PROPAEDEUTICS
OF INTERNAL MEDICINE

Collection of clinical lectures by T. Khomazyuk

PART 2

State Establishment
«Dnepropetrovsk Medical Academy
of Health Ministry of Ukraine»

PROPAEDEUTICS
OF INTERNAL MEDICINE

Collection of clinical lectures by T. Khomazyuk

The educational and visual guide
on training students of the second (master's) level of higher education, educational qualification "Master of Medicine", professional qualification "Doctor"
for English speaking students

In two parts | PART 2

Dnipro | «GERDA»
2019

УДК 616.1/.4:616.6]-07(042.4)(075.8)
Х76

Рекомендовано до друку з грифом вченої ради ДЗ «ДМА МОЗ України» (протокол № 12 від 13.06.2019 р.).

Автор: док. мед. наук., проф. кафедри пропедевтики внутрішньої медицини **Т.А. Хомазюк**

Рецензенти:

Долженко М.М. – док. мед. наук., професор, завідувач кафедри кардіології НМАПО ім. П.Л.Шупика

Ілащук Т.О. – док. мед. наук., професор, завідувач кафедри пропедевтики внутрішньої медицини Буковинського медичного університету

Учбово-наочний посібник «Propaedeutics of internal medicine. Collection of clinical lectures» є виданням «Курсу лекцій з пропедевтики внутрішньої медицини» в авторській редакції, призначений для підготовки фацівців другого (магістерського) рівня вищої освіти, освітньої кваліфікації «Магістр медицини» професійної кваліфікації «Лікар», які навчаються на англійській мові.

В ілюстраціях до клінічних лекцій автор використав інформаційні матеріали з відкритої мережі Інтернету.

Ілюстрації на обкладинці: «Твори Гіппократа», 1932–1934 рр. (Кольоровий літо) Друк Жикле Джозефа Куна-Реньє.

The author: M.D., D.Med.Sc., Professor TA Khomazyuk. Department of Propaedeutics of Internal Medicine

Reviewers:

Dolzhenko MM – M.D., D.Med.Sc., Professor, Head of the Cardiology Department, PL Shupyk National Medical Academy of Postgraduate Education

Ilaschuk TO – M.D., D.Med.Sc., Professor, Head of the Department of Propaedeutics of Internal Medicine, Bukovina Medical University

Cover Illustrations: "The Works of Hippocrates", 1932–1934 (Colour Litho) Giclee Print by Joseph Kuhn-Regnier.

Khomazyuk T.

Х76 Propaedeutics of internal medicine. Collection of clinical lectures: the educational and visual guide: in two parts. Part 2. – Dnipro: Gerda, 2019. – 352 p.

ISBN 978-617-7639-18-2 (ч. 1, pdf)

Textbook designed for the training of specialists of the second (master's) level of higher education, educational qualification "Master of Medicine", professional qualification "Doctor" for English speaking students.

УДК 616.1/.4:616.6]-07(042.4)(075.8)

ISBN 978-617-7639-17-5
ISBN 978-617-7639-19-9 (ч. 2, pdf)

CONTENTS

Part 1

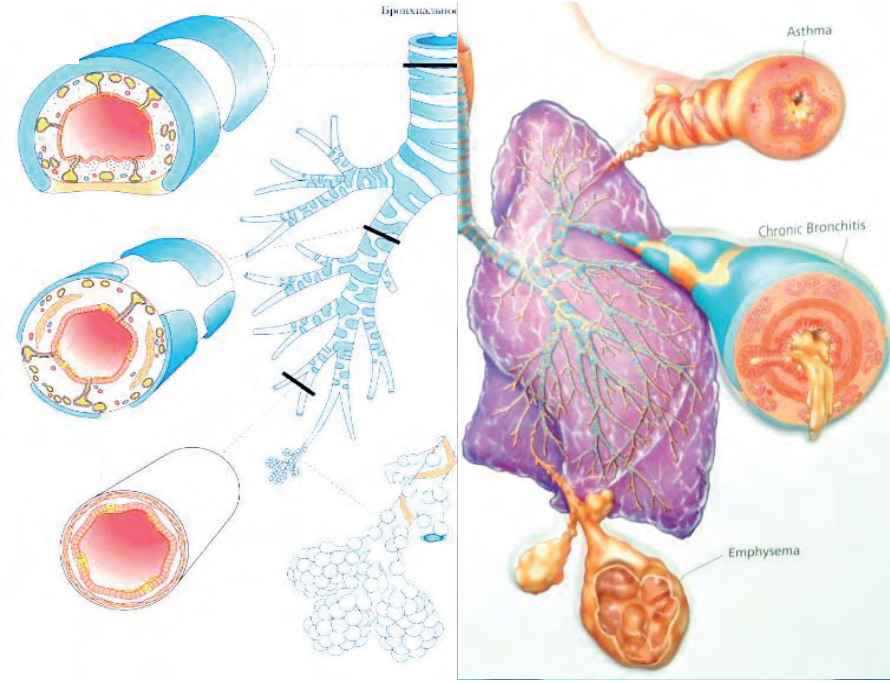
Part 2

LECTURE # 10

THE MAIN SYNDROMES OF DISEASES OF THE RESPIRATORY SYSTEM

THE PLAN

- Anatomy of the bronchopulmonary system
- The Main SYNDROMES of respiratory diseases
- Survey algorithm
- General inflammatory syndrome
- Focal consolidation of the lung tissue
- Adventitious Lung Sounds
- Cavity in the lung
- Accumulation of fluid in the pleural cavity
- Diagnostic thoracentesis
- Air accumulation in the pleural cavity. Pneumothorax
- Patient Phenotypes
- Spirometry
- Bronchial obstruction syndrome
- ASTHMA ATTACK
- Eponymous syndromes
- Sleep Apnea Syndrome
- Upper airway obstruction
- Respiratory failure syndrome
- The syndrome of pulmonary hypertension
- Cor pulmonale syndrome
- References



What is it ? **Why ?**

Answer the questions:

1. Bronchopulmonary infection is characterized by:

1- fever, cough, shortness of breath;
2 - cyanosis, cough, wheezing in the lungs;
3 - fever, herpes on the lips, shortness of breath;
4 - fever, runny nose, headache;
5 - shortness of breath, tachycardia, cough

2. Bronchial obstruction is characterized by:

1 - shortness of breath, wheezing, lengthening exhalation;
2 - increased respiration, coughing, sputum;
3 - rare breathing, lengthening exhalation;
4 - constant dry cough, distant wheezing;
5 - dyspnea with lack of air, chest tightness, palpitations

What is it ? Why ?

Answer the questions:

3. Respiratory failure is:

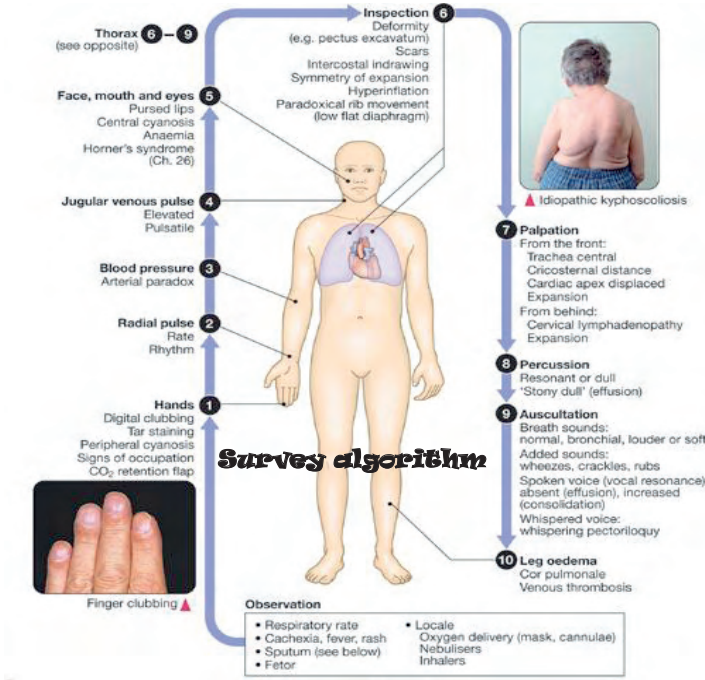
1- shortness of breath, cyanosis, tachycardia;
2- fatigue of the respiratory muscles;
3- dysfunction of external respiration;
4- respiratory impairment during sleep;
5- all of the above

4. The rate of hemoglobin oxygen saturation in the blood (*SatO₂%*):

1- 90-94%;
2- more than 95%;
3- more than 99%;
4- less than 90%;
5- less than 95%

THE MAIN SYNDROMES
of respiratory diseases

- Syndrome of bronchopulmonary infection
- Focal consolidation of lung tissue
- Cavity in the lung
- Accumulation of fluid in the pleural cavity
- Air accumulation in the pleural cavity
- Bronchial obstruction syndrome
- Bronchiectasis syndrome
- Shift of the mediastinum Syndrome
- Respiratory failure syndrome
- The syndrome of pulmonary hypertension
- Cor pulmonale syndrome



General inflammatory syndrome

bronchopulmonary infection S. !

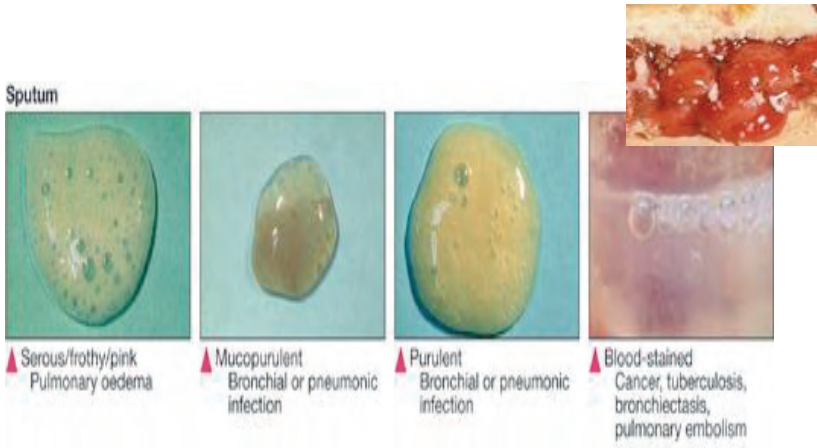
CURB-65*

CRB-65 (Lim et al., 2003)

- Confusion,
- Urea nitrogen (> 7 ммоль/л),
- Respiratory rate (≥ 30/мин),
- Blood pressure (DBP < 60, SBP < 90 Hg),
- Age ≥ 65 лет

cough !

Types of sputum



Focal consolidation of The lung tissue

- Common complaint – dyspnea
- Thoracic lagging of the affected side during respiration
- Tactile fremitus – intensified in the consolidated area
- The percussion sound - slightly or absolutely dull
- Auscultation – bronchial respiration, exaggerated bronchophony, crepitation,

CRACKLES

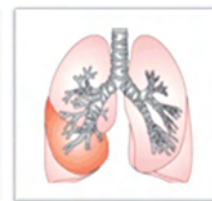
- X-ray – focus of consolidation (area of increased density)

Differentiation of Common Pulmonary Conditions

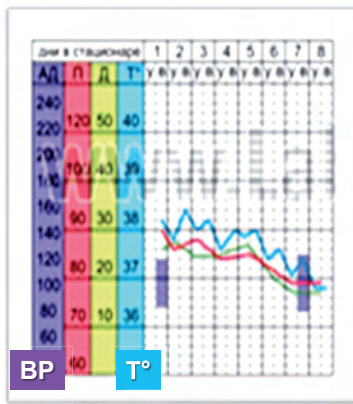
Condition	Vital Signs	Findings: Inspection	Palpation	Percussion	Auscultation
Asthma*	Tachypnea; tachycardia	Dyspnea; use of accessory muscles; possible cyanosis; hyperinflation	Often normal; decreased fremitus	Often normal; hyperresonant; low diaphragm	Prolonged expiration; wheezes; decreased lung sounds
Emphysema	Stable	Increased anteroposterior diameter; use of muscles; thin individual	Decreased tactile fremitus	Increased resonance; decreased excursion of diaphragm	Decreased lung sounds; decreased vocal fremitus
Chronic bronchitis	Tachycardia	Possible cyanosis; patients tend to be short and stocky	Often normal	Often normal	Early crackles; rhonchi
Pneumonia	Tachycardia; fever; tachypnea	Possible cyanosis; possible splinting on affected side	Increased tactile fremitus	Dullness	Late crackles; bronchial breath sounds†
Pneumothorax	Tachypnea; tachycardia	Often normal; lag on affected side	Absent fremitus; trachea may be shifted to other side	Hyperresonant	Absent breath sounds
Pleural effusion	Tachypnea; tachycardia	Often normal; lag on affected side	Decreased fremitus; trachea shifted to other side	Dullness	Absent breath sounds
Atelectasis	Tachypnea	Often normal; lag on affected side	Decreased fremitus; trachea shifted to same side	Dullness	Absent breath sounds
Acute respiratory distress syndrome	Tachycardia; tachypnea	Use of accessory muscles; cyanosis	Usually normal	Often normal	Normal initially; cackles and decreased lung sounds, late

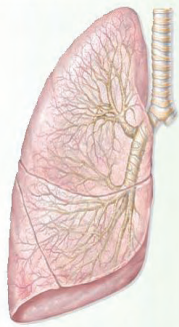
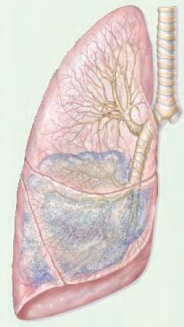
*The physical findings in asthma are often not reliable in predicting its severity.
†Bronchophony, whispered pectoriloquy, and egophony are also often present.
‡Elevated jugular venous distention, pedal edema, and hepatomegaly.

Focal



Lobar CAP



	Normal Air-Filled Lung	Airless Lung, as in Lobar Pneumonia
		
Breath Sounds	Predominantly vesicular	Bronchial or bronchovesicular over the involved area
Transmitted Voice Sounds	Spoken words muffled and indistinct Spoken "ee" heard as "ee" Whispered words faint and indistinct, if heard at all	Spoken words louder (*bronchophony*) Spoken "ee" heard as "ay" (*egophony*) Whispered words louder, clearer (*whispered pectoriloquy*)
Tactile Fremitus	Normal	Increased

Transmitted Voice Sounds. If you hear abnormally located bronchovesicular or bronchial breath sounds, assess transmitted voice sounds. With a stethoscope, listen in symmetric areas over the chest wall as you assess any abnormal vocal resonances suspicious for pneumonia or pleural effusion.

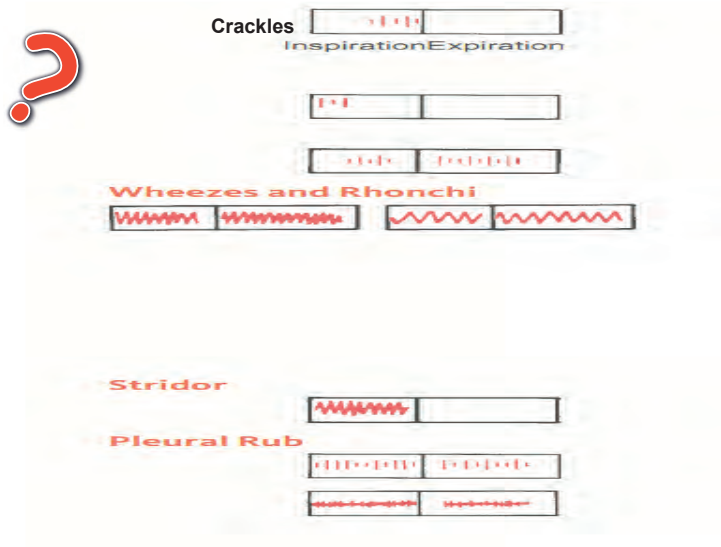
- Ask the patient to say "ninety-nine." Normally the sounds transmitted through the chest wall are muffled and indistinct.
- Ask the patient to say "ee." You will normally hear a muffled long E sound.
- Ask the patient to whisper "ninety-nine" or "one-two-three." The whispered voice is normally heard faintly and indistinctly, if at all.

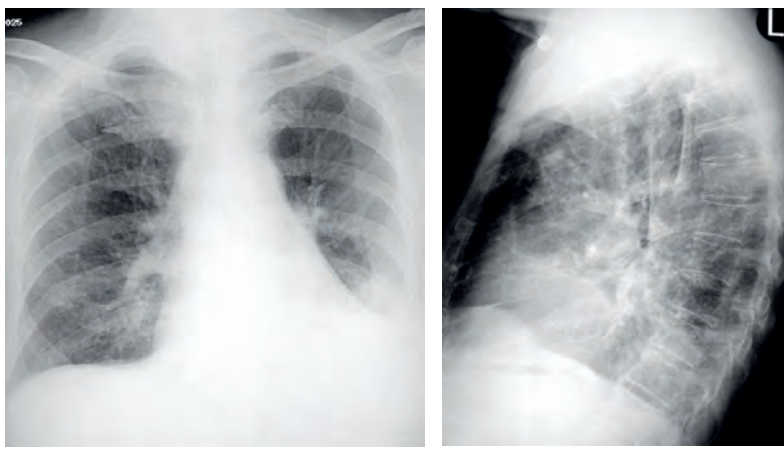
Louder voice sounds are called *bronchophony.*

Louder, clearer whispered sounds are called *whispered pectoriloquy*.

