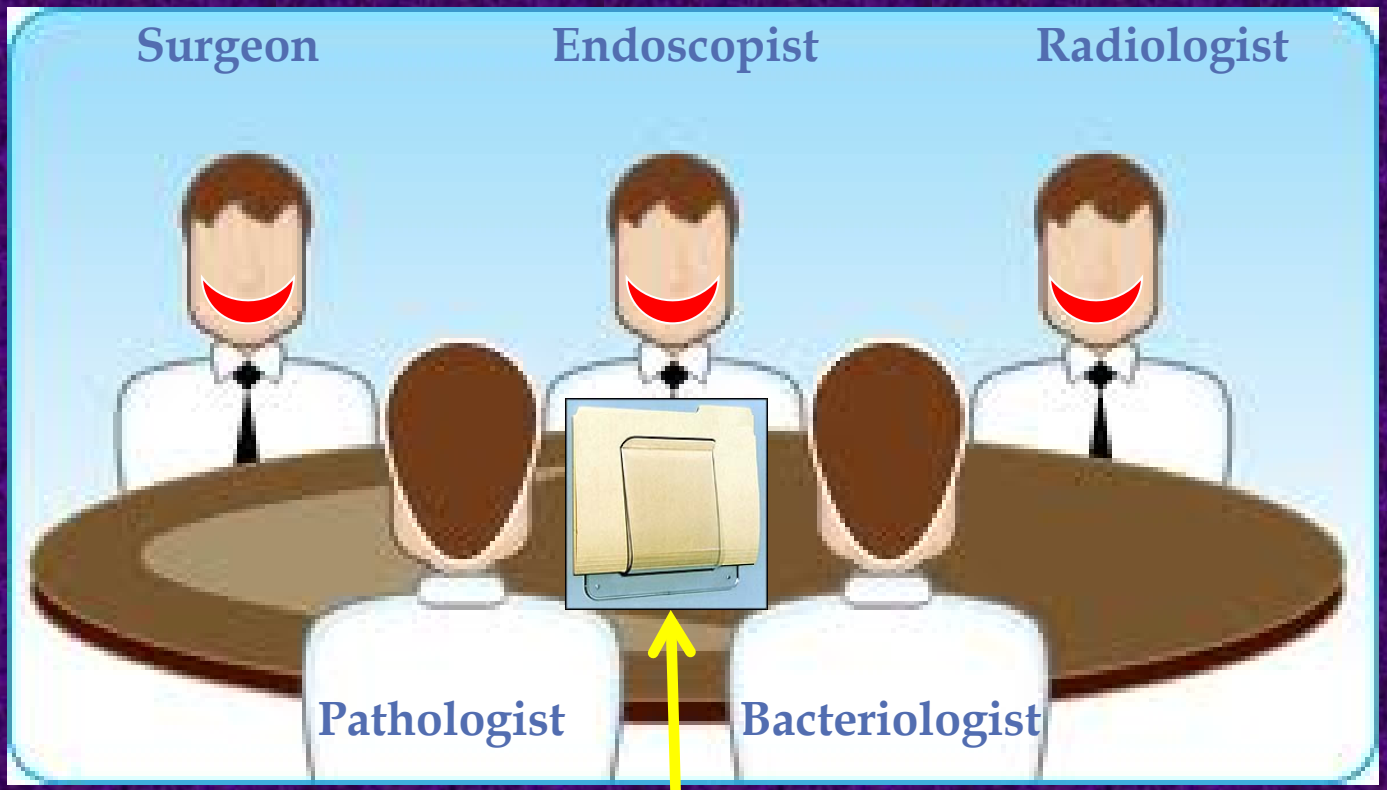
exceeds 40 µmol/L (~2.5 mg/dL). .

Manifestations

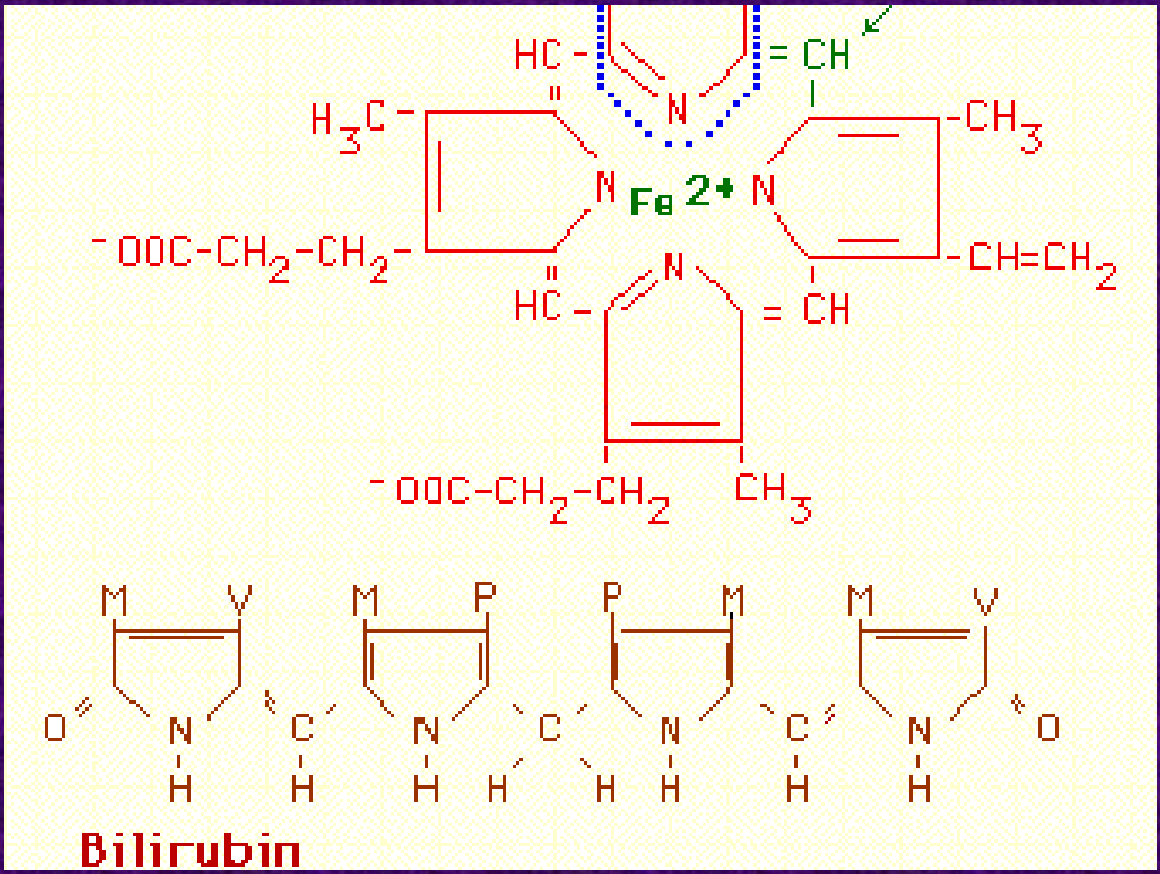
- Liver injury and its manifestations tend to follow characteristic morphologic and clinical patterns, regardless of cause.