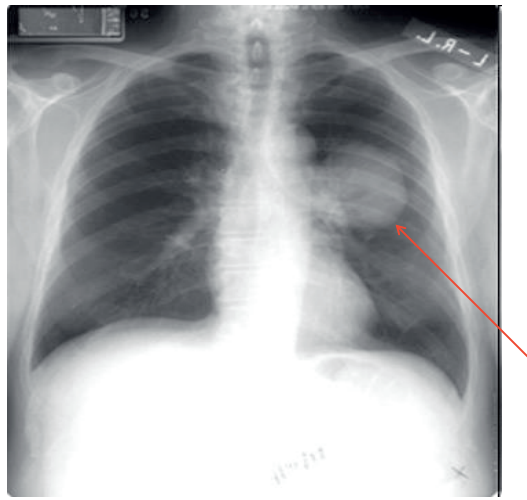
If "ee" sounds like "A," an E-to-A change, or *egophony*, is present, seen in lobar consolidation from *pneumonia*. The "A" has a nasal bleating quality, and should be localized. In patients with fever and cough, the presence of bronchial breath sounds and egophony more than triples the likelihood of pneumonia.[22]

ADVENTITIOUS LUNG SOUNDS

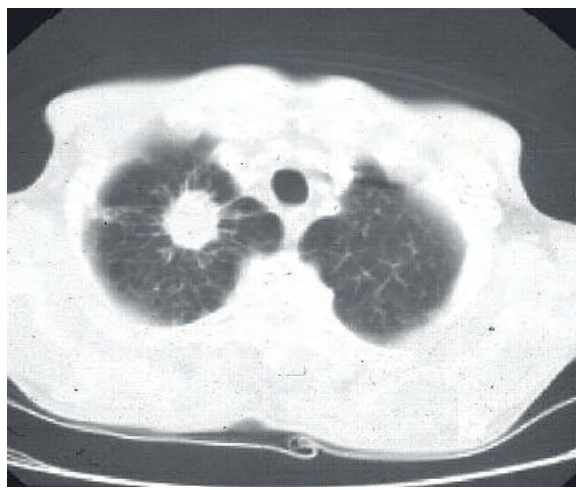




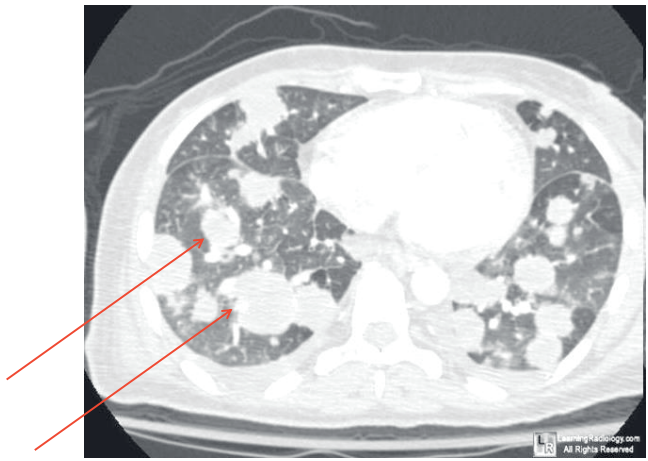
Aspiration pneumonia. An 84-year-old man in generally good health had fever and cough. Posteroanterior radiograph demonstrates a left lower lobe opacity



The chest x-ray shows a shadow in the left lung, which was later diagnosed as lung cancer



A CT scan of the lung shows a mass lesion in the right lung. The mass turned out to be lung cancer on examination of the needle biopsy sample



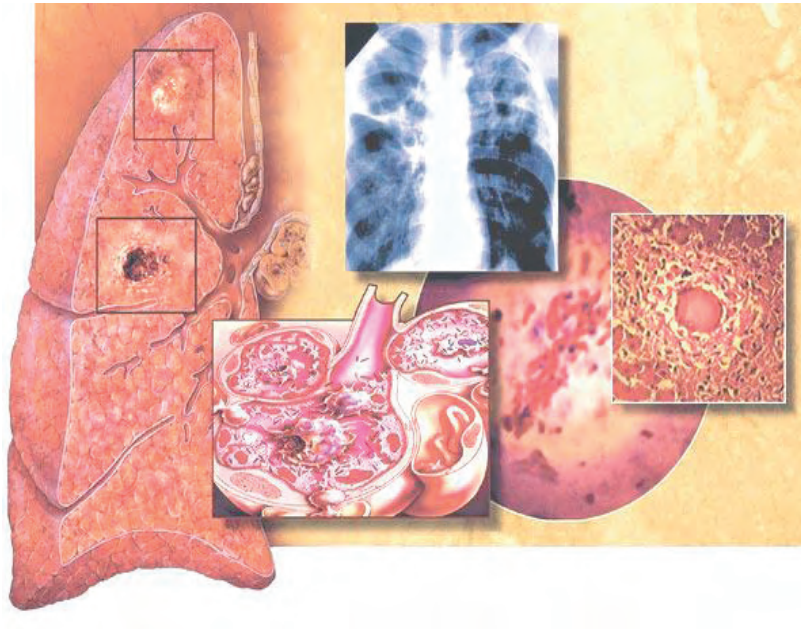
Cannonball Metastases-large, hematogebously spread metstatic lesions in the lungs of varying sizes most often from colon, breast, renal, thyroid primaries

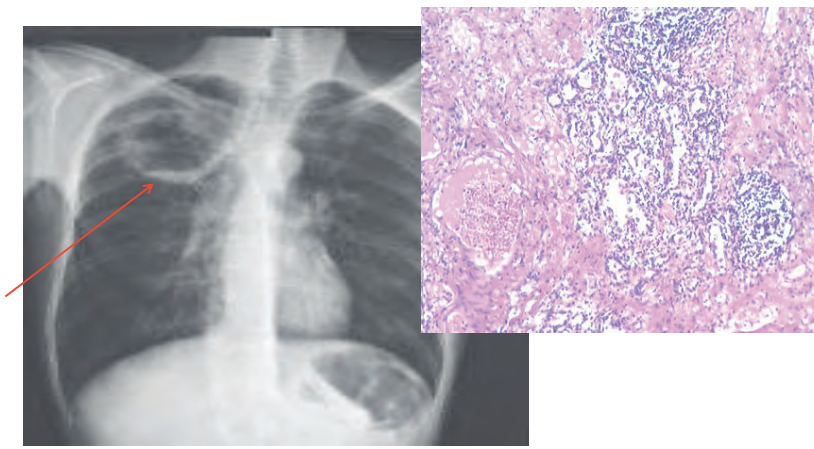
CAVITY IN THE LUNG

- Unilateral thoracic lagging
- Tactile fremitus – intensified
- The percussion sound – tympanic or (if c. large and peripheral) with a metallic tinkling
- **Auscultation** – amphoral breathing, intensified bronchophony, medium and coarse

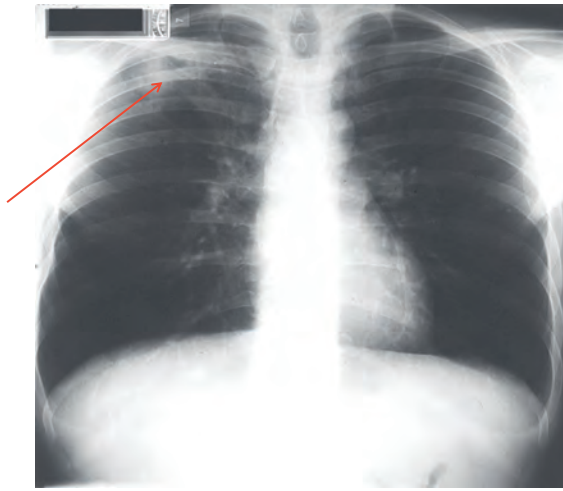
CRACKLES

- **X-ray** – cavity in the lung

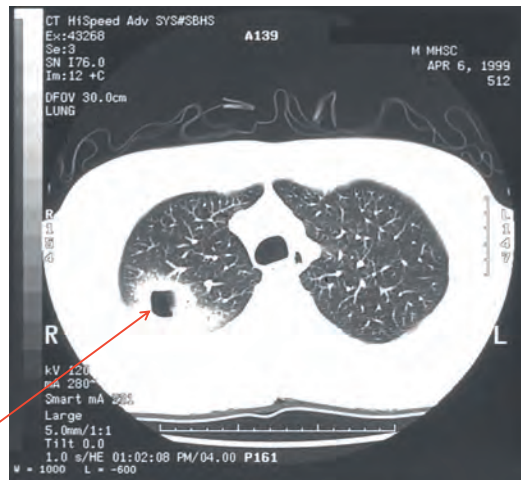




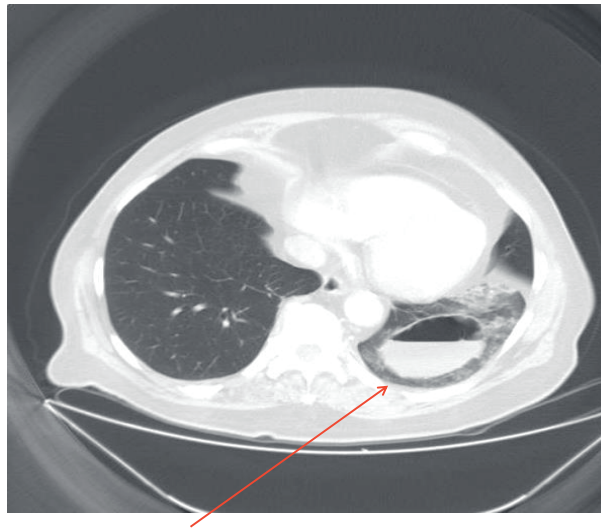
Chest radiograph of a patient who had foul-smelling and bad-tasting sputum, an almost diagnostic feature of anaerobic lung abscess. Histology of a lung abscess shows dense inflammatory reaction (high power)



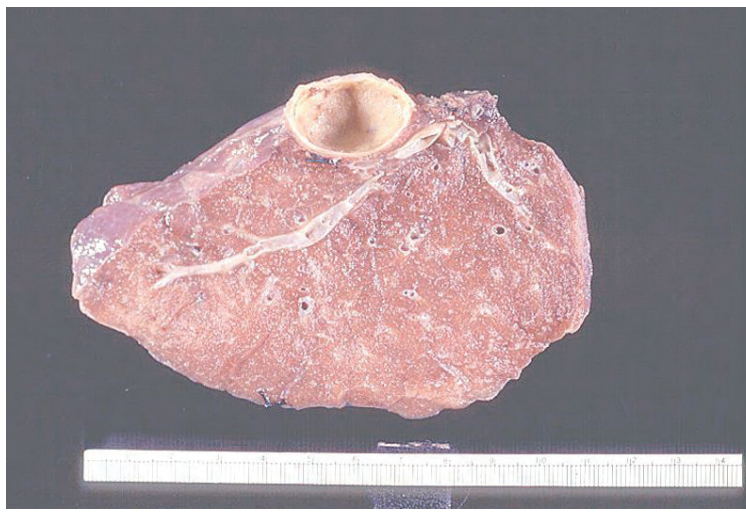
A 42-year-old man developed fever and production of foul-smelling sputum. He had a history of heavy alcohol use, and poor dentition was obvious on physical examination. Chest radiograph shows lung abscess in the posterior segment of the right upper lobe



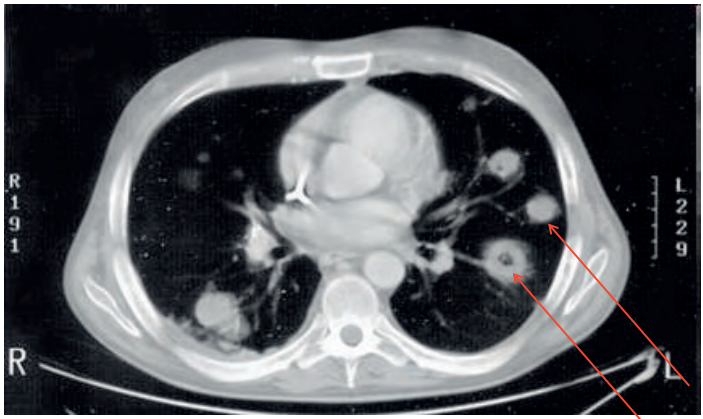
A 42-year-old man developed fever and production of foul-smelling sputum. He had a history of heavy alcohol use, and poor dentition was obvious on physical examination. Lung abscess in the posterior segment of the right upper lobe was demonstrated on chest radiograph. CT scan shows a thin-walled cavity with surrounding consolidation



CT scan. Cavity in the left lung with fluid level

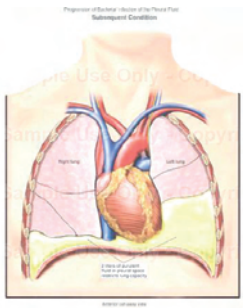


A thick-walled lung abscess



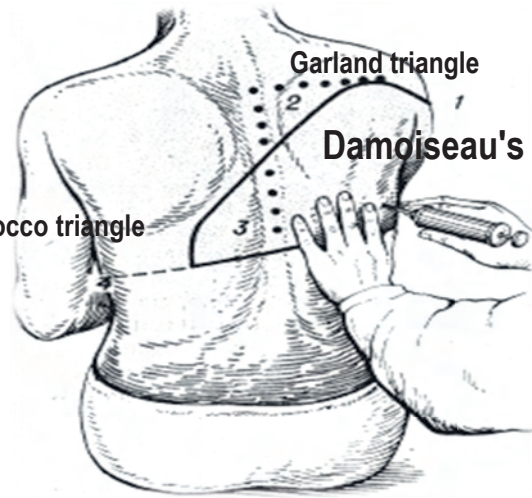
CT scan of a patient with invasive aspergillosis showing multiple lung lesions, some with cavitation

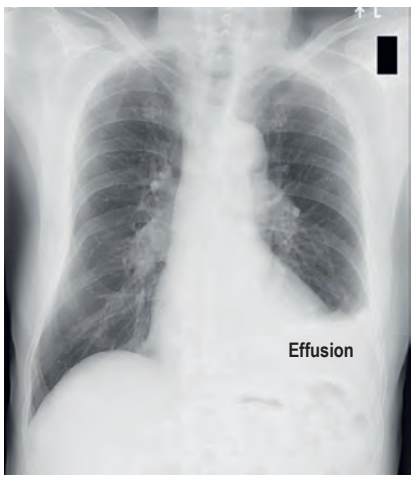
Accumulation of fluid in the pleural cavity



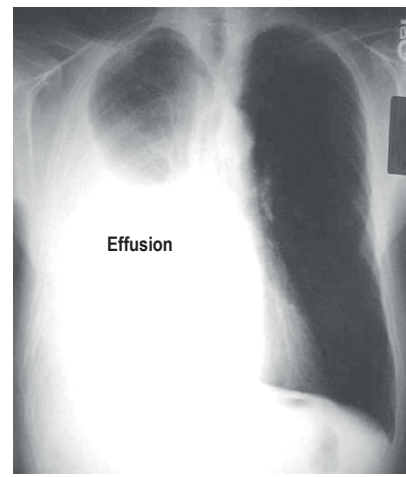
- Hydrotorax **- transudate**
- Plevristy with effusion **- excaudate**

- **Dyspnea**
- Asymmetry of the cest (enlargement of the affected side)
- Unilateral thoracic lagging during respiration
- Tactile fremitus weakened, undeterminable
- Percussion – dulled sound or absolute dullness (Damoiseau's curve, Garland trianle, Rauchfuss-Grocco triangle)
- Auscultation – breath sounds and bronchophony are weakened or absrent
- X-ray – increased density area

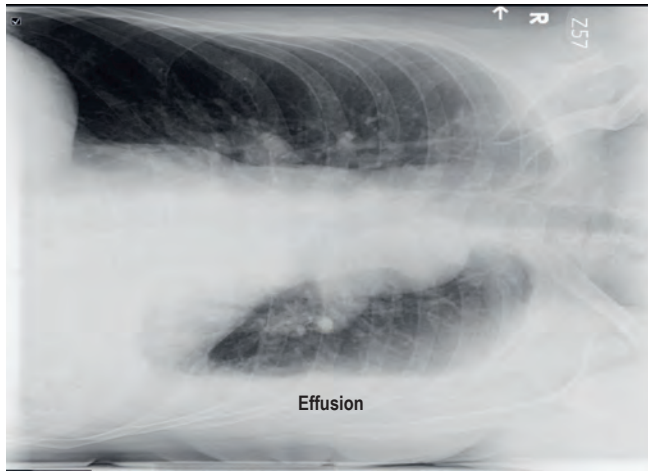




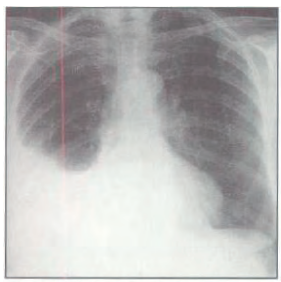
Chest radiograph showing left-sided pleural effusion

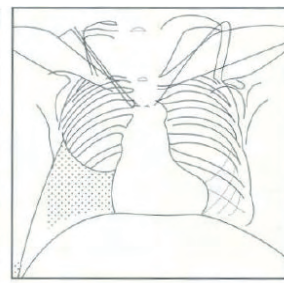


Large, malignant, right-sided pleural effusion



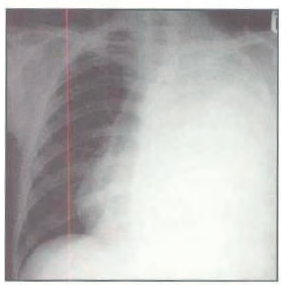
Left lateral decubitus film showing freely layering pleural effusion

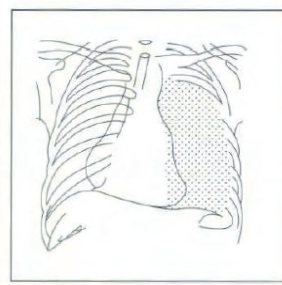




Mediastinum usually central
Expansion ↓
Percussion ↓
Breath sounds ↓
Sometimes bronchial breathing or a pleural rub at upper level

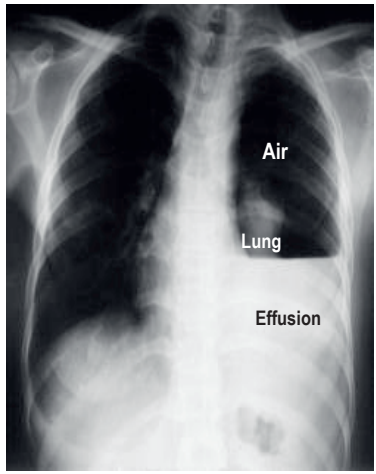
Fig. 5.50 Small effusion.



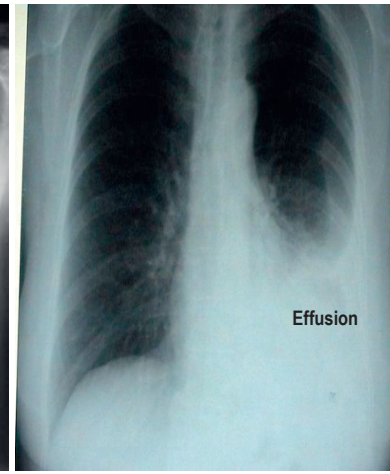


Mediastinum displaced
Expansion ↓
Percussion ↓
Breath sounds ↓

Fig. 5.51 Large effusion with mediastinal displacement.

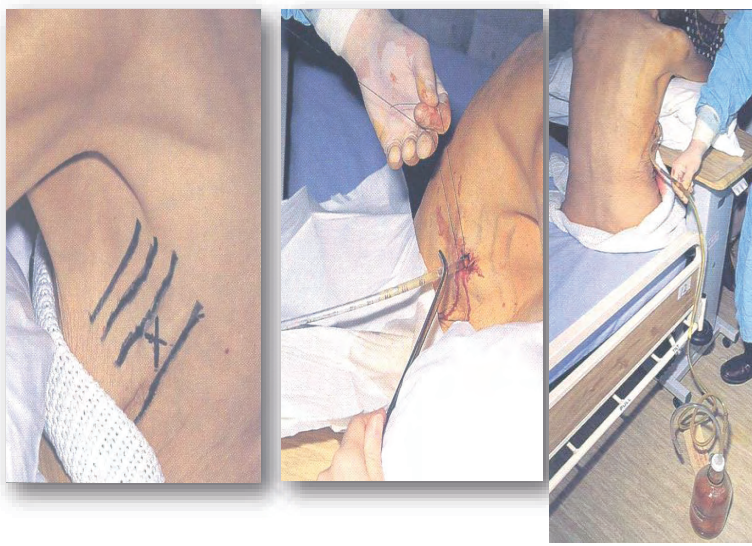


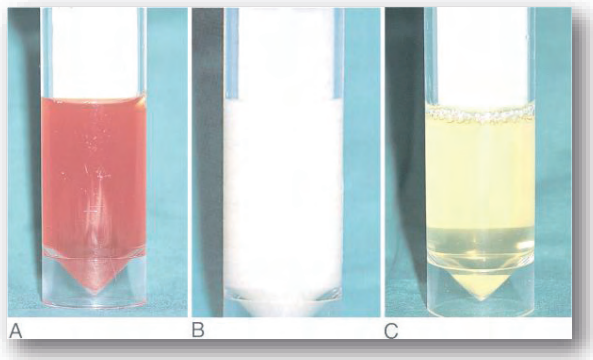
Pneumohemothorax left



Exudate in the left pleural cavity

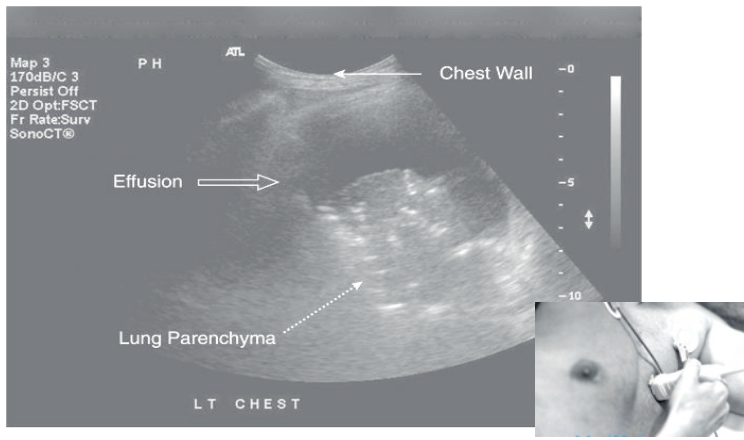
Diagnostic thoracocentesis





Pleural effusion. A, Blood-stained pleural aspirate. This patient had pleural metastases from carcinoma of the breast. B, Chylous pleural effusion. This patient had bronchial carcinoma that had invaded and obstructed the thoracic duct. C, Pleural transudate. This pale effusion is typically found in patients with heart failure or other causes of generalized edema.

(From Forbes CD, Jackson WF: Color Atlas and Text of Clinical Medicine, 3rd ed. London, Mosby, 2003.)



Ultrasound image of the left hemithorax. Bilateral pleural effusions from pneumonia are apparent in the patient whose computed tomography scan is shown in . The chest wall is indicated by the thin arrow, the effusion by the thick arrow. The underlying consolidated lung is evident by the echolucent area outlined by the dotted arrow.

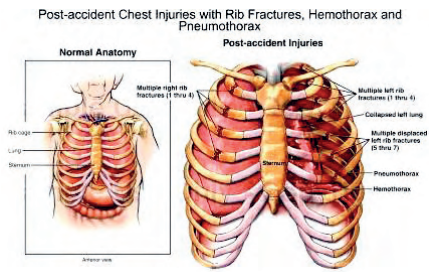
(Courtesy of David Lee, MD, Department of Radiology, Caritas-St. Elizabeth's Medical Center, Boston.)

AIR ACCUMULATION IN THE PLEURAL CAVITY

PNEVMOTHORAX

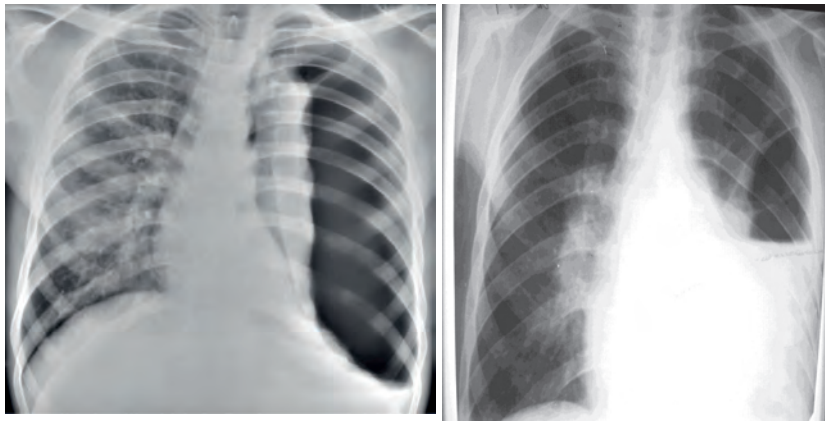
- **Sharp pain at onset, dyspnea**
- Affected side enlarged, cannot take part in respiratory act
- **Tactile fremitus** weakened, undeterminable
- **Percussion** – tympanic sound
- **Auscultation** – breath sounds and bronchophony are weakened or absent
- **X-ray** – darker lung field without vascular markings, shadow of collapsed lung toward the root

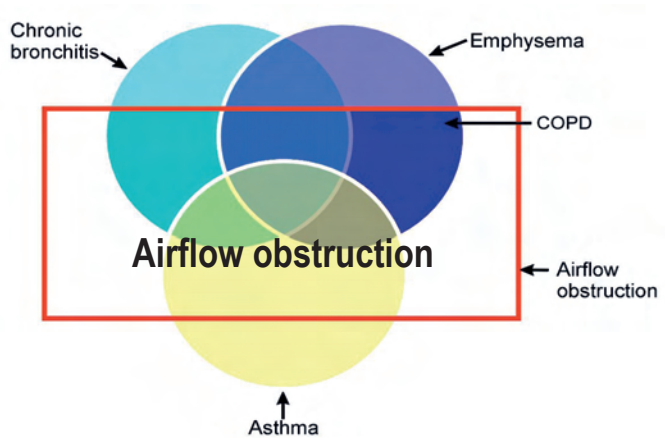
PNEUMOTHORAX



Pneumothorax is defined as an accumulation of gas in the pleural space. It may be caused by (1) perforation of the visceral pleura and entry of gas from the lung; (2) penetration of the chest wall, diaphragm, mediastinum, or esophagus; or (3) gas generated by microorganisms in an empyema. When gas originates in the lung, rupture may occur in the absence of known disease (simple pneumothorax) or as a result of parenchymal disease (secondary pneumothorax)

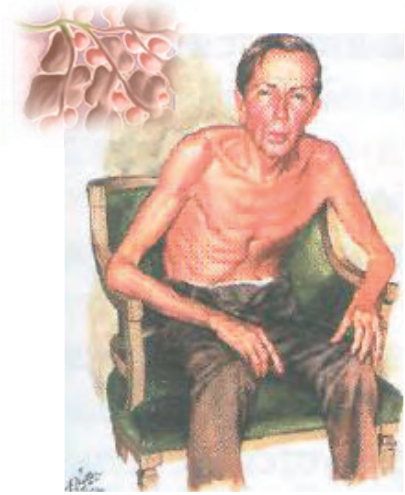
Air accumulation in the pleural cavity
PNEVMOTHORAX





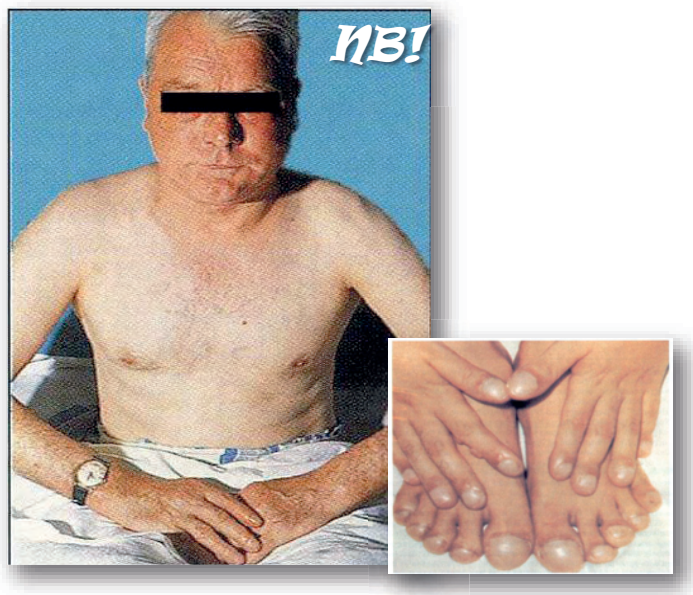
Venn diagram of chronic obstructive pulmonary disease (COPD). Chronic obstructive lung disease is a disorder in which subsets of patients may have dominant features of chronic bronchitis, emphysema, or asthma. The result is irreversible airflow obstruction

Patient Phenotypes



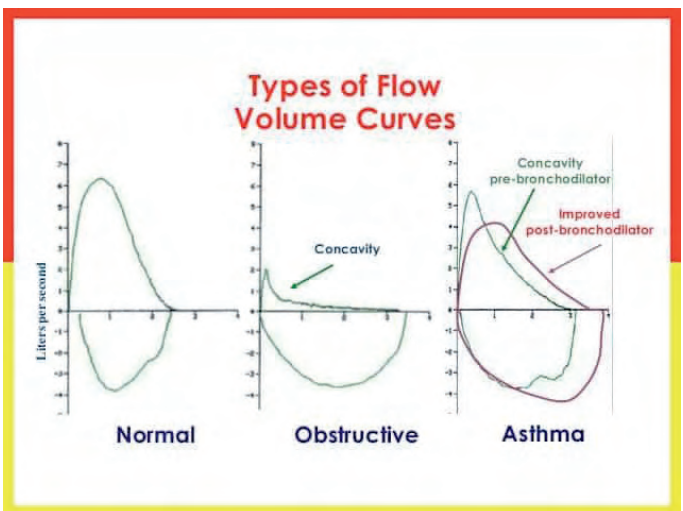
Pink “puffers”

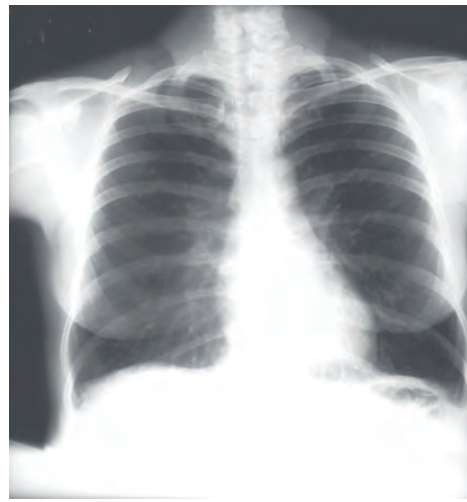
Blue “edematous”



SPIROMETRY

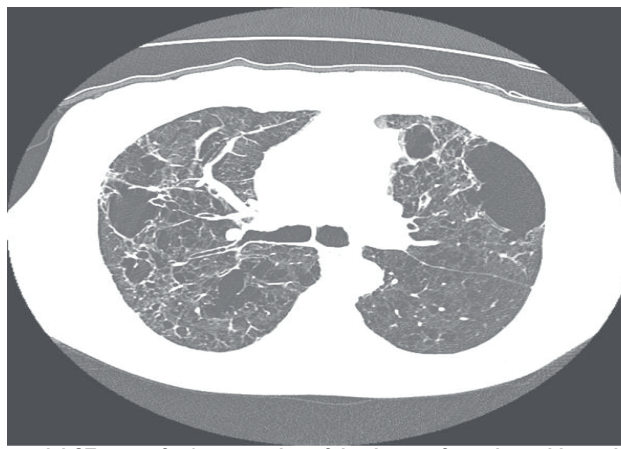
Spirometry, the measurement of the FEV_1 and FVC, is the "gold standard" for diagnosis of COPD and is easy to perform in the office setting



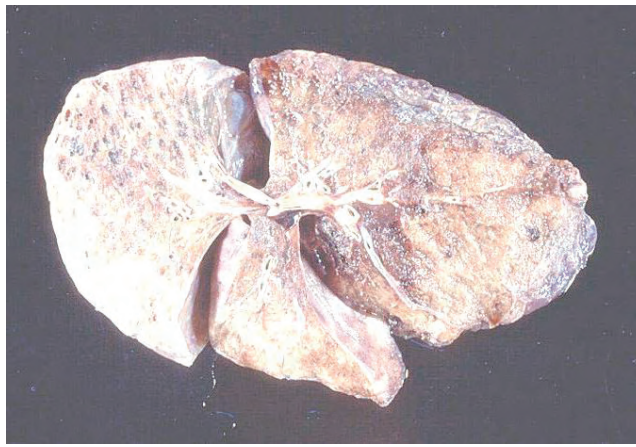


Chronic obstructive pulmonary disease (COPD).
A lung with emphysema shows increased anteroposterior (AP) diameter, increased retrosternal airspace, and flattened diaphragms on posteroanterior chest radiography

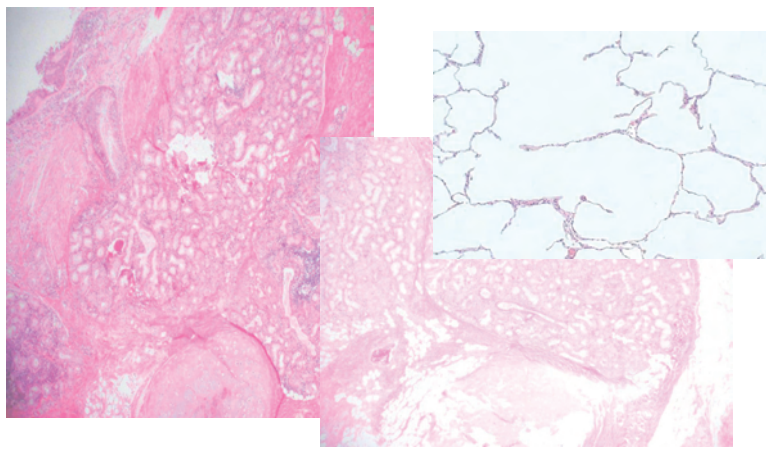
Computed tomographic (CT) scans are of considerable value in assessing the presence, distribution, and extent of emphysema. There are no standard grading systems. Emphysematous spaces are seen as "holes" in the lung



High-resolution axial CT scan of a 1-mm section of the thorax of a patient with emphysema at the level of the tracheal carina. The right lung is on the left. Multiple large bullae—black holes—are evident. Many smaller areas of similar tissue destruction are also present in both lungs. The right upper lobe bronchus is seen entering the lung; its walls are thickened, suggesting chronic inflammation

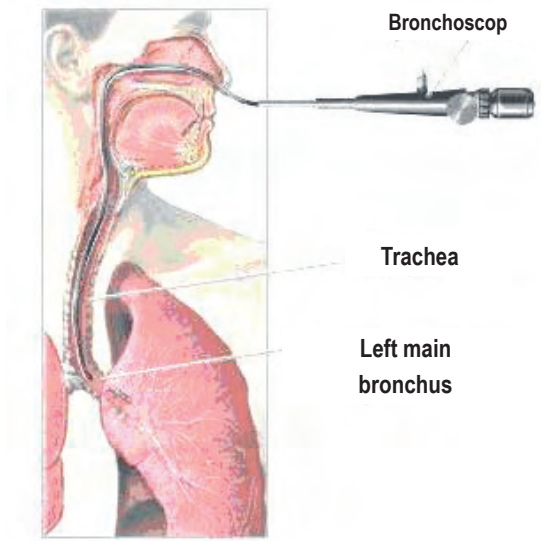


**Chronic obstructive pulmonary disease (COPD).
Gross pathology of advanced emphysema.
Large bullae are present on the surface of the lung**



**Chronic obstructive pulmonary disease (COPD).
Histopathology of chronic bronchitis showing hyperplasia of mucous glands and infiltration of the airway wall with inflammatory cells (high-powered view).
At high magnification, in emphysema, loss of alveolar walls and dilatation of airspaces occurs**

BRONCHIECTASIS SYNDROME



Bronchoscopy

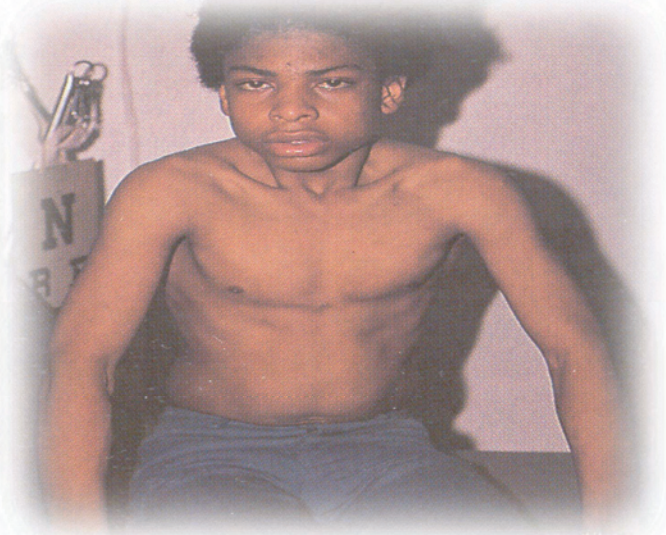
BRONCHIAL OBSTRUCTION SYNDROME

- Recurrent episodes of wheezing,
- breathlessness,
- and coughing,
- particularly at night or
- in the early morning.