Multidisciplinary approach !



Patient Chart & imaging

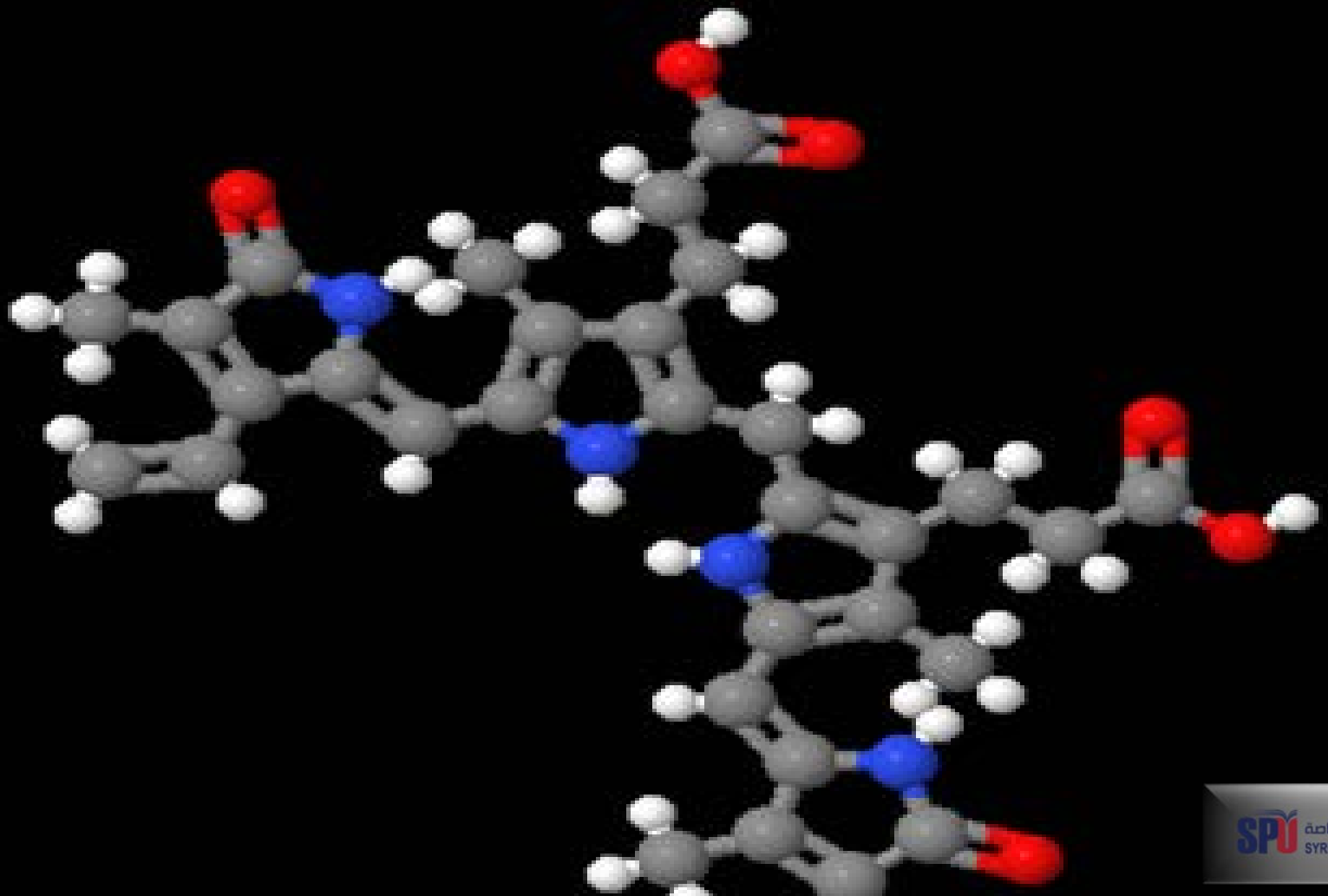


The brake down product of haem

the body usually produces about 300mg of bilirubin

Iron is removed haem molecule and porphyrin ring is opened to form bilirubin

Bilirubin



Bilirubin

Direct: water soluble

Indirect: lipid soluble

Red blood cells

Ineffective erythropoiesis

Other haem protein such as myoglobin and cytochromes

80%

20%

Transport in plasma and hepatic up take

In plasma
((bilirubin bound to albumin))

Not filtered at the glomerulus
unless there is glomerular proteinurea

On reaching the liver the bilirubin is taken into the hepatocyte

unconjugated bilirubin

=

Most of Plasma bilirubin

Conjugation of bilirubin

Endoplasmic reticulum of hepatocyte

Bilirubin + glucuronic acid —(**Bilirubin UDP-glucuronyltransferase**)→ bilirubin glucuronides "conjugated bilirubin" "Water soluble and readily transported into bile"

Bilirubin glucuronides (CONJUGATED BILIRUBIN)
cant be reabsorbed from the gut

degraded by bacterial action mainly in the colon

Urobilinogen
mixture of colorless, water soluble compounds

OXIDISE

UROBILINS AND STERCOBILINS "Brown"

Excreted in faeces

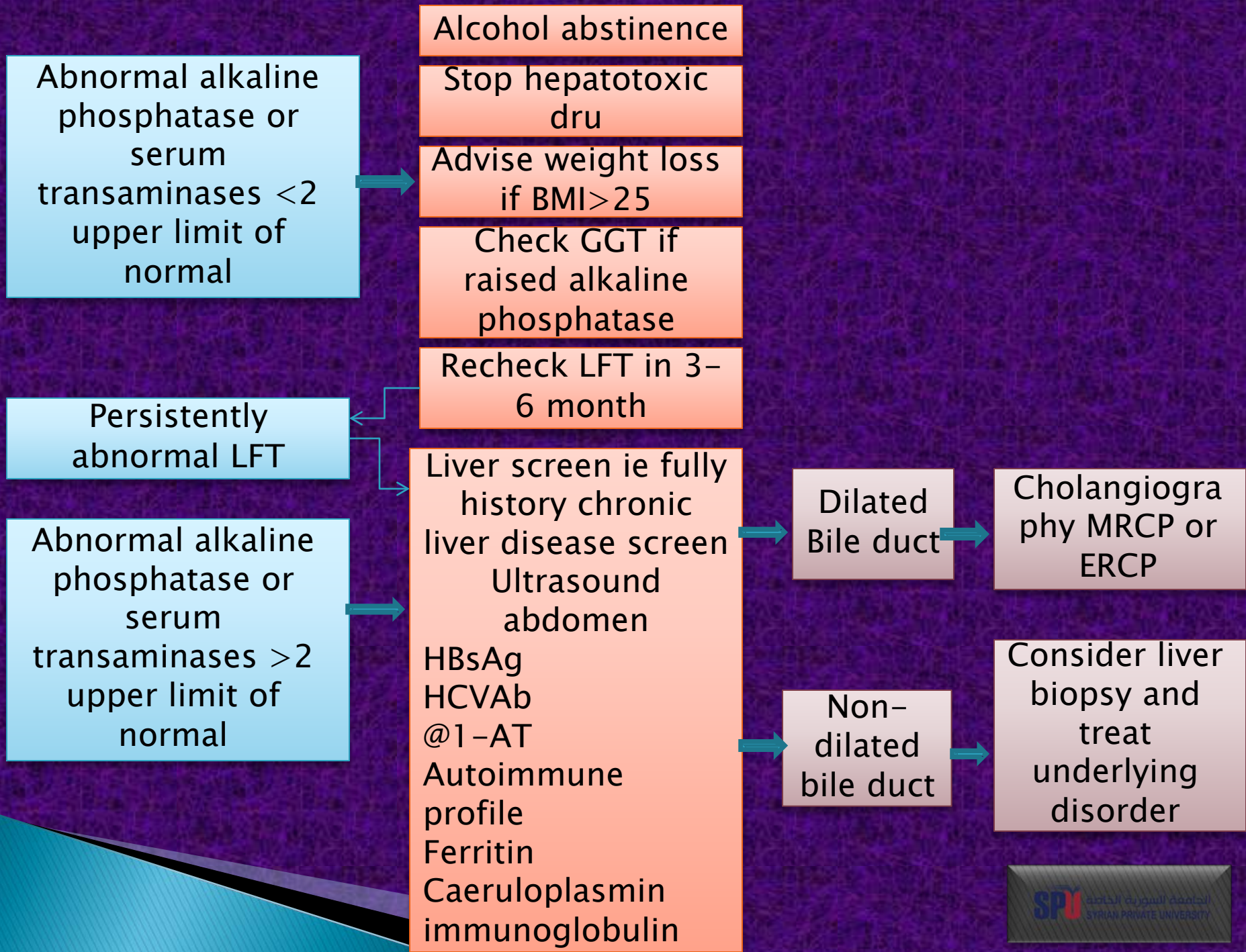
A small percentage of urobilinogen undergoes enterohepatic circulation