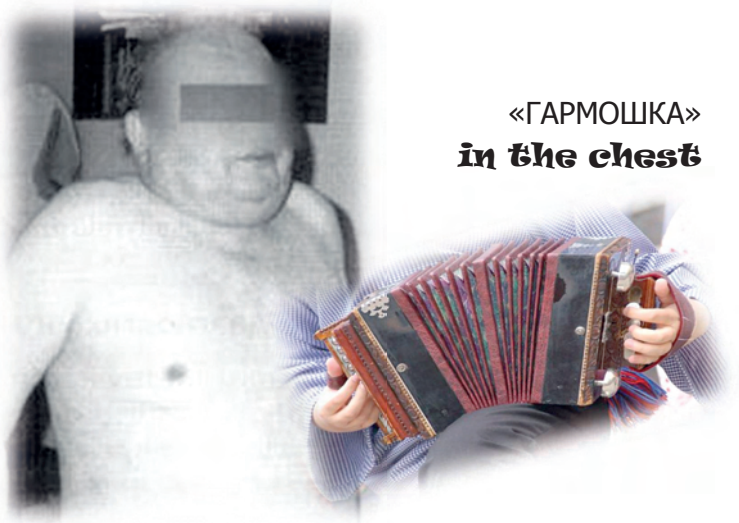
❑ These episodes are associated with diffuse narrowing of the airways (bronchospasm) that is reversible

WHO definition

ASTHMA ATTACK



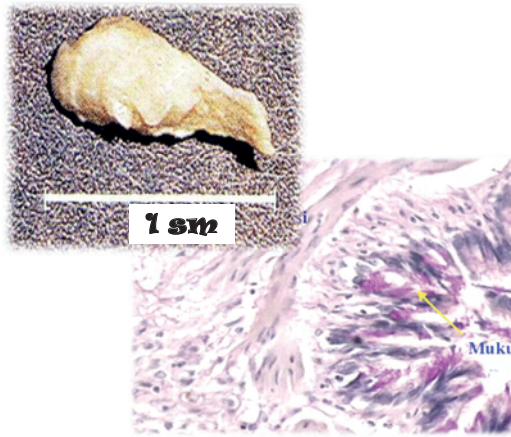
Forced tripod position



«ГАРМОШКА»
in the chest

Prolonged exhale. Barrel's shape chest

BRONCHIAL MUCOUS CORK



An adult with asthma using a spirometer to measure how forcefully she can exhale

A person with asthma receives an inhalation treatment using a hand-held nebulizer

A pulse oximeter measures the amount of oxygen in bloodstream

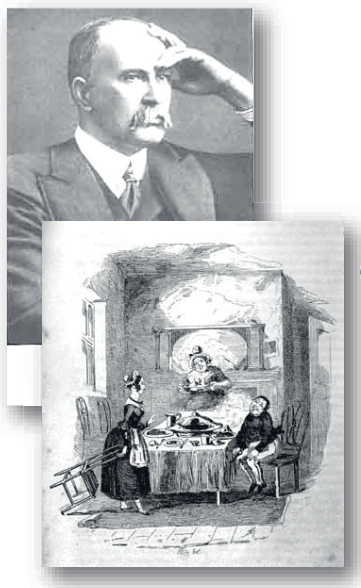
EPONYMOUS SYNDROMES

- **Pickwick syndrome**

  (*Pickwick - obesity-hypoventilation syndrome*)

- **Pink “puffers”**
- **Blue “edematous”**

Daniel lambert

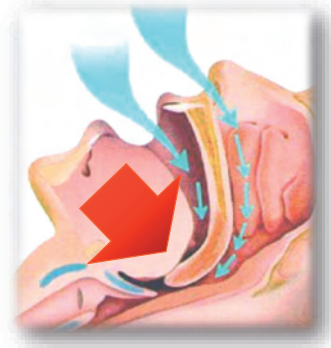


- It is believed that in 1905, William Osler was the first in the scientific literature to describe obesity syndrome - hypoventilation and likened it to the state of one of the minor characters of the "Death Note“

- It was about the constantly falling asleep young man Joe (Joseph) - this is "the beloved page of Mr.Wardl, better known to the readers of this unvarnished tale under the name of a fat guy." Dickens, in turn, compares Joe to Lambert

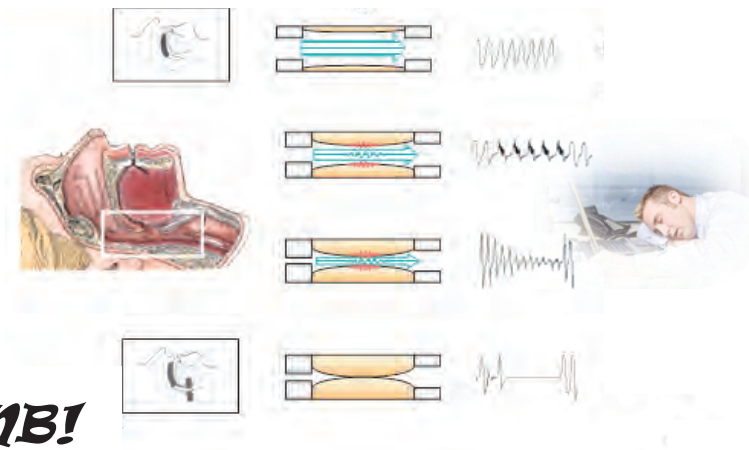
SPECIAL «PULMONARY» SYNDROMES

- **Sleep Apnea Syndrome**
  (episodes of stop of breathing in sleep)



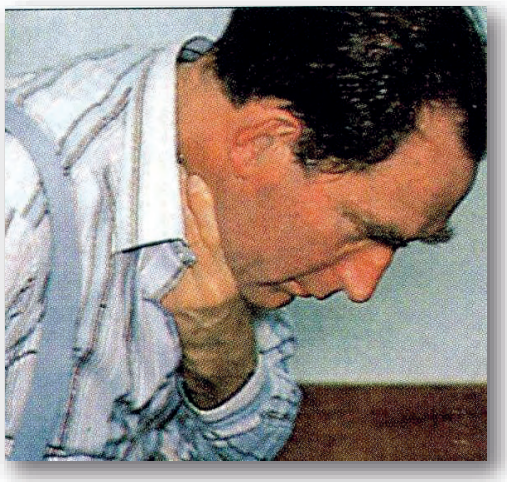
- **central type**
- **obstructive type**

SLEEP APNEA SYNDROME



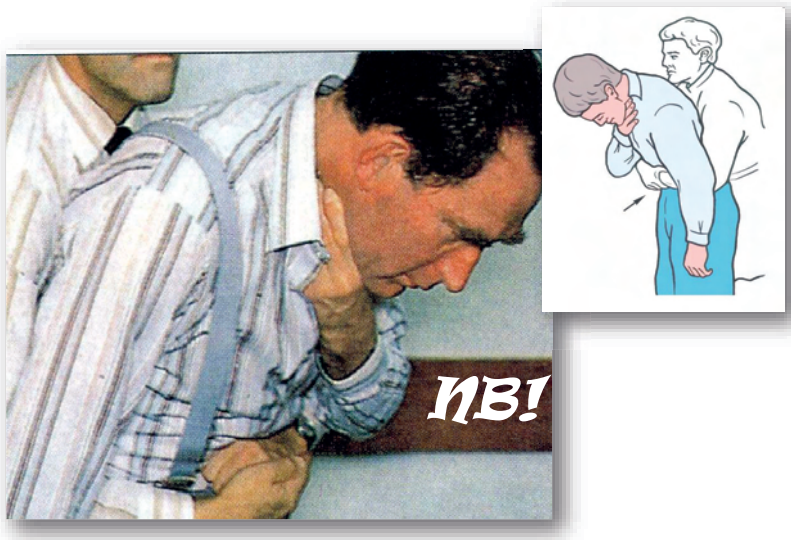
NB!

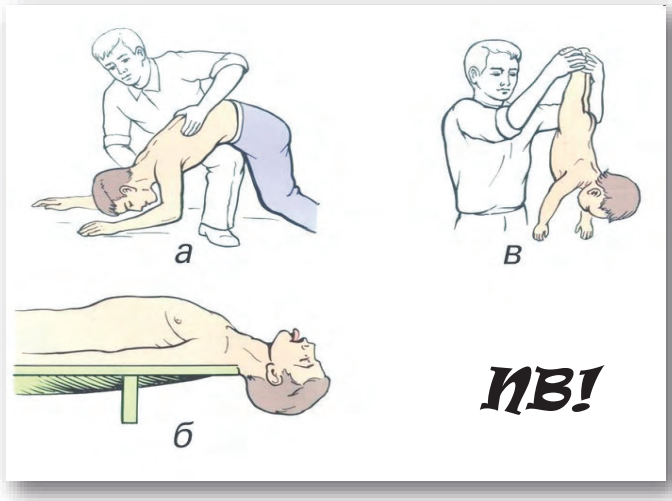
Upper airway obstruction



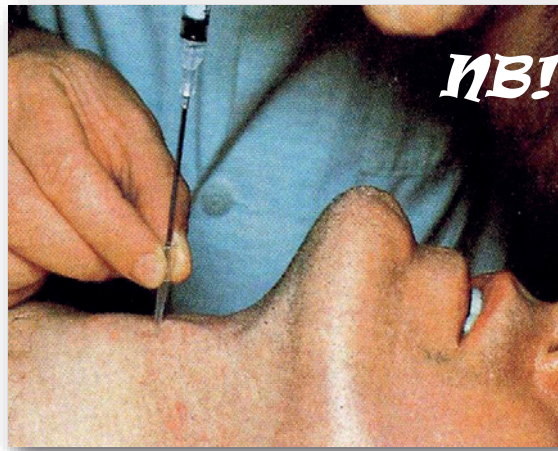
- foreign body
- edema of the larynx

Stridor




а
в
б
ПВ!


а
б
в
г



Respiratory failure syndrome

Respiratory failure is a pathological syndrome that accompanies a number of diseases, which is based on a violation of gas exchange in the lungs

The basis of the clinical picture is the signs of **hypoxemia** and **hypercapnia** (cyanosis, tachycardia, sleep and memory disorders), respiratory muscle fatigue syndrome and shortness of breath

RF is diagnosed on the basis of clinical data, confirmed by indicators of the gas composition of blood, respiratory function

Source: https://www.krasotaimedicinaina/diseases/zabolevanija_pulmonology/respiratory-insufficiency

Respiratory failure

acute, chronic

- Obstractive
- Restrictive
- Mixed

- Dyspnea
- Tachypnea, tachycardia
- Intensified work of the respiratory muscles as well as accessory m.
- Cor pulmonale

Degrees: 1,2,3

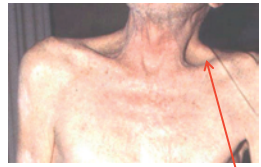
Stagers :

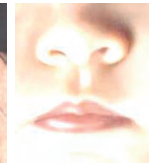
- latent pulmonary,
- pronounced pulmonary,
- cardiopulmonary insuffciency

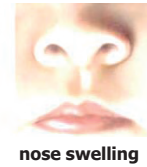
The partial pressure of oxygen and carbon dioxide in arterial blood

n = $PaO_2 \geq 60$ мм рт. ст.,

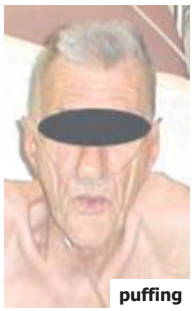
$PaCO_2 \leq 40$ мм рт. ст.



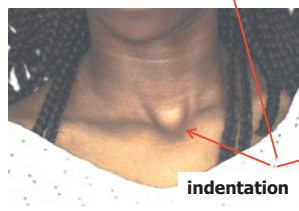




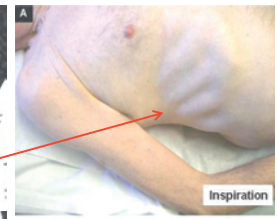
nose swelling

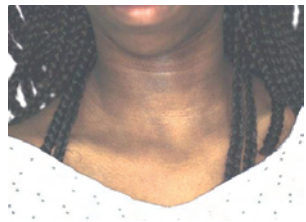


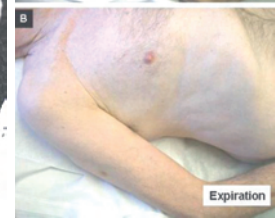
puffing

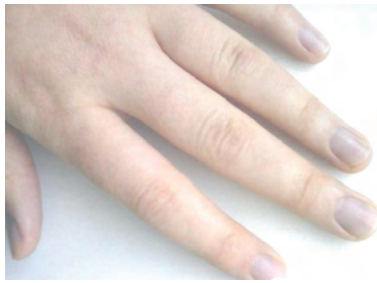


indentation

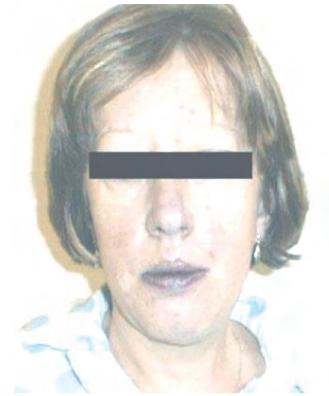








Cyanosis of nail beds



Cyanotic lips & nasolabial triangle in a woman with hypoxia

Respiratory failure syndrome

Classification of respiratory failure by pathogenesis and rate of development

Forms of respiratory failure	Signs
Hypoxic, (parenchymal, "pulmonary", or DN 1-st type).	pO2 <55 mm Hg inhalation of an oxygen-air mixture containing 60% O2 or more
Hypercapnic (ventilating, "pumping", or DN 2-nd type)	pCO2>45 mm Hg
Acute	Develops in minutes, hours, or days
Chronic	It develops over several weeks, months or years.

Respiratory failure syndrome

Classification of respiratory failure
by severity

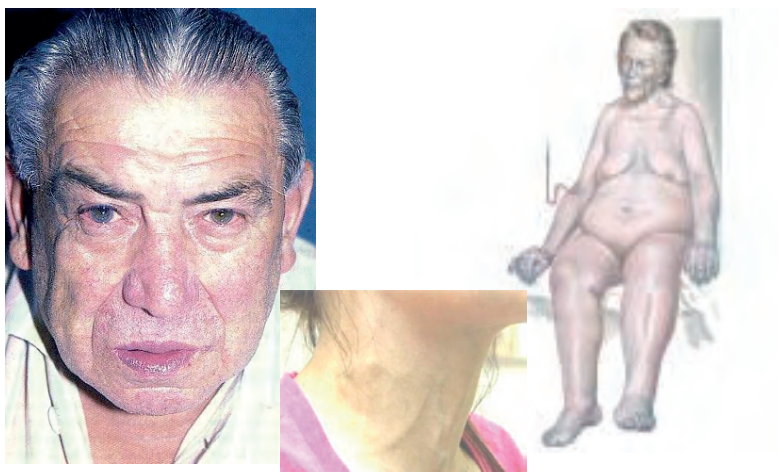
Main clinical sings: dyspnea on exertion, cyanosis, HR

Severity	pO2, mm Hg	Sat O2, %
0 (normal)	>80	>95
I	60-79	90-94
II	40-59	75-89
III	<40	<75

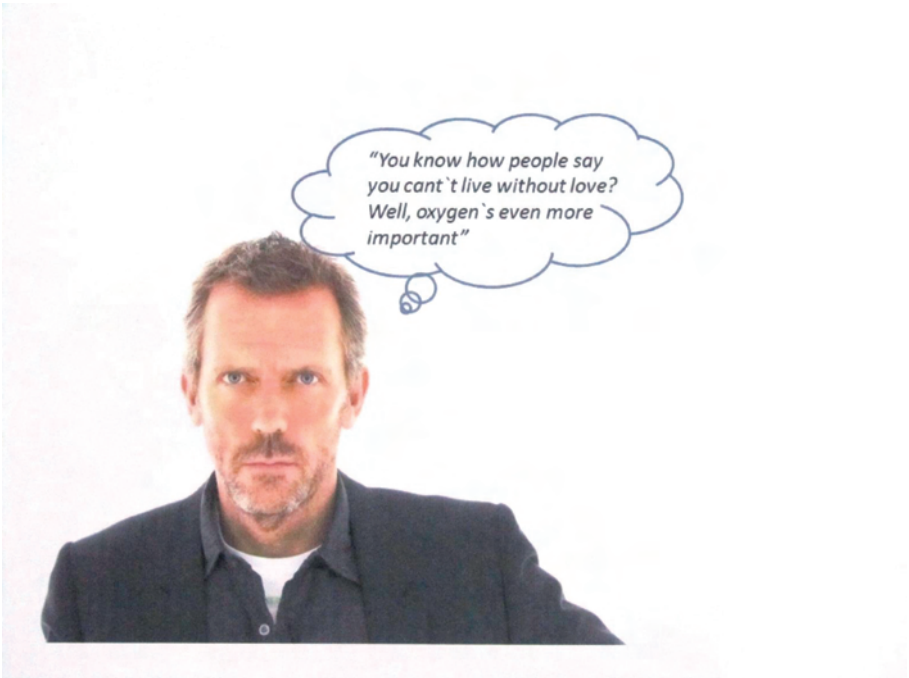
Degrees: 1,2,3

I degree - the appearance of shortness of breath with increased load,
II - the appearance of shortness of breath during normal exercise,
III - the appearance of shortness of breath at rest.

The syndrome of pulmonary hypertension



Cor pulmonale syndrome



REFERENCES

Kovalyova O.N., Ashcheulova T.V. Propedeutics to Internal Medicine. Part 2. – Vinnytsya: NOVA KNYHA, 2017. – 264 p.

Bickley, Lynn S.; Szilagyi, Peter G. Bates' Guide to Physical Examination and History Taking, 10th Edition. – 934 p. Copyright ©2009 Lippincott Williams & Wilkins

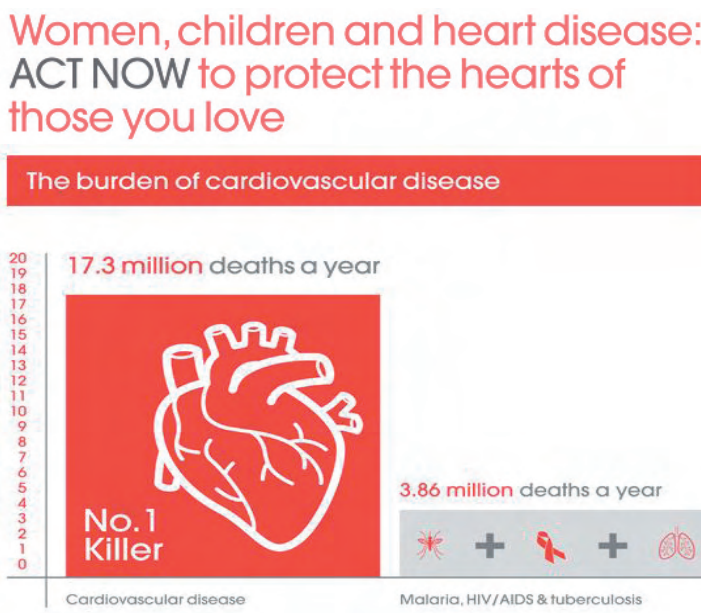
The Point online resources, http://thepoint.lww.com

LECTURE # 11

ARTERIAL HYPERTENSION SYNDROME

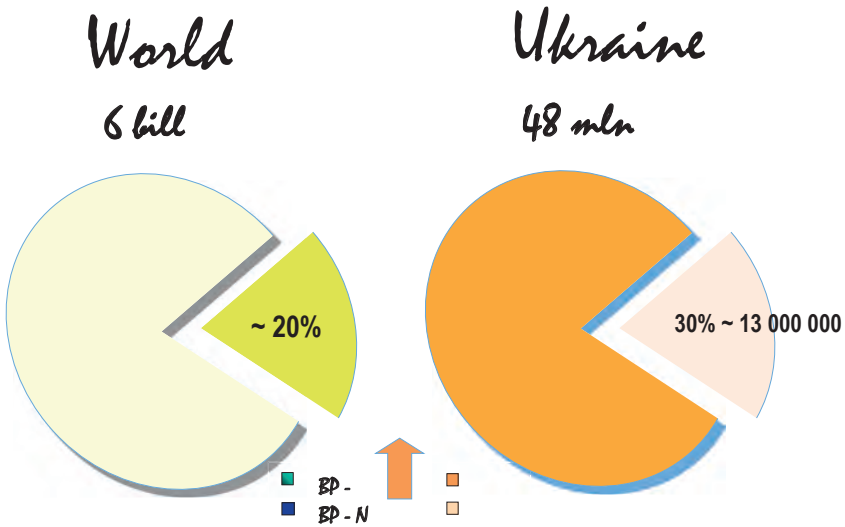
THE PLAN

- Definition
- Prevalence
- Killer # 1
- Silent killer
- Treatable risk factor
- Franklin Roosevelt Case History…
- Global risk Factors
- Classification of HBP stages according to BP levels
- Risk Factors
- History of HBP
- Cardiovascular CONTINUUM
- Pathobiology
- I. Page MOSAIC THEORY
- Small artery disease
- Endothelium inflammation
- Causes of secondary HBP
- The role of stress
- Specific Arterial Pulse
- Hemodynamic types of HBP
- HBP: SYNDROMES
- Rules for measuring blood pressure
- TARGET ORGAN DAMAGE
- EH classification based on TARGET ORGAN DAMAGE
- RISK TIME of CV EVENTS
- References



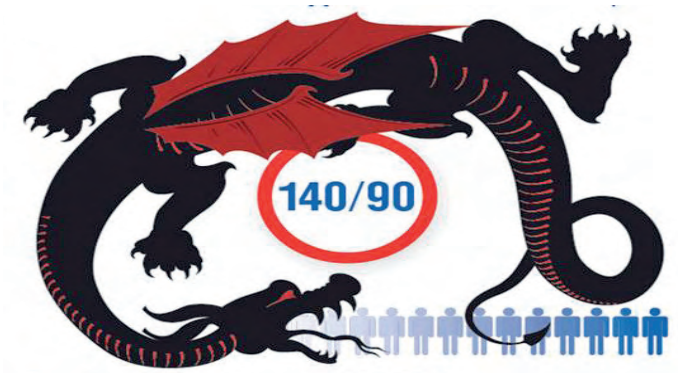
ARTERIAL HYPERTENSION

- **On the basis of results of randomized clinical drug trials, *hypertension* currently is defined as a usual blood pressure of 140/90 mm Hg or higher the value above which the benefits of treatment appear**



Edward J. Rocella, PhD, MPH. National Heart, Lung and Blood Institute. Bethesda, Maryland. Communication at ASH. New York. May 1999

ARTERIAL HYPERTENSION



Killer #1

Clinical Manifestations

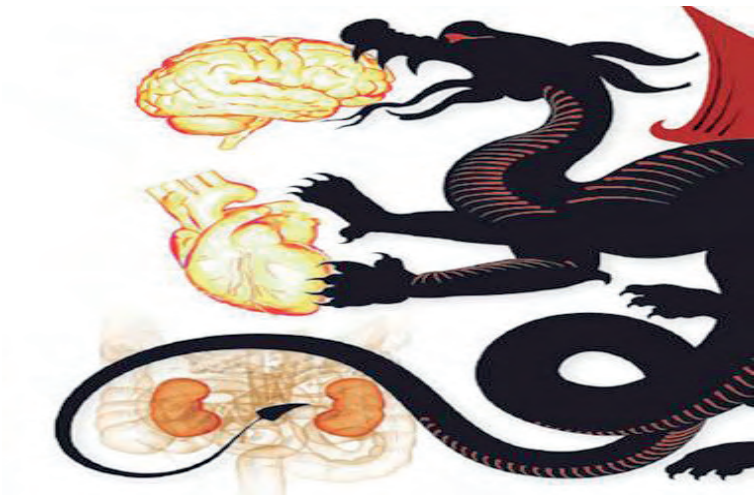
Hypertension has been termed the

silent killer,

an asymptomatic chronic disorder that silently damages the blood vessels, heart, brain, and kidneys if it is undetected and untreated

• Although headaches are common in patients with mild to moderate hypertension, episodes of headaches do not correlate with fluctuations in ambulatory blood pressure. Rather, they correlate with a person's awareness of his or her diagnosis

ARTERIAL HYPERTENSION



ARTERIAL HYPERTENSION

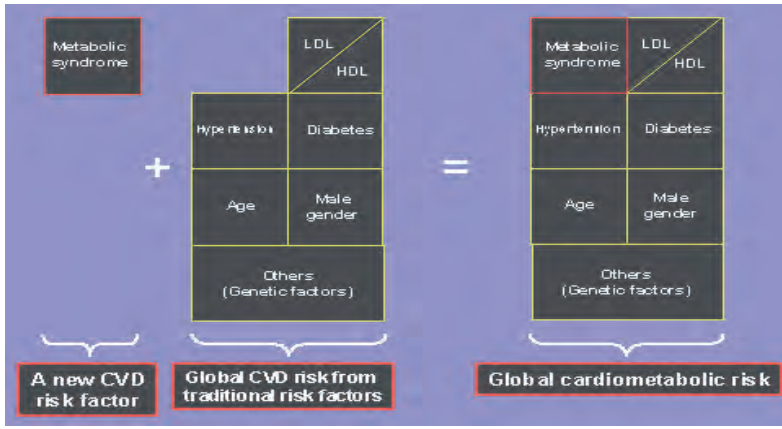
- **Affecting one quarter of the adult population (60 million in the United States and 1 billion people worldwide), arterial hypertension is the leading cause of death in the world and the most common cause for an outpatient visit to a physician; it is the most easily recognized treatable risk factor for**

  - stroke,
  - myocardial infarction,
  - heart failure,
  - peripheral vascular disease,
  - aortic dissection,
  - atrial fibrillation,
  - and end-stage kidney disease

Case History...

Case History...

- Age: 63
- Male
- Smoking
- BP:>180 и 100 mm Hg



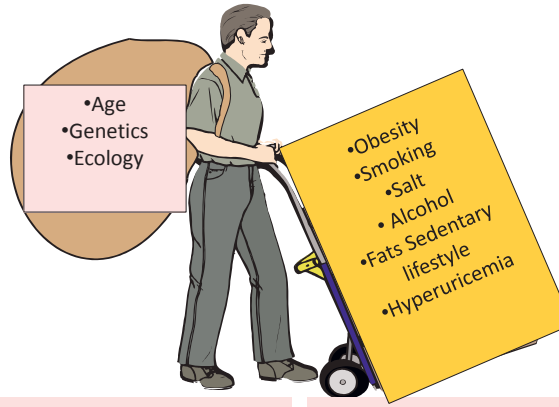
Classification of HBP stages according to BP levels, presence of CV risk factors, hypertension-mediated organ damage, or comorbidities

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130-139 DBP 85-89	Grade 1 SBP 140-159 DBP 90-99	Grade 2 SBP 160-179 DBP 100-109	Grade 3 SBP ≥180 or DBP ≥110
	No other risk factors				
	1 or 2 risk factors				
	≥3 risk factors				
	HMOD, CKD grade 3, or diabetes mellitus without organ damage				
	Established CVD, CKD grade ≥4, or diabetes mellitus with organ damage				

ESC/ESH 2018

CV risk is illustrated for a middle-aged male. The CV risk does not necessarily correspond to the actual risk at different ages. The use of the SCORE system is recommended for formal estimation of CV risk for treatment decisions. BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; DBP = diastolic blood pressure; HMOD = hypertension-mediated organ damage; SBP = systolic blood pressure; SCORE = Systematic COronary Risk Evaluation.

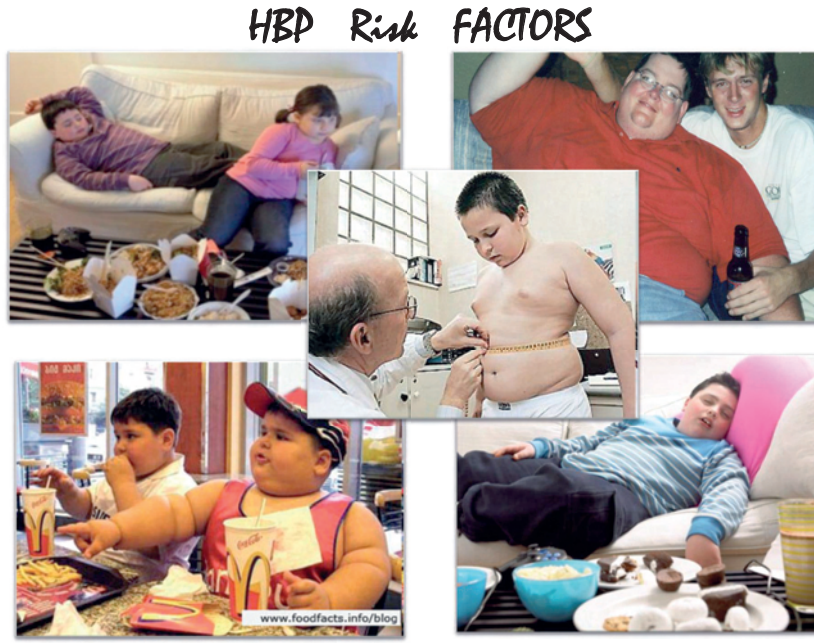
HBP Risk FACTORS



UNMODIFIED

MODIFIED

HBP Risk FACTORS



ARTERIAL HYPERTENSION

History

Family history, lifestyle (exercise, salt intake, smoking habit) and other risk factors should be recorded. A careful history will identify those patients with drug- or alcohol-induced hypertension and may elicit the symptoms of other causes of secondary hypertension, such as phaeochromocytoma (paroxysmal headache, palpitation and sweating) or complications such as coronary artery disease (e.g. angina, breathlessness).

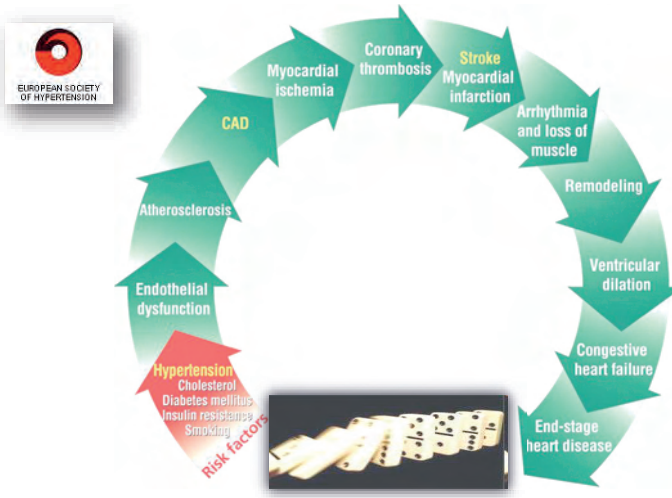
HBP Risk FACTORS

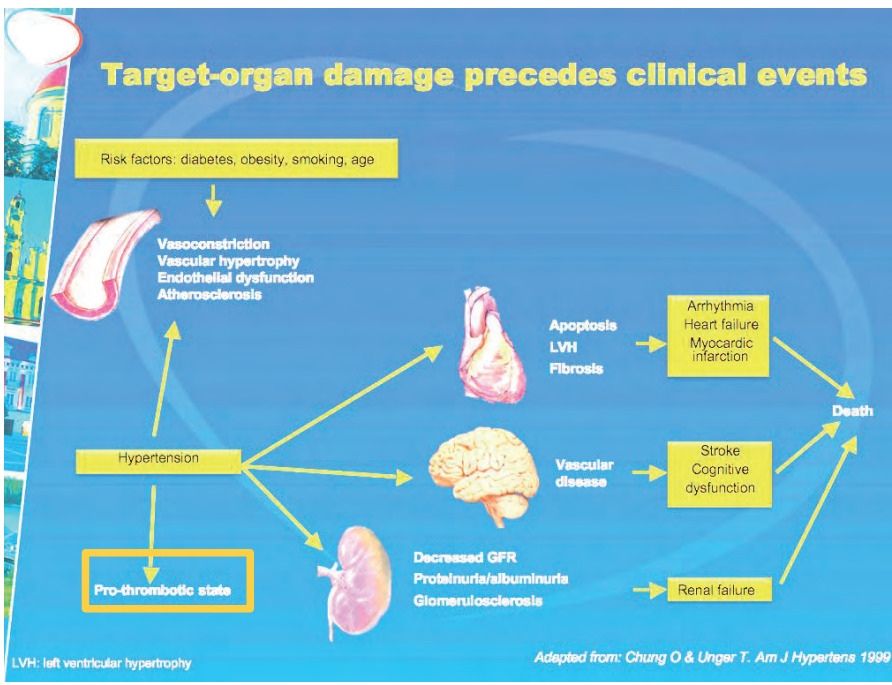
Risk factors

Hypertension is more common in some ethnic groups, particularly African Americans and Japanese, and approximately 40–60% is explained by genetic factors. Important environmental factors include a high salt intake, heavy consumption of alcohol, obesity, lack of exercise and impaired intrauterine growth. There is little evidence that 'stress' causes hypertension.

In about 5% of cases, hypertension can be shown to be a consequence of a specific disease or abnormality leading to sodium retention and/or peripheral vasoconstriction (secondary hypertension).

Cardiovascular CONTINUUM



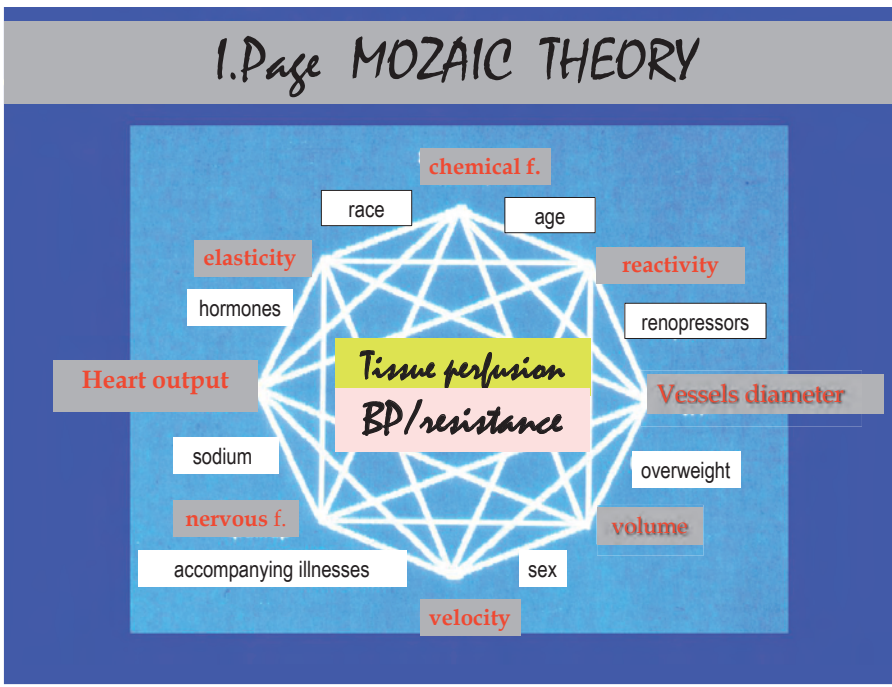


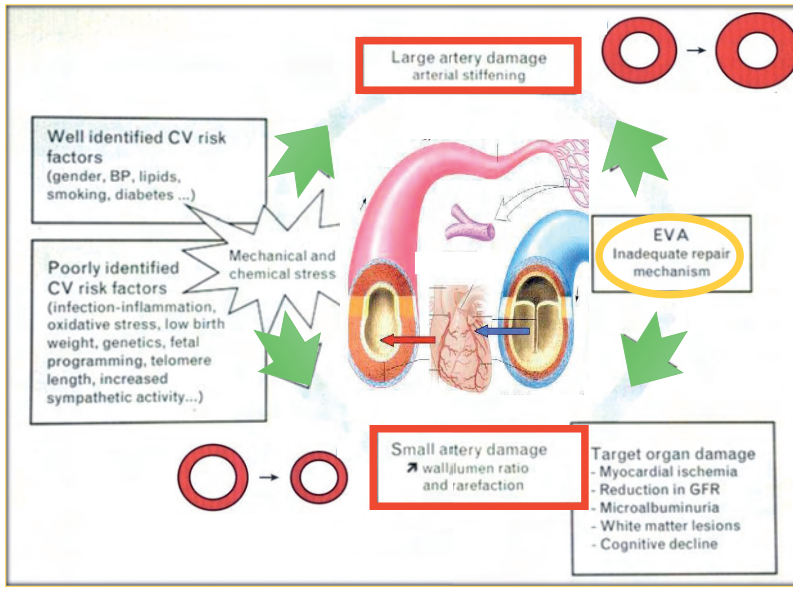
Pathobiology

- At the organ-system level, hypertension results from a gain in function of pathways that promote vasoconstriction and renal sodium retention or a loss in function of pathways that promote vasodilation and renal sodium excretion

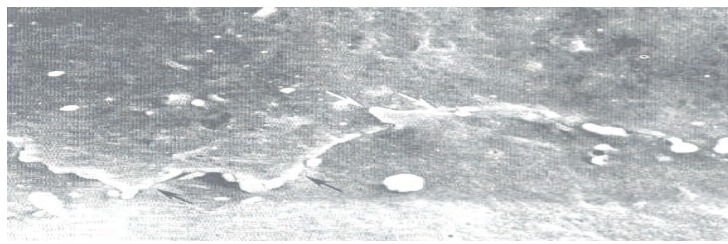
- Neural, hormonal, and vascular mechanisms are involved

- There is increasing evidence that neurohormonal activation contributes to the early pathogenesis by compromising vascular function (e.g., endothelium-dependent vasodilation) and structure (e.g., inward remodeling) that precede hypertension

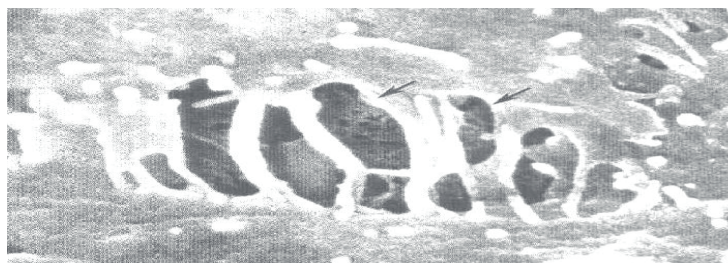




N



Endothelium inflammation

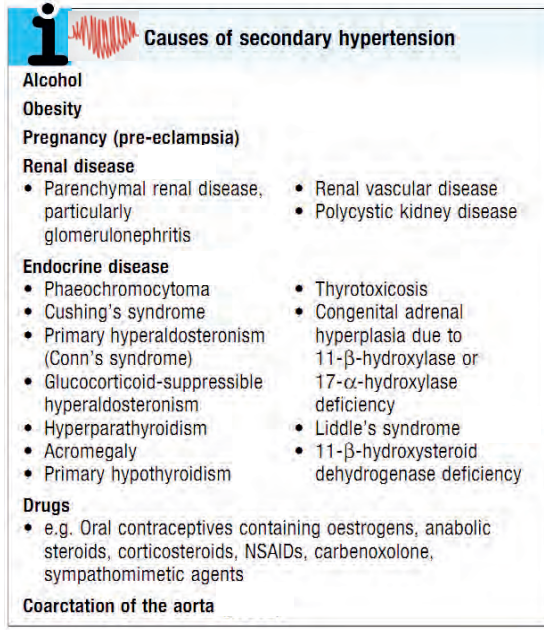


Pathobiology

- **In 90 to 95% of hypertensive patients, a single reversible cause of the elevated blood pressure cannot be identified, hence the term *primary hypertension***

- **However, in most patients with primary hypertension, readily identifiable behaviors—habitually excessive consumption of calories, salt, or alcohol—contribute to the elevated blood pressure**

- **In the remaining 5 to 10%, a more discrete mechanism can be identified, and the condition is termed *secondary or identifiable hypertension***