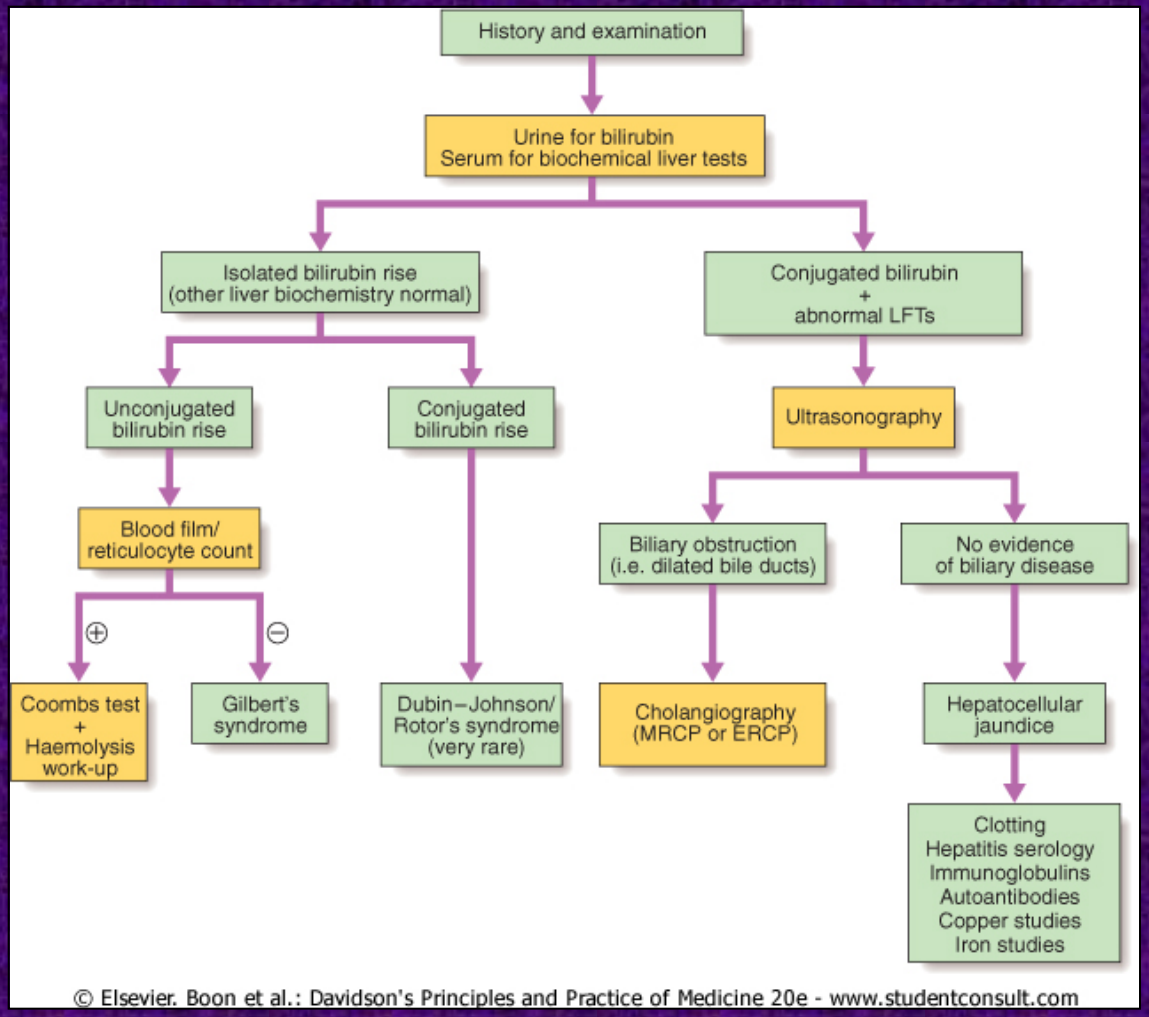
Most of it is cleared by the liver

Proportion filtered at the kidney and appears in the urine

	Urine tests	
Condition	Urobilinogen	bilirubin
Healthy individuals	**Trace**	**Nil**
Gilbert's syndrome	Trace	Nil
Haemolytic disease	Increased	Nil
Hepatitis **•prodormal** **•icteric stage**	**Increased** **Undetectable**	**detectable** **present**
Biliary obstruction	**Undetectable**	**present**

Syndrome	Inheritance	Abnormality	Clinical features/treatment
Unconjugated hyperbilirubinaemia			
Gilbert's	Autosomal dominant	↓ Glucuronyl transferase ↓ Bilirubin uptake	Mild jaundice, especially with fasting No treatment necessary
Crigler–Najjar			
Type I	Autosomal recessive	Absent glucuronyl transferase	Rapid death in neonate (kernicterus)
Type II	Autosomal dominant	↓↓ Glucuronyl transferase	Presents in neonate Phenobarbital, ultraviolet light or liver transplant as treatment
Conjugated hyperbilirubinaemia			
Dubin–Johnson	Autosomal recessive	↓ Canalicular excretion of organic anions, including bilirubin	Mild No treatment necessary
Rotor's	Autosomal recessive	↓ Bilirubin uptake ↓ Intrahepatic binding	Mild No treatment necessary

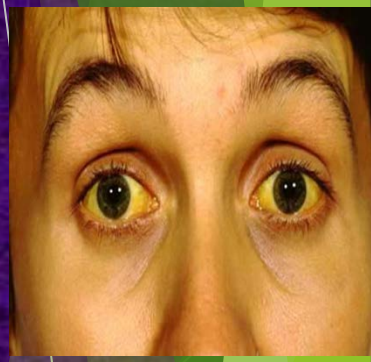

Abnormal alkaline phosphatase or serum transaminases <2 upper limit of normal
Alcohol abstinence
Stop hepatotoxic dru
Advise weight loss if BMI>25
Check GGT if raised alkaline phosphatase
Recheck LFT in 3-6 month
Persistently abnormal LFT
Abnormal alkaline phosphatase or serum transaminases >2 upper limit of normal
Liver screen ie fully history chronic liver disease screen
Ultrasound abdomen
HBsAg
HCVAb
@1-AT
Autoimmune profile
Ferritin
Caeruloplasmin
immunoglobulin
Dilated Bile duct
Cholangiography MRCP or ERCP
Non-dilated bile duct
Consider liver biopsy and treat underlying disorder

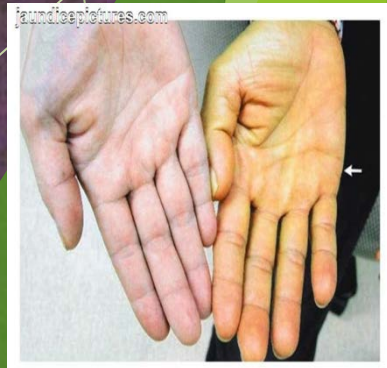


What is jaundice?

- yellowish pigmentation of the
- skin, the sclera, and other mucous membranes

- Jaundice is usually detectable clinically when the plasma bilirubin exceeds 50 μmol/L





Hepatocellular jaundice

- Both unconjugated and conjugated bilirubin in the blood increase!!!

Hepatocellular jaundice

results from an inability of the liver to transport bilirubin into the bile, as a consequence of parenchymal liver disease.

INABILITY TO SECRETE BILE
CHOLESTASIS

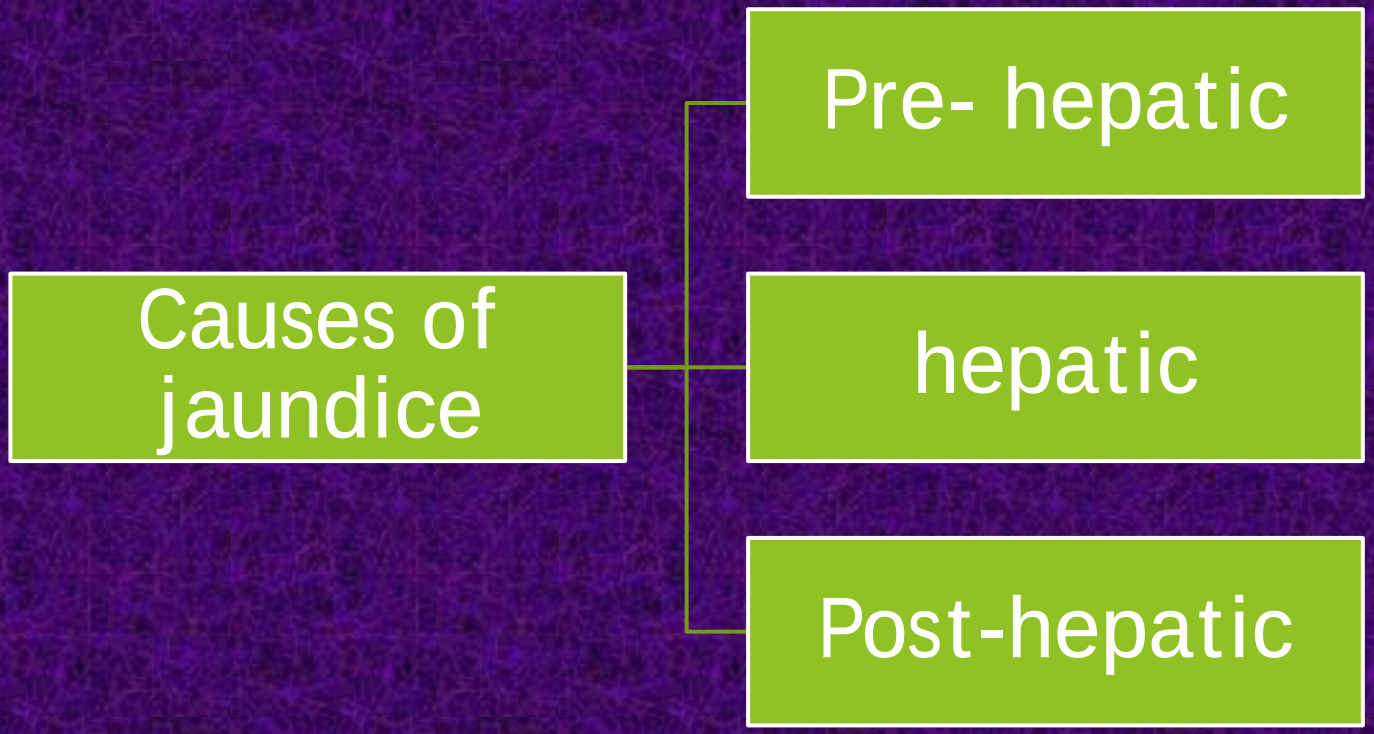
Cholestatic jaundice may be caused by:

- Failure of hepatocytes to initiate bile flow.
- Obstruction of the bile ducts or portal tracts.
- Obstruction of bile flow in the extrahepatic bile ducts.

BILE

The only way in which we can get rid of cholesterol and copper from the body

Enterohepatic circulation 90% of bile is re absorbed


Causes of jaundice
Pre- hepatic
hepatic
Post-hepatic

PRE-HEPATIC JAUNDICE

This is caused either by
1-Haemolysis or
2-congenital hyperbilirubinaemia,
and is characterised by an
isolated raised bilirubin level.

PRE-HEPATIC JAUNDICE

bilirubin load **six times** greater than normal before unconjugated bilirubin accumulates in the plasma.

.

- This does not apply to the newborn, who have a reduced capacity to metabolise bilirubin.

Liver function tests

serum bilirubin

Aminotransferaes ALT/AST

Alkaline phosphatase

Gama-glutamyle transferase GGT

Albumin

Prothrombin time (INR)

HEPATIC SYNTHETIC FUNCTION

PT

Albumin

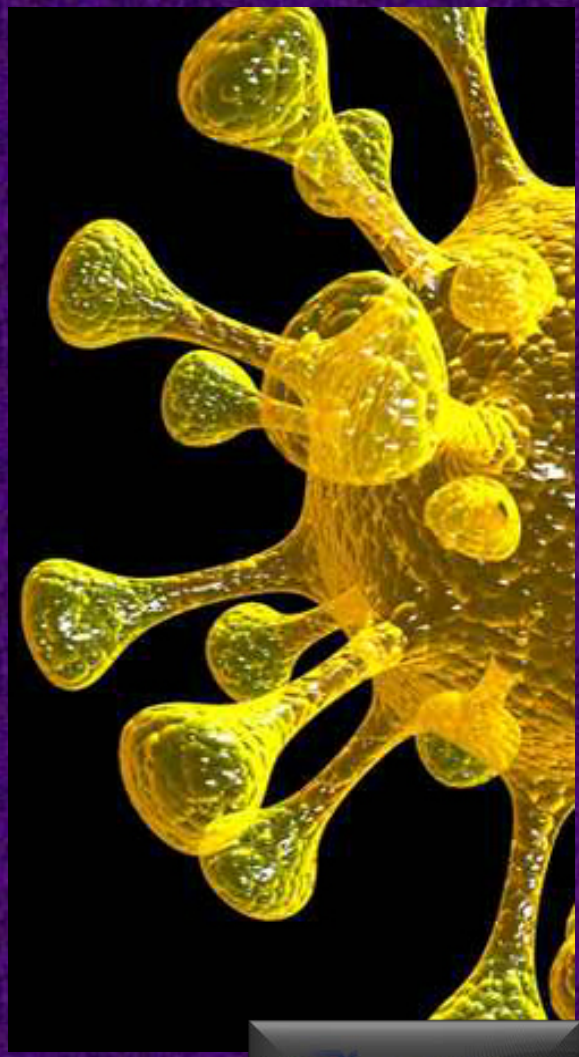
PT

Assess hepatic function

Involves factor II, V, VII, and X, synthesized by the liver

Albumin 8-14g/day

Half-life is 20 days



Aminotransferase

Amino transferase: -ALT

-AST

Both transfer amino group from amino acid to ketoacid producing pyruvate and oxalo-acetate

Tests of hepatic function

Serum albumin
Serum bilirubin
Prothrombin

Tests of hepatocellular injury or cholestasis

Aminotransferase
Alkaline phosphatase
Gama-glutamyl transferase

Common causes of elevated serum transaminases

Minor elevation (< 100 U/L)

- Chronic hepatitis C
- Chronic hepatitis B
- Haemochromatosis
- Fatty liver disease

Moderate elevation (100–300 U/L)

As above plus:

- Alcoholic hepatitis
- Non-alcoholic steatohepatitis
- Autoimmune hepatitis
- Wilson's disease

Major elevation (> 300 U/L)

- Drugs (e.g. paracetamol)
- Acute viral hepatitis
- Autoimmune liver disease
- Ischaemic liver
- Toxins (e.g. *Amanita phalloides* poisoning)
- Flare of chronic hepatitis B

- تكشف اضطرابات الكبد عادة أثناء اجراء فحص دموي روتيني (مثلاً: يظهر ارتفاع بخمائر الكبد لدى 3.5 % من المرضى الذين يتحضرون لعمل جراحي).
  يوجد مرض كبدي ما عند أغلب المرضى الذين لديهم ارتفاع مستمر بهذه القيم

GGT:

Microsomal enzyme
transfer glutamyl groups from gama-glutamyl peptides to other peptides and amino acid