Causes of secondary hypertension

Alcohol

Obesity

Pregnancy (pre-eclampsia)

Renal disease

- Parenchymal renal disease, particularly glomerulonephritis
- Renal vascular disease
- Polycystic kidney disease

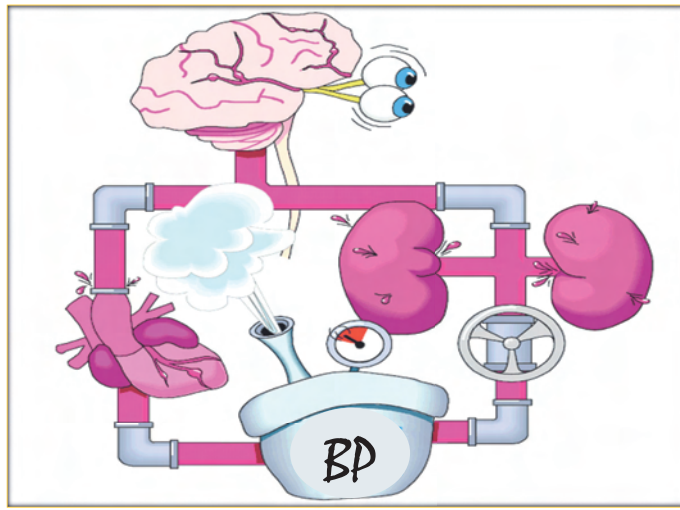
Endocrine disease

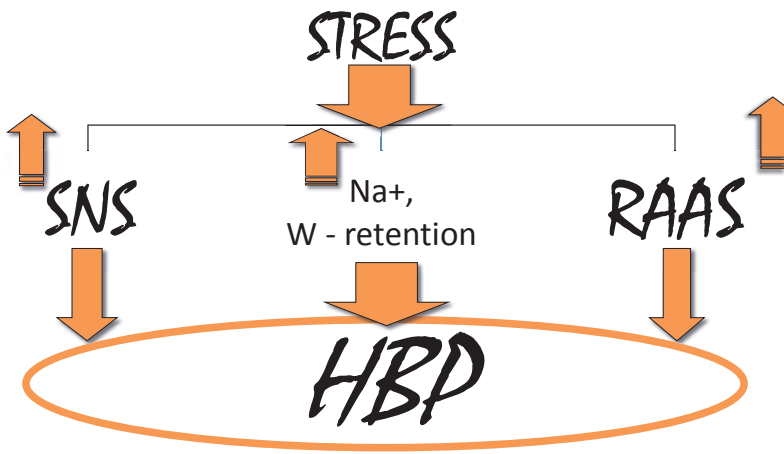
- Phaeochromocytoma
- Cushing's syndrome
- Primary hyperaldosteronism (Conn's syndrome)
- Glucocorticoid-suppressible hyperaldosteronism
- Hyperparathyroidism
- Acromegaly
- Primary hypothyroidism
- Thyrotoxicosis
- Congenital adrenal hyperplasia due to 11-β-hydroxylase or 17-α-hydroxylase deficiency
- Liddle's syndrome
- 11-β-hydroxysteroid dehydrogenase deficiency

Drugs

- e.g. Oral contraceptives containing oestrogens, anabolic steroids, corticosteroids, NSAIDs, carbenoxolone, sympathomimetic agents

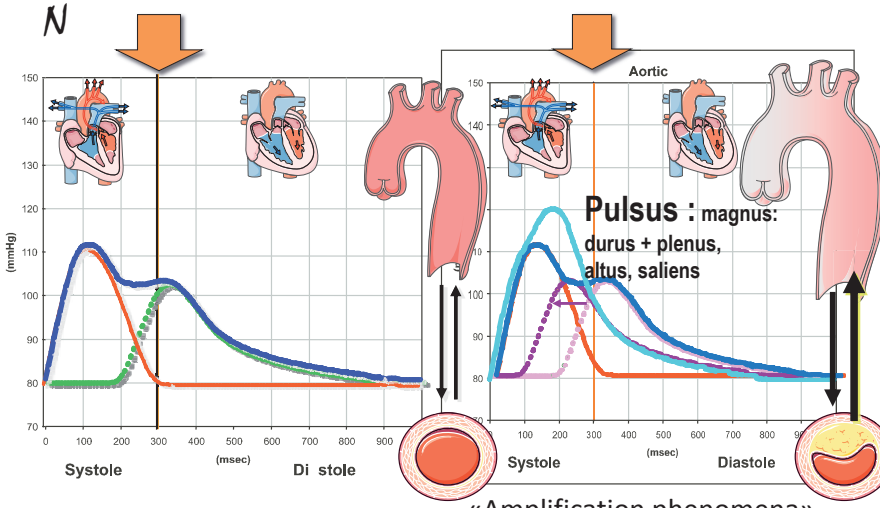
Coarctation of the aorta


BP


STRESS
SNS
Na+,
W - retention
RAAS
HBP

Arterial Pulse:

N



«Amplification phenomena»

AH

BP = M Heart V + V Resistence + B Viscosity (rheology)

SBP

DBP

Heart V x HR

NB!!!

EUROPEAN SOCIETY OF HYPERTENSION

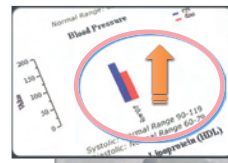
Definition of hypertension

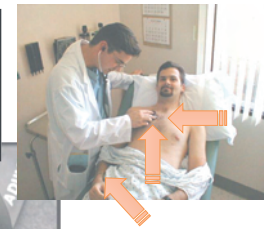
Category	Systolic BP (mmHg)	Diastolic BP (mmHg)
BP		
Optimal	< 120	< 80
Normal	< 130	85
High normal «pre-HBP»	130–139	85–89
Hypertension		
Grade 1 (mild)	140–159	90–99
Grade 2 (moderate)	160–179	100–109
Grade 3 (severe)	≥ 180	> 110
Isolated systolic hypertension		
Grade 1	140–159	< 90
Grade 2	≥ 160	< 90

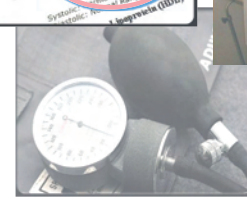
Haemodynamic types of HBP

	HYPERkinetic	EUkinetic	HYPOkinetic
SBP	↑	↑	↑
DBP	N	↑	↑
HB	↑	N	↓

HBP: SYNDROMS



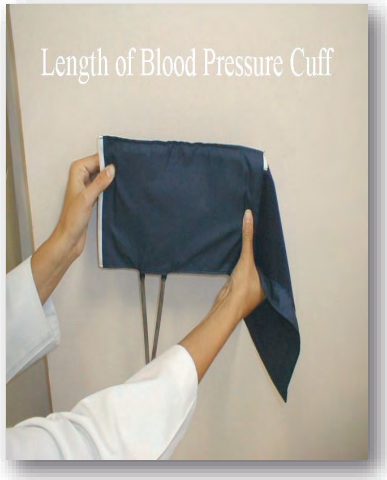




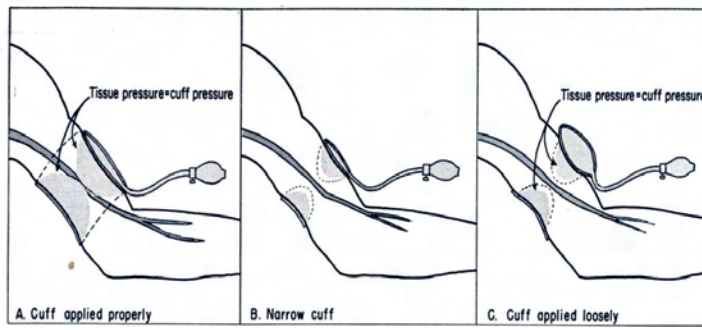
- HBP *S.*
- **CARDIAL** ***S.:***
- ***Chest pain s.***
- ***LVH-Heart s.***
- ***Arittmya s.***
- ***HF s.***
- **BRAIN** ***S.***
- **RENAL** ***S.***
- **PAV** ***S.***

Issues with Measurement: Tips for Accurate BP Measurement

- Patient in sitting position, at rest, back supported, with the arm at heart level
  - Otherwise ↑ DBP ~6 mm Hg
- Remove constricting clothing on the upper extremity (do not push up clothing)
- No caffeine or tobacco use at least 30 minutes prior to BP measurement
- Patients should have both feet planted on a flat surface
  - Crossing legs ↑ SBP ~2-8 mm Hg
- Use the correct size cuff. Ideal cuff bladder: 80% length and 40% width of arm circumference
  - Cuff too large = falsely low BP; cuff too small = falsely elevated BP
- Patient and clinician should not talk during the measurement (↑ BP)
- 1st visit: take 2 readings (average them), 5 minutes apart
  - Confirm elevated reading in contralateral arm; if one arm consistently higher, use that arm for subsequent measurements (~ 20% of individuals have BP differences >10 mm Hg)



TRANSMISSION OF CUFF PRESSURES TO THE TISSUES OF THE ARM



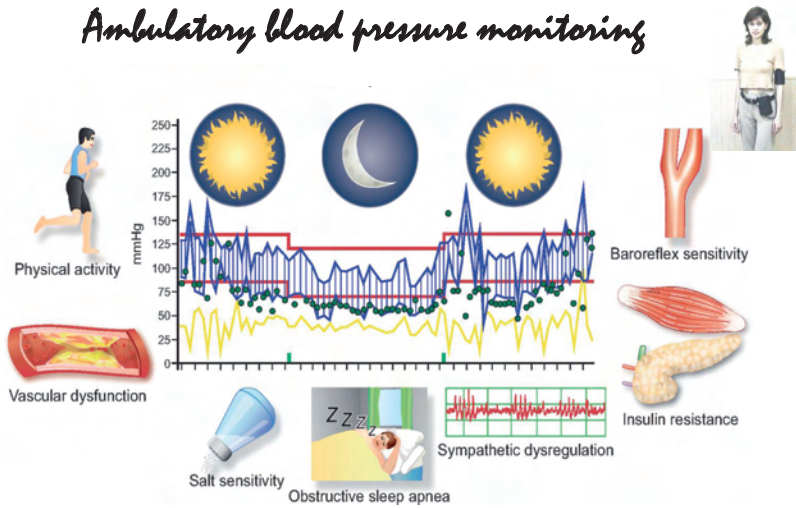
	SBPmmHg	DBPmmHg
Office BP	140	90
24-H	125 - 130	80
Day	130 - 135	85
Night	120	70
Home	130 - 135	85

- Suspected “white coat” hypertension (only at office)

- Suspected masked hypertension (only sometimes out of office) or

  suspected nocturnal hypertension

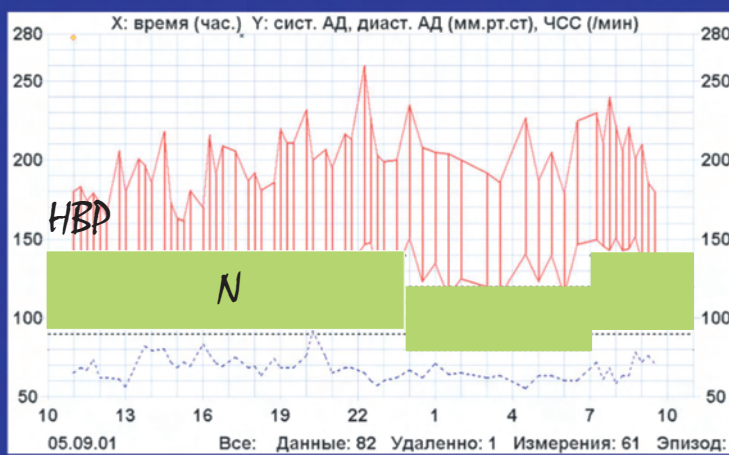
Ambulatory blood pressure monitoring



Asleep blood pressure: a target for cardiovascular event reduction?

Heart J. 2018;39(47):4172-4174. doi:10.1093/eurheartj/ehy557

Ambulatory blood pressure monitoring



Hypertension: investigation of all patients

- Urinalysis for blood, protein and glucose
- Blood urea, electrolytes and creatinine
  N.B. Hypokalaemic alkalosis may indicate primary hyperaldosteronism but is usually due to diuretic therapy
- Blood glucose
- Serum total and HDL cholesterol
- Thyroid function tests
- 12-lead ECG (left ventricular hypertrophy, coronary artery disease)

(HDL = high-density lipoprotein)

Hypertension: investigation of selected patients

- Chest X-ray: to detect cardiomegaly, heart failure, coarctation of the aorta
- Ambulatory BP recording: to assess borderline or 'white coat' hypertension
- Echocardiogram: to detect or quantify left ventricular hypertrophy
- Renal ultrasound: to detect possible renal disease
- Renal angiography: to detect or confirm presence of renal artery stenosis
- Urinary catecholamines: to detect possible phaeochromocytoma
- Urinary cortisol and dexamethasone suppression test: to detect possible Cushing's syndrome
- Plasma renin activity and aldosterone: to detect possible primary aldosteronism

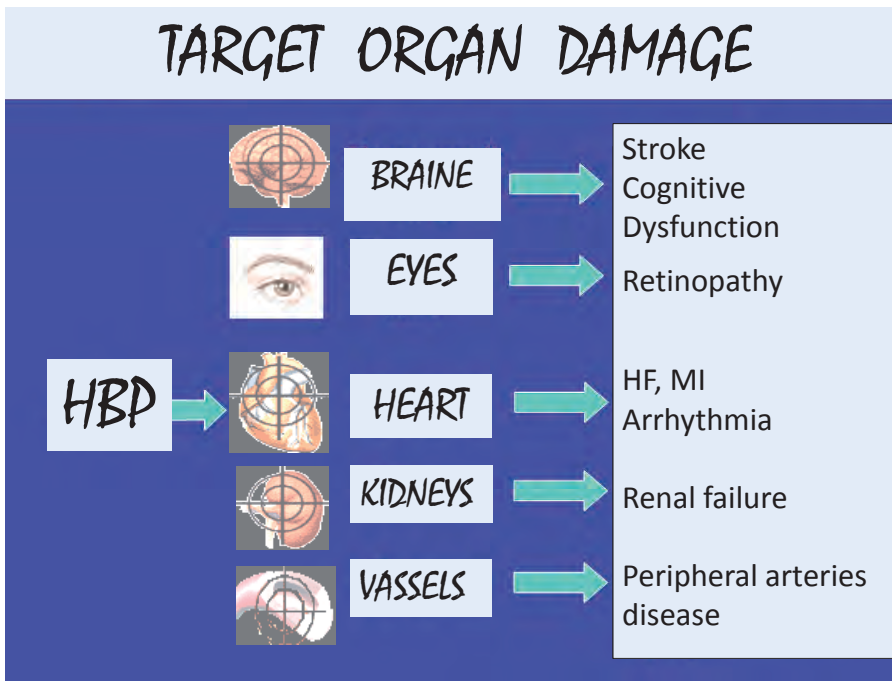
What is it ?
Answer the questions:

1. Primary AH is:
a) cause of hypertension is unknown
b) thyrotoxicosis
c) aorta sclerosis
d) kidney disease
e) head injury

2. «White coat" AH is:
a) BP only office is equal to or higher than 140 and 90
b) HELL is constantly equal to or higher than 140 and 90
c) BP only episodically equal to or higher than 140 and 90

3. Masked AH is:
a) BP only office is equal to or higher than 140 and 90
b) HELL is constantly equal to or higher than 140 and 90
c) BP only episodically equal to or higher than 140 and 90

4. Modifiable risk factors for cardiovascular events:
a) obesity, salt abuse
b) hypertension, smoking
c) physical passivity
d) obstructive sleep apnea
e) all of the above



Subclinical organ damage

Routine exams

1. ECG
2. Estimated GFR from serum creatinine and suitable formulae (MDRD, Cockroft-Gault)
3. Microalbuminuria (albumin/creatinine ratio on spot urine)

Recommended exams

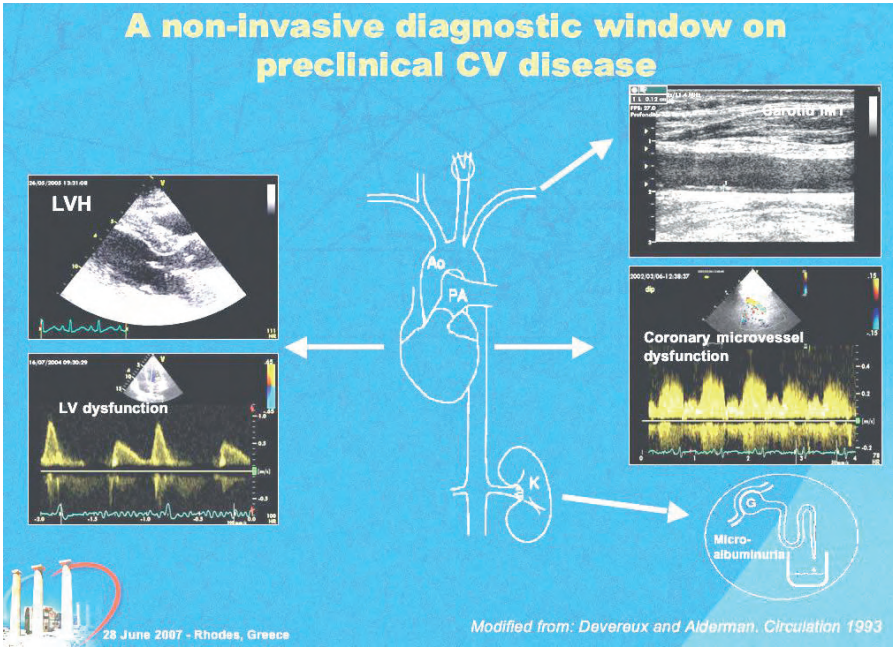
1. Echocardiogram
2. Carotid ultrasonograph

GFR: glomerular filtration rate

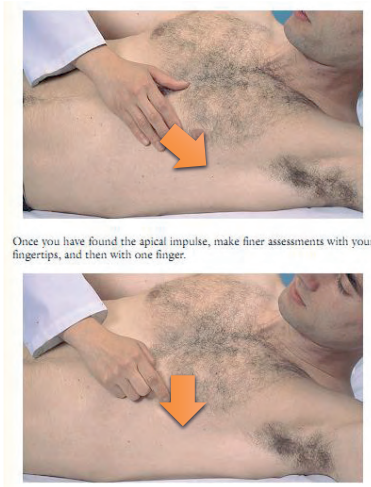
The concept of cardiovascular (CV) remodelling

- Cardiovascular (CV) remodelling is a process induced by common CV risk factors which concur to modify both the functional and structural characteristics of the heart and vessels
- CV remodelling includes a *preclinical stage*, which can be identified by the modern, non-invasive diagnostic tools, and a *clinical stage of disease*, in which organ damage becomes overt

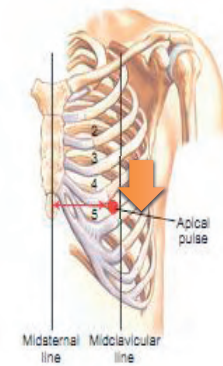
28 June 2007 - Rhodes, Greece



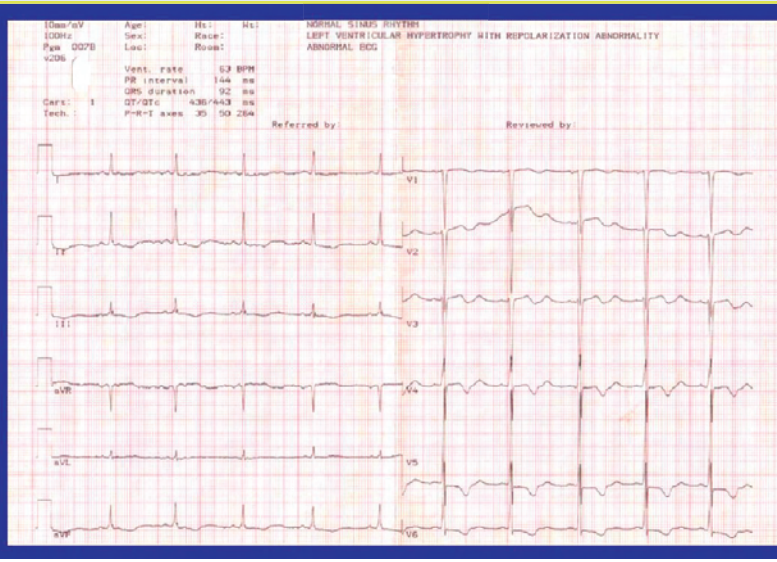
CARDIAC REMODELLING



Once you have found the apical impulse, make finer assessments with your fingertips, and then with one finger.