GGT

Alcohol use
BMI

Anticonvulsant
Warfarin
Age gender
Smoking

Alkaline phosphatase

Enzymes Are capable of hydrolysing phosphatesteras at alkaline PH

Bilirubin glucuronides (CONJUGATED BILIRUBIN)
cant be reabsorbed from the gut

degraded by bacterial action mainly in the colon

OXIDISE

STERCOBILINS

Excreted in faeces
"Brown"

LIVER AND COAGULATION

	clotting	Anti-clotting
Vitamin k dependent	II VII IX X	Protein C protein S
independent of Vit K	I V Viii	Antithrombin III

COAGULATION PROTEINS /BALANCING CF

Measurable

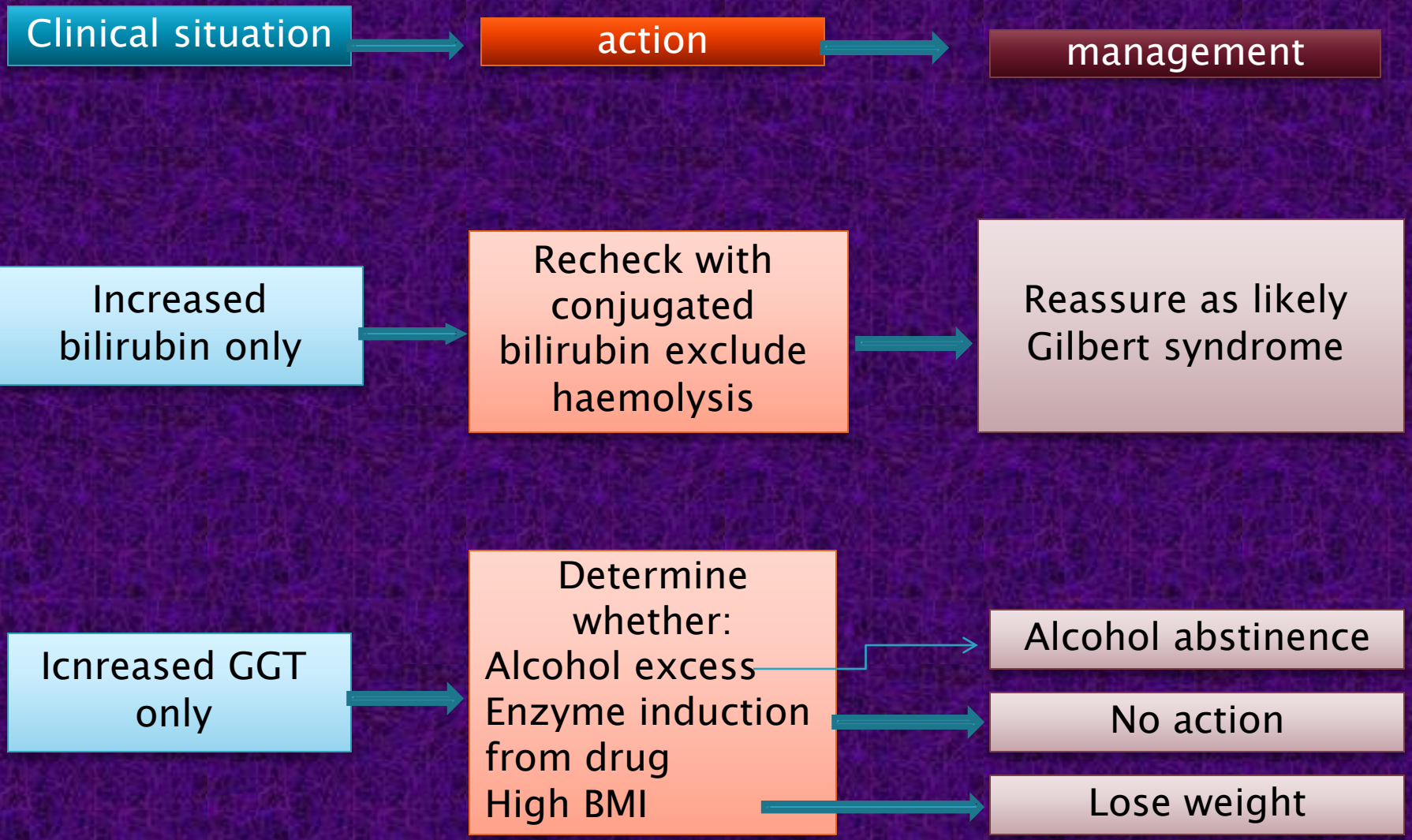
Not Measurable

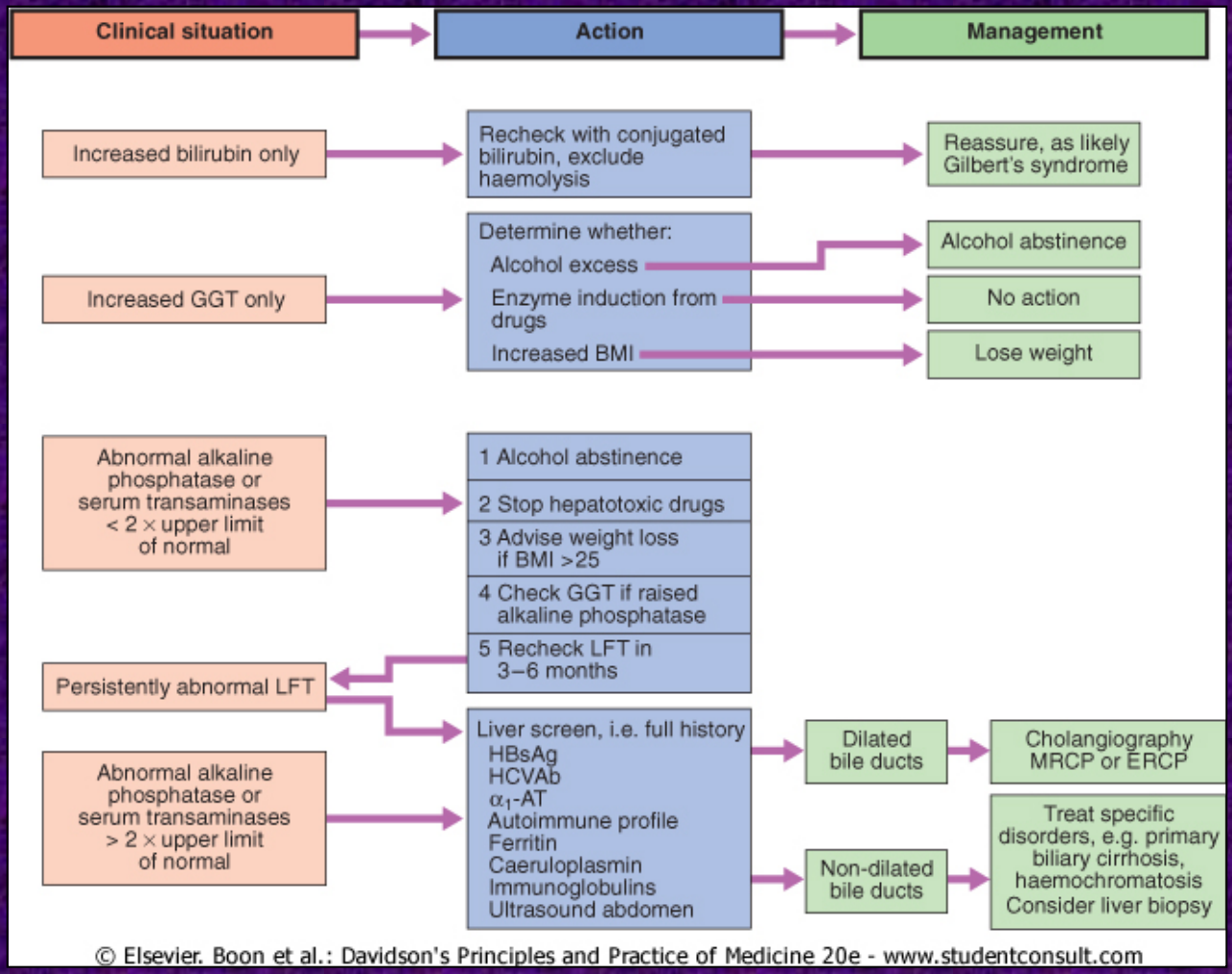
IMPORTANT

the presence or absence of stigmata of chronic liver disease

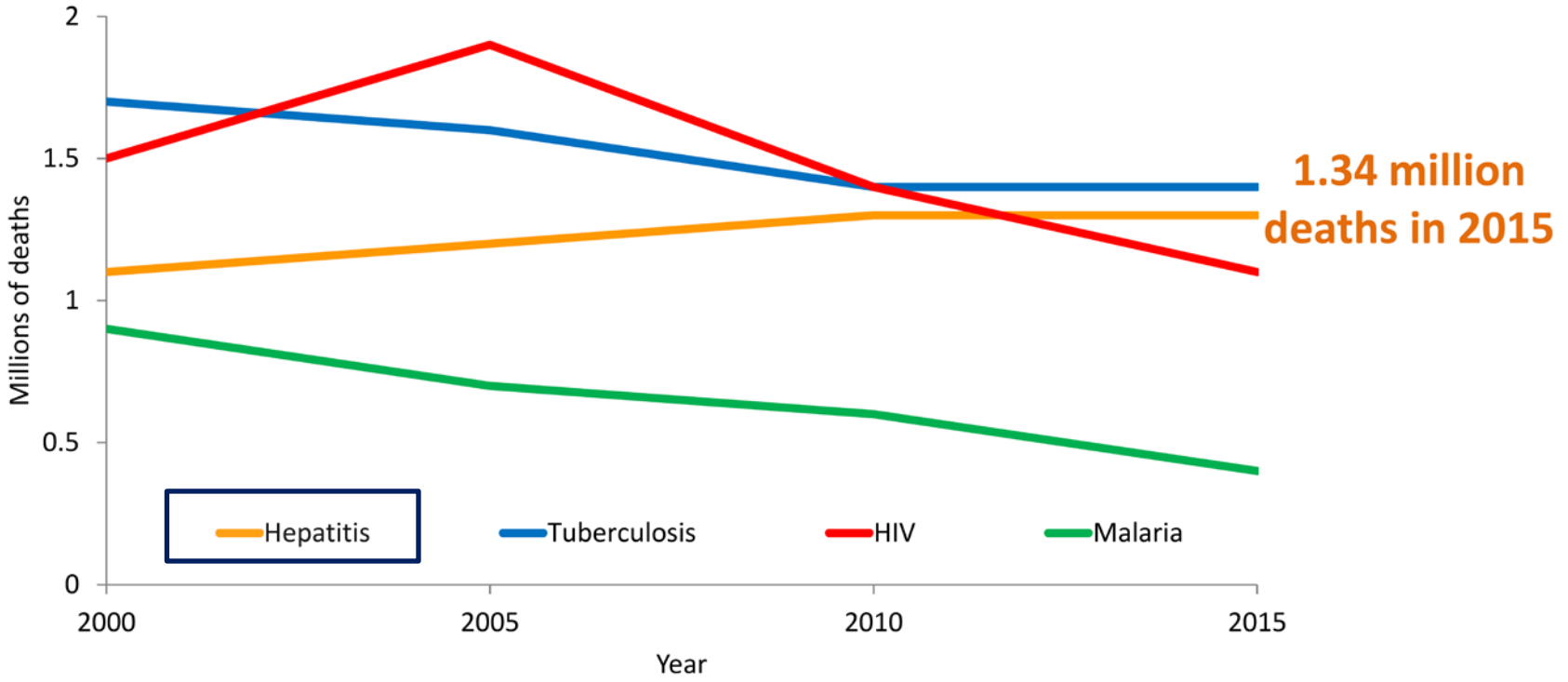
does not reliably identify patients with significant chronic liver disease.