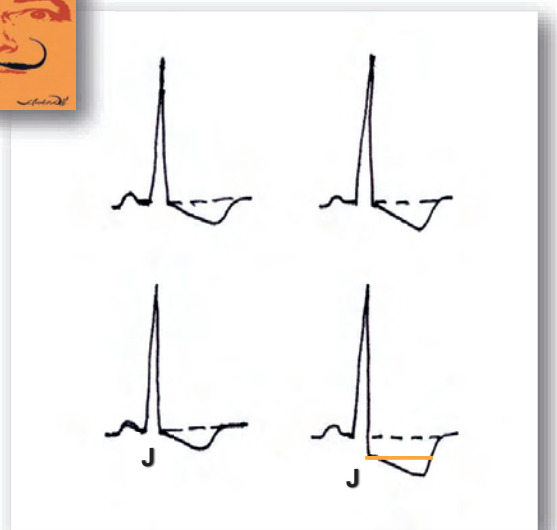


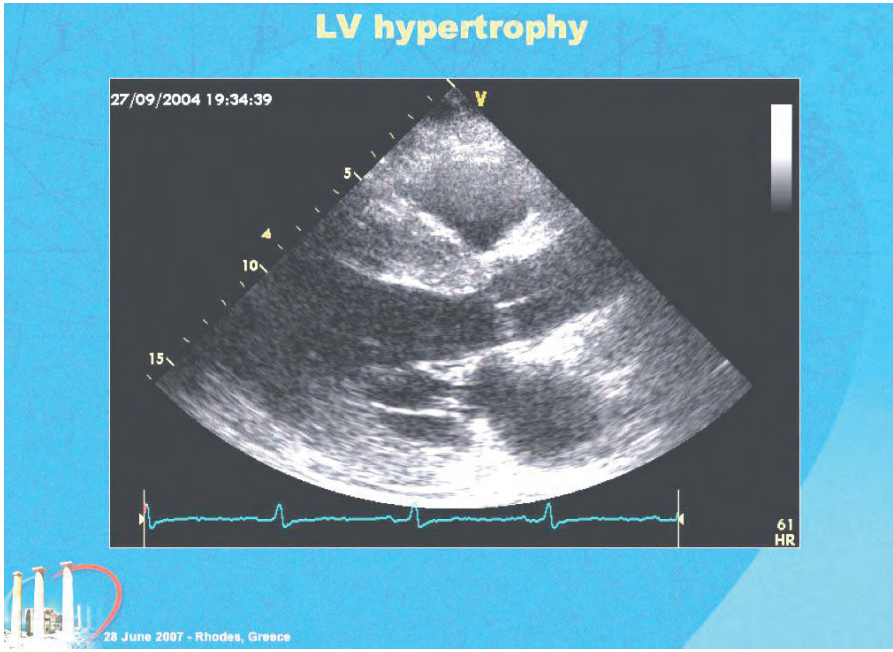
LVH

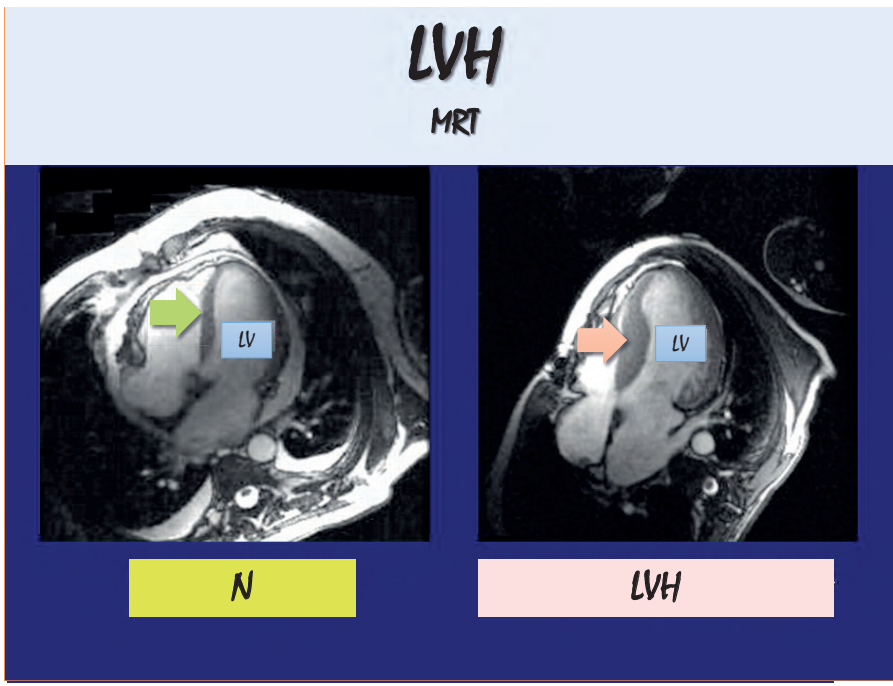


Normal physical reaction

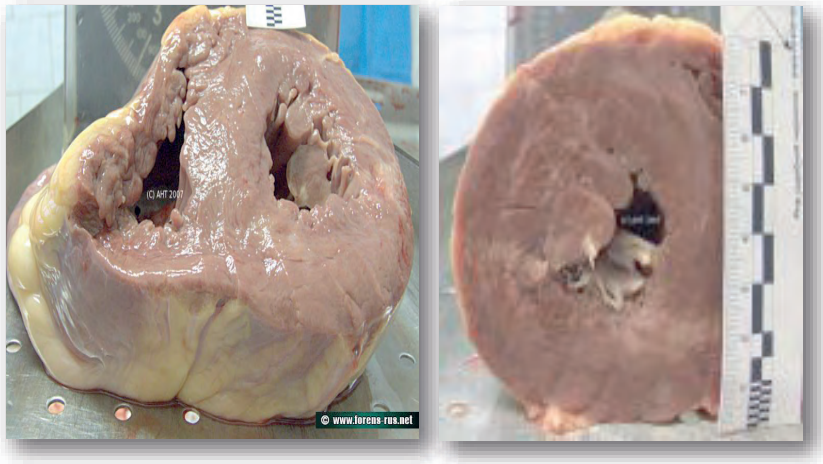
ischemia



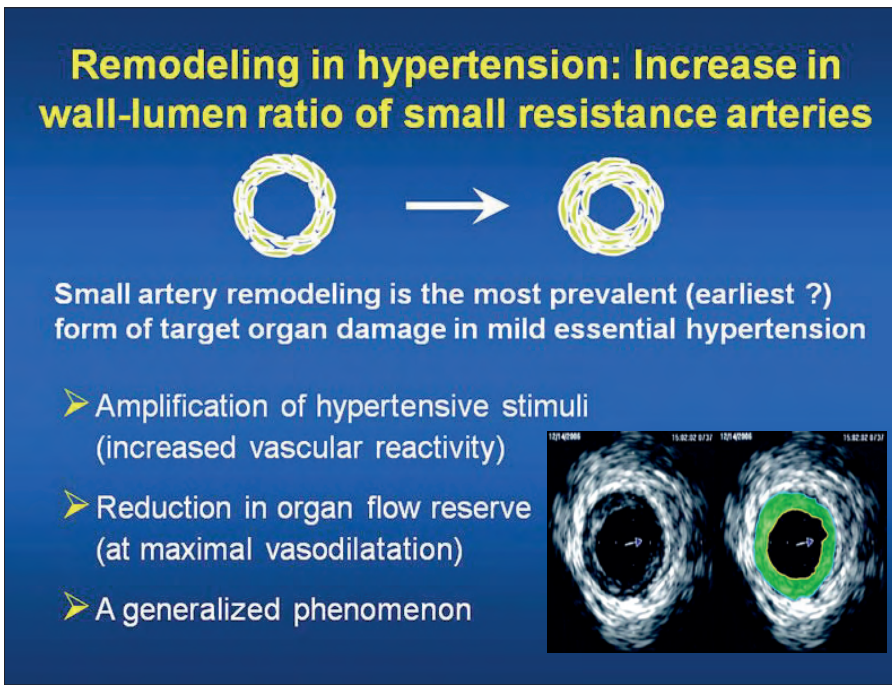

LV hypertrophy
27/09/2004 19:34:39
V
5
4
10
15
61
HR
28 June 2007 - Rhodes, Greece

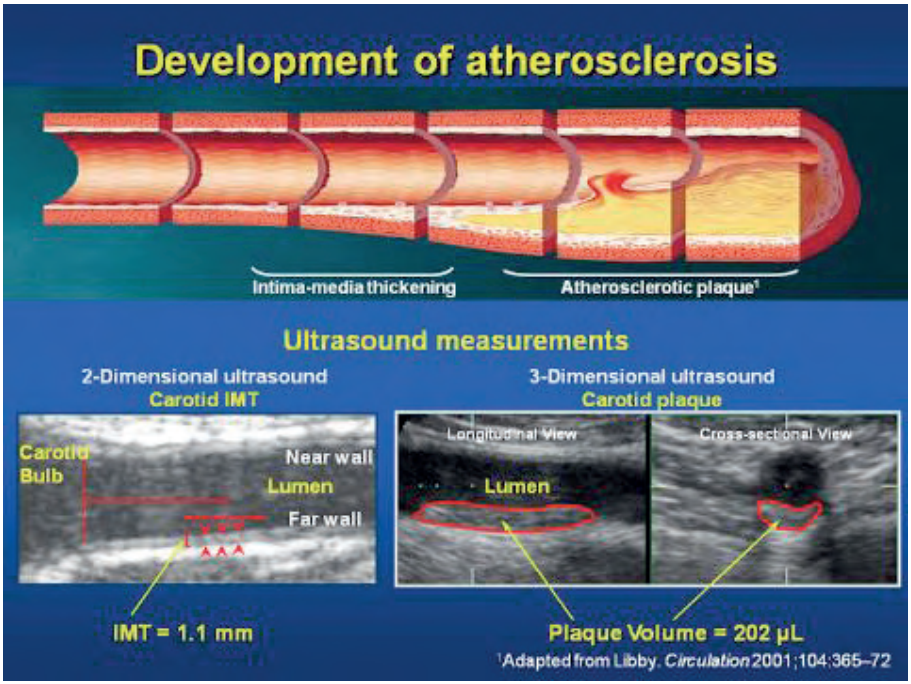

LVH
MRT
LV
LV
N
LVH

LVH

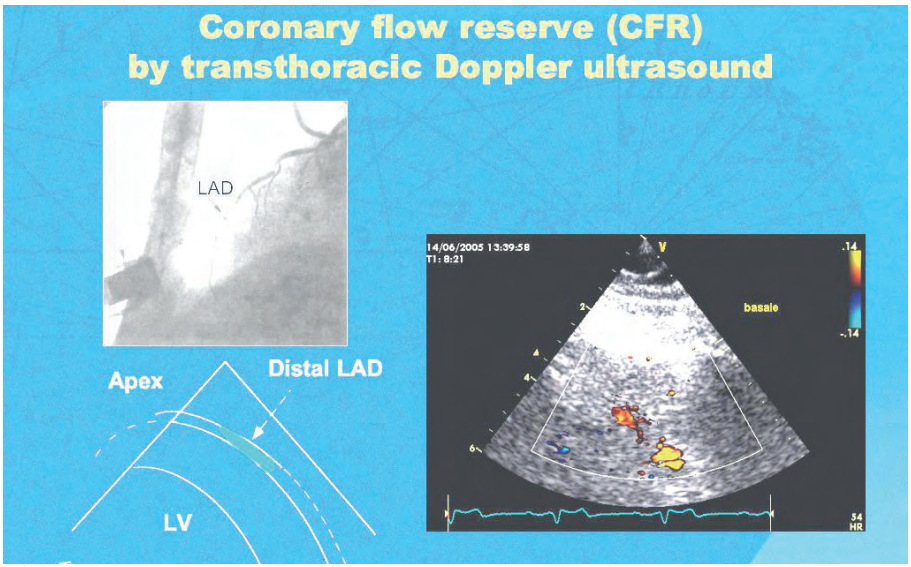


VASCULAR REMODELLING

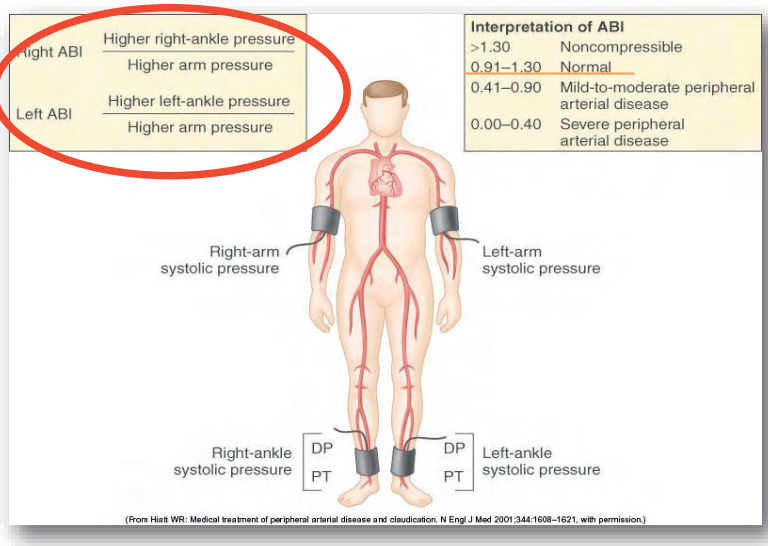




VASCULAR REMODELLING OF THE CORONARY CIRCULATION

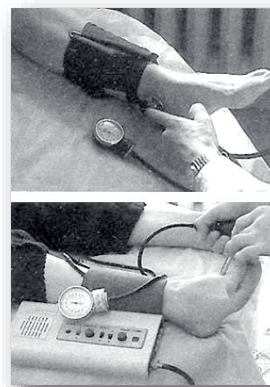


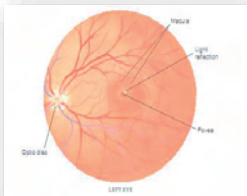
The Ankle-Brachial index (ABI)

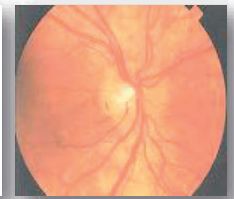


Measurement and interpretation of the ankle-brachial index (ABI). DP = dorsalis pedis; PT = posterior tibial.

Vascular stiffness syndrome
ABI (<0,9)

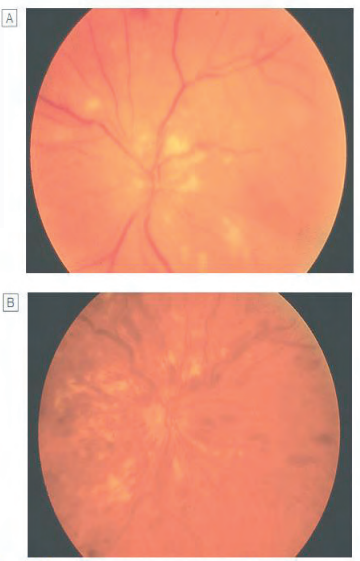






Hypertensive retinopathy

• Grade 1	Arteriolar thickening, tortuosity and increased reflectiveness ('silver wiring')
• Grade 2	Grade 1 plus constriction of veins at arterial crossings ('arteriovenous nipping')
• Grade 3	Grade 2 plus evidence of retinal ischaemia (flame-shaped or blot haemorrhages and 'cotton wool' exudates)
• Grade 4	Grade 3 plus papilloedema



Retinal changes in hypertension. A Grade 4 hypertensive retinopathy showing swollen optic disc, retinal haemorrhages and multiple cotton wool spots (infarcts). B Central retinal vein thrombosis showing swollen optic disc and widespread fundal haemorrhage, commonly associated with systemic hypertension.

Classification of HBP stages according to BP levels, presence of CV risk factors, hypertension-mediated organ damage, or comorbidities

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130-139 DBP 85-89	Grade 1 SBP 140-159 DBP 90-99	Grade 2 SBP 160-179 DBP 100-109	Grade 3 SBP ≥180 or DBP ≥110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to Moderate risk	Moderate to high risk	High Risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (established disease)	Established CVD, CKD grade ≥4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

©ESC/ESH 2018

CV risk is illustrated for a middle-aged male. The CV risk does not necessarily correspond to the actual risk at different ages. The use of the SCORE system is recommended for formal estimation of CV risk for treatment decisions. BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; DBP = diastolic blood pressure; HMOD = hypertension-mediated organ damage; SBP = systolic blood pressure; SCORE = Systematic COronary Risk Evaluation.