The absence of these stigmata should not therefore preclude further investigation


Clinical situation
action
management
Increased bilirubin only
Recheck with conjugated bilirubin exclude haemolysis
Reassure as likely Gilbert syndrome
Icnreased GGT only
Determine whether:
Alcohol excess
Enzyme induction from drug
High BMI
Alcohol abstinence
No action
Lose weight



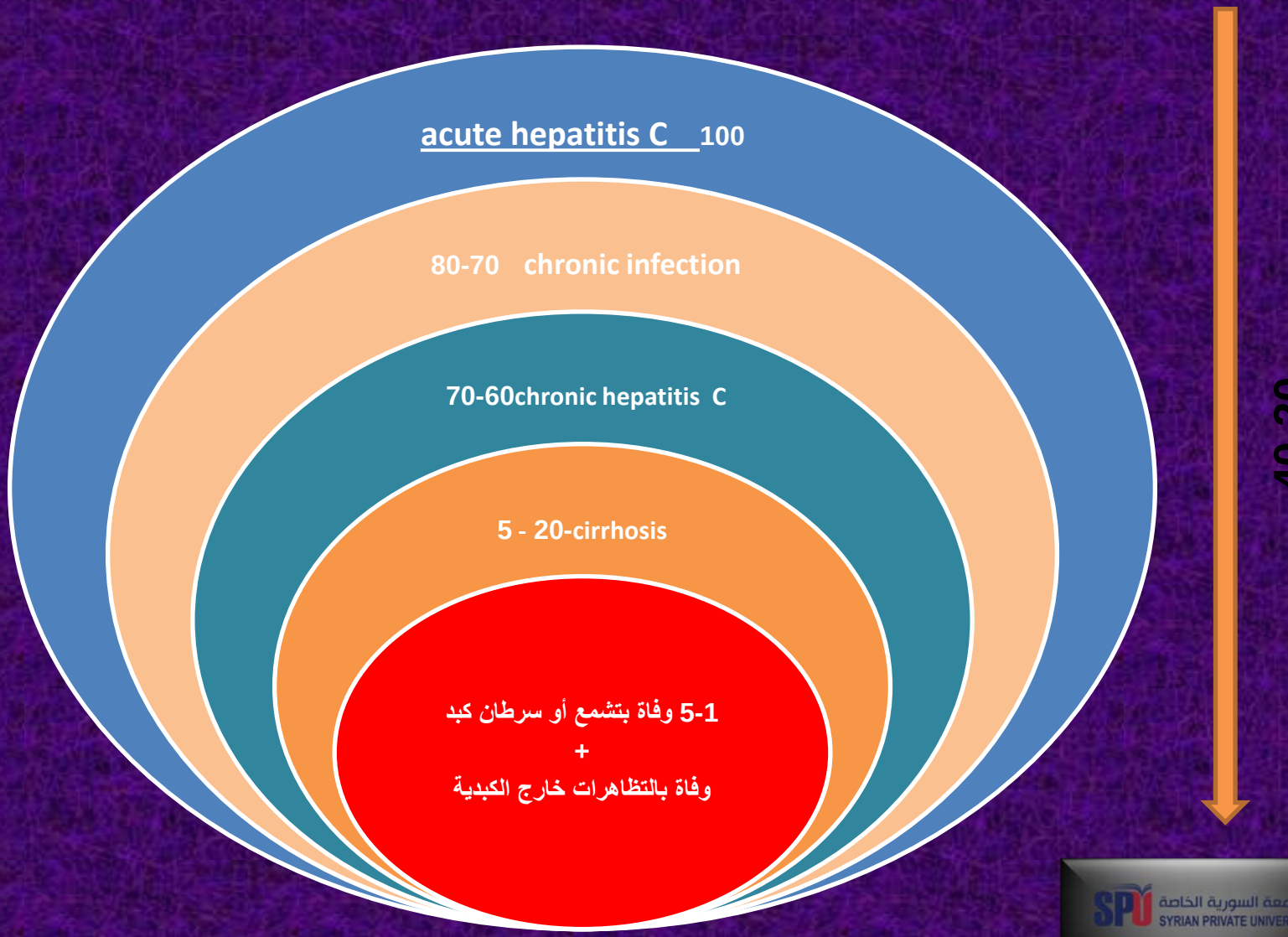
Hepatitis Mortality is increasing 2000-2015



By the year 2030:
20 million new deaths will occur if No Action is going to be undertaken

WHO Global hepatitis report, 2017. Available at: http://apps.who.int/iris/bitstream/10665/255017/1/WHO-

The course of HCV infection with no treatment



Serologic Diagnosis of Acute Hepatitis

DIAGNOSIS	SCREENING ASSAYS	SUPPLEMENTAL ASSAYS
Hepatitis A	IgM anti-HAV	None needed
Hepatitis B	HBsAg, IgM anti-HBc	HBeAg, anti-HBe HBV DNA
Hepatitis C	Anti-HCV by EIA	HCV RNA by PCR; anti-HCV by Immunoblot
Hepatitis D	HBsAg	Anti-HDV
Hepatitis E	History	Anti-HEV
Mononucleosis	History, white blood cell differential counts	Monospot test Heterophil antibody
Drug-induced hepatitis	History	

	Hepatitis B	Hepatitis C	Hepatitis D
Virus			
Spread			
Faeces	No	No	No
Blood	Yes	Yes	Yes
Saliva	Yes	Yes	?
Sexual	Yes	Uncommon	Yes
Vertical	Yes	Uncommon	Yes
Chronic infection	Yes	Yes	Yes
Prevention			
Active	Vaccine	No	Prevented by
Passive	Hyperimmune immunogobulin	No	**hepatitis B vaccine**

Route of transmission	Risk of chronic infection
Horizontal transmission	10%
Injection drug use	
Infected unscreened blood products	
Tattoos/acupuncture needles	
Sexual (homosexual and heterosexual)	
Vertical transmission	90%
HbsAg-positive mother	

Global Burden of Viral Hepatitis (Estimates)

- 2000 million (2 billion) infected with hepatitis B (> 350 million chronically)
- 130–170 million chronically infected with hepatitis C
- 57% of liver cirrhosis and 78% of primary liver cancer due to hepatitis B or C
- ~600,000 deaths annually – hepatitis B
- > 350,000 deaths annually – hepatitis C
- 2.7% all deaths due to acute hepatitis B and C, cancer/ cirrhosis of liver (increasing over time)

Hepatitis C prevalence in people who inject drugs

People who inject drugs – the most affected population group

Prevalence estimates

30% to 98% in EU countries (2002)

21% to 86% in 9 EU countries (2012)

Sources: Roy K, et al 2002. Monitoring hepatitis C virus infection among injecting drug users in the European Union: a review of the literature. *Epidemiology & Infection.* 129: 577-85; Rondy M, et al 2012. Hepatitis C prevalence in injecting drug users in Europe, 1990-2007: impact of study recruitment setting. *Epidemiology & Infection*

Liver biopsy

Why?

- a liver biopsy is often required to stage the degree of liver damage.

scoring system

- The most common scoring system used is the Metavir system,
- which scores fibrosis from 1 to 4, the
- latter equating to cirrhosis

What is a Liver Biopsy?