EH CLASSIFICATION BASED ON TARGET ORGAN DAMAGE

GRADE I

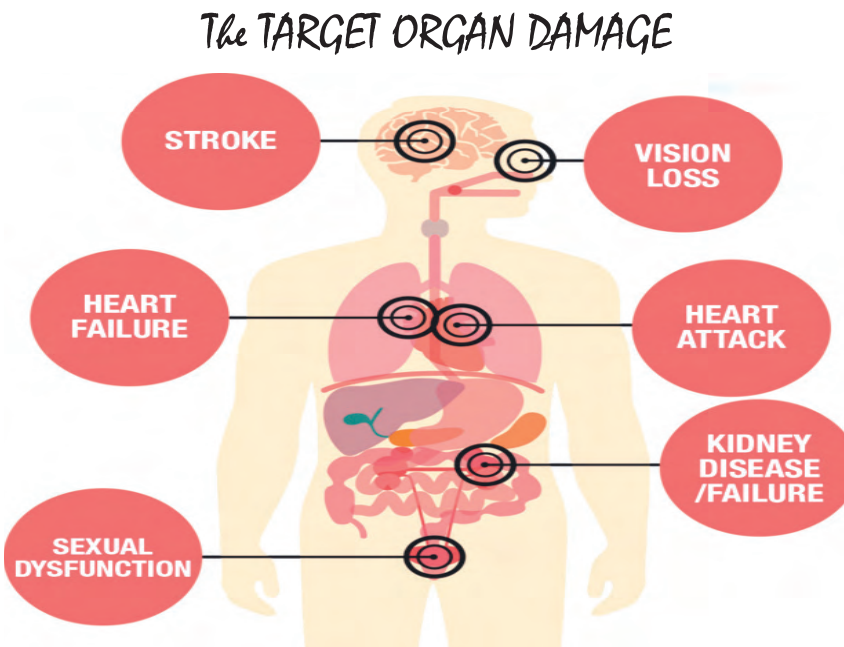
Absence of TARGET ORGAN DAMAGE

GRADE II

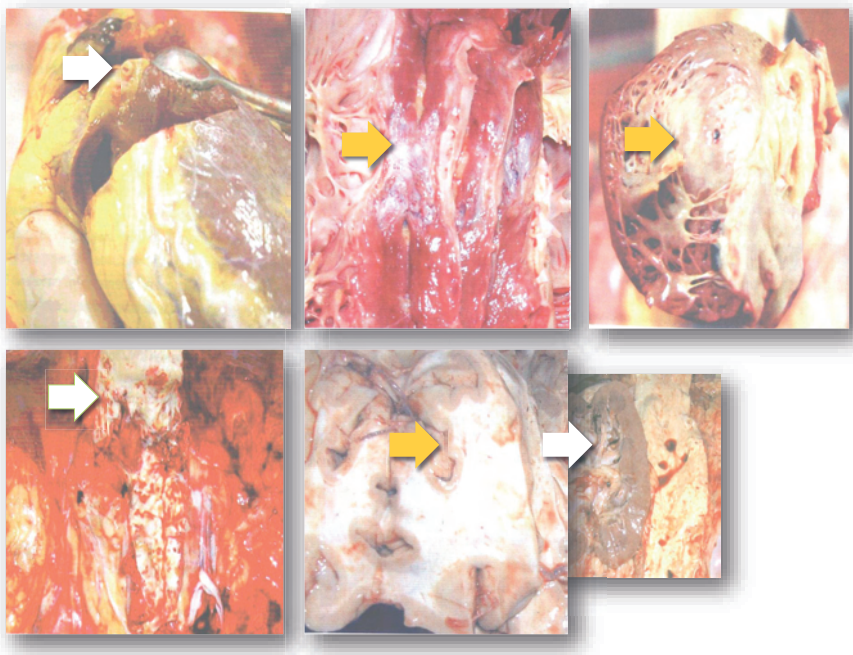
The presence of at least one of the signs of damage of target organs (subclinical)

GRADE III

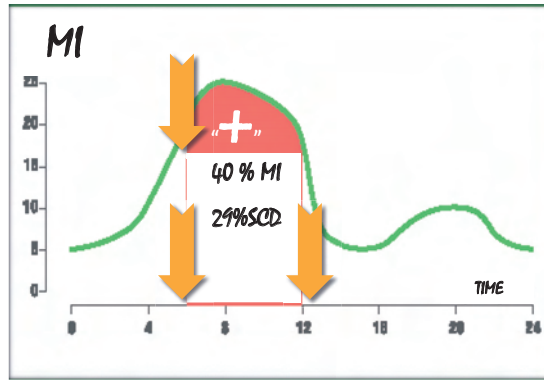
The Presence of clinical manifestation of target organs damage



Cartoonist George Cruikshank «The Headache»



RISK TIME of CV EVENTS



«Heart can be treated only by heart».

A.Almazov

REFERENCES

Kovalyova O.N., Ashcheulova T.V. Propedeutics to Internal Medicine. Part 2. – Vinnytsya: NOVA KNYHA, 2017. – 264 p.

Kovalyova O.N., Asheulova T.V. General inspection: manual for students. – Kharkov: "Turbo". – 2004. – 60 p.

Khomazjuk V.A., Ostashevska T.G., Krasyuk I.V. Propaedeutics of Internal Medicine and Patient Care: Study guide for the practical classes. Part I. – Kyiv: NMU, 2005. – 44 p.

KovalyovaO.N., AsheulovaT.V., ShapovalovaS.A. Instrumental methods examination of cardiovascular system: manual for students. – Kharkov: KSMU. – 2004. – 147 p.

Bickley, Lynn S.; Szilagyi, Peter G. Bates' Guide to Physical Examination and History Taking, 10th Edition. - 934p. Copyright ©2009 Lippincott Williams & Wilkins

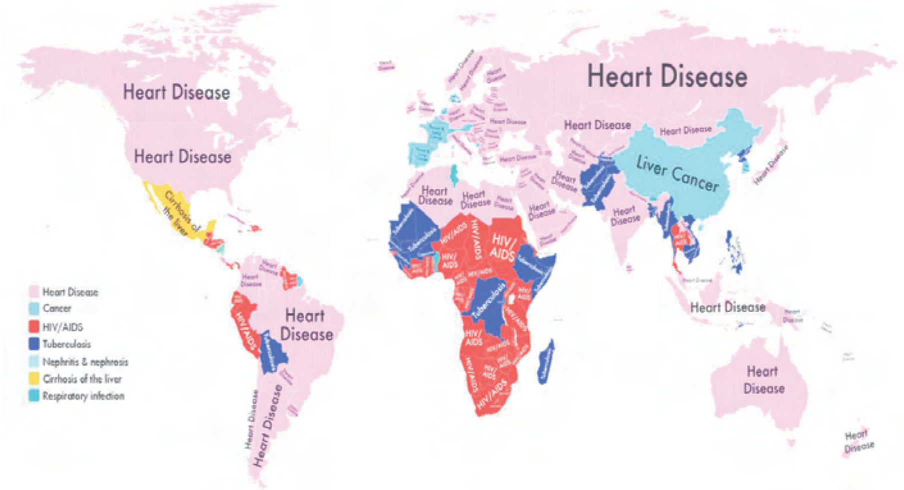
The Point online resources, http://thepoint.lww.com

LECTURE # 12

CORONARY SYNDROME

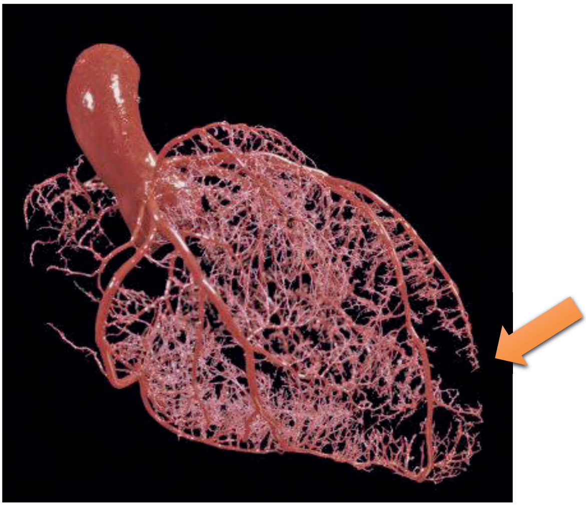
THE PLAN

- Epidemiology
- Clinical Types of CS. What is IHD (CAD) ?
- Risk factors
- Atherogenic pathway
- Coronary Remodeling
- Pathogenesis of IHD
- Clinical Types of CAD
- Ischemic cascade
- The causes of chest pain
- Canadian Cardiovascular Society classification of stable angina
- Angina pectoris. How to Diagnose?
- Unstable or crescendo angina
- 24-h monitoring of ECG
- IHD: Investigations
- OTHER LABORATORY TESTS SUGGESTED IN PATIENTS WITH STABLE ANGINA
- Physical exertion test
- Other Instrumental Methods of examination
- ACS: Chest pain
- ACS without ST-elevation
- ACS with ST-elevation
- IHD: MI types
- MI: Outcomes or complications
- Chronic CS. Chronic Ischemic Heart Disease. Sudden cardiac death
- References



Collaterals !!!

CS



Epidemiology

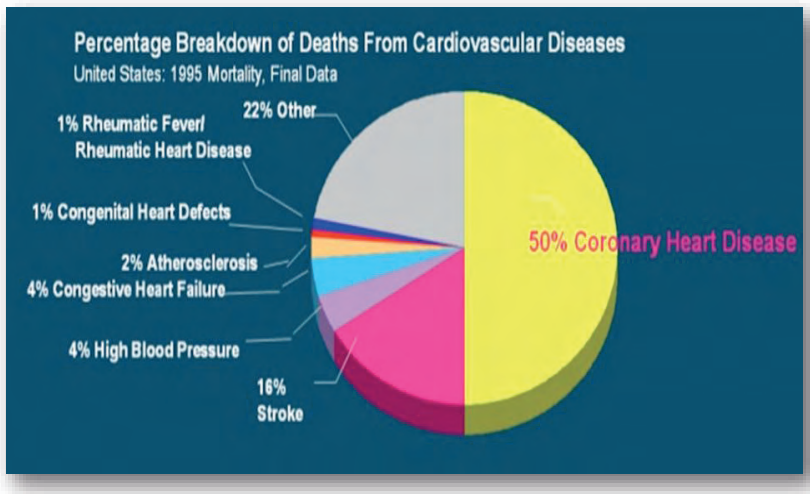
- **Cardiovascular disease is the leading global cause of death, accounting for more than 17.9 million deaths per year in 2015, a number that is expected to grow to more than 23.6 million by 2030**

- CVD and stroke accounted for **14%** of total health expenditures in 2013-2014. This is more than any major diagnostic group
-
- Total direct medical costs of CVD are projected to increase to $749 billion in 2035
-
- Cardiovascular disease, listed as the underlying cause of death, accounts for nearly 836,546 deaths in the US. **That's about 1 of every 3 deaths in the US**

- **About 2,300 Americans die of cardiovascular disease each day, an average of 1 death every 38 seconds**

e. Heart disease and stroke statistics2018 update: a report from the American Heart Association [published online ahead of print January 31, 2018]. Circulation. DOI: 10.1161/CIR.0000000000000558.

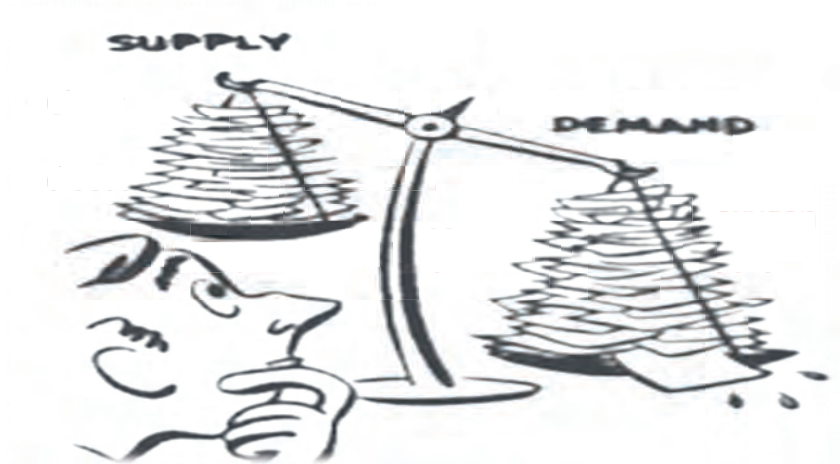
CS: Despite Advances, Still the #1 Killer



What is IHD ?

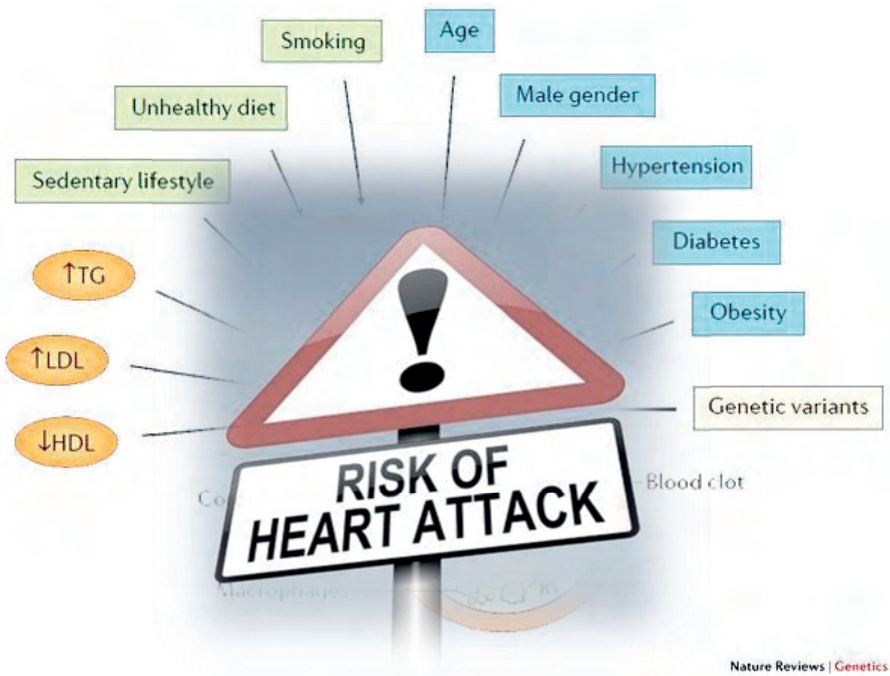
- What is IHD?
- Is a condition that affects the blood supply (coronary arteries of the heart)
- Another name for it : Coronary artery disease (CAD)
- Results when there is an imbalance between myocardial oxygen supply and demand due to partial blockage of the artery.

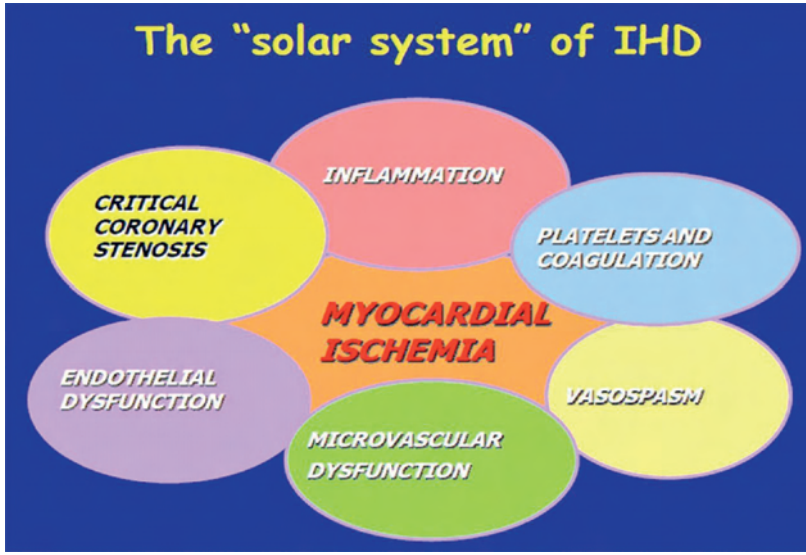
CS: CAD/IHD

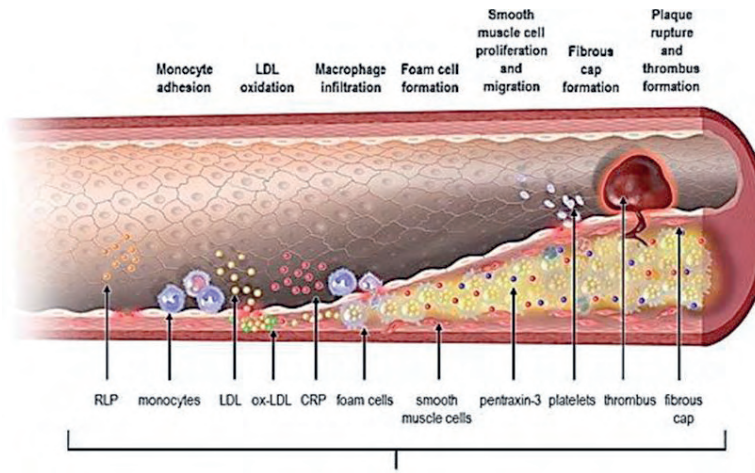


Ischemic Heart Disease: Epidemiology

- Peak incidence: 60y for males and 70y for females.
- Men are more affected than women until the ninth decade.
- Contributing factors:
  - Hypertension.
  - Diabetes mellitus.
  - Smoking.
  - High levels of LDL.
  - Genetic factors (direct or indirect).
  - Lack of exercise.

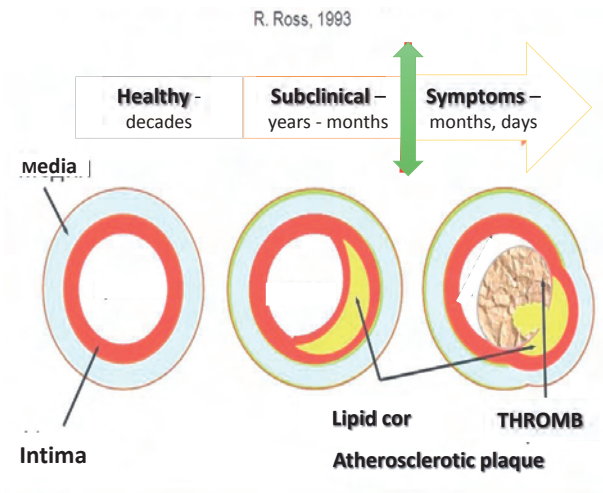






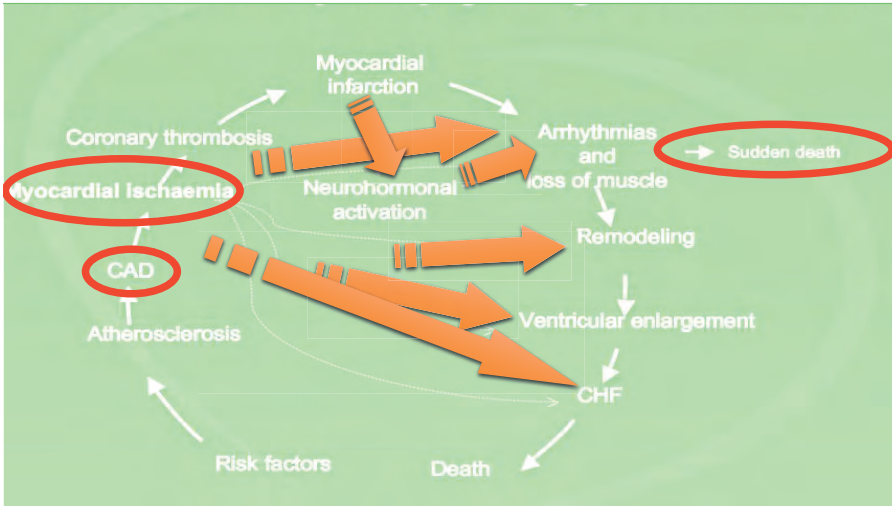
Atherogenic pathway

NEW THEORY of ATHEROGENESIS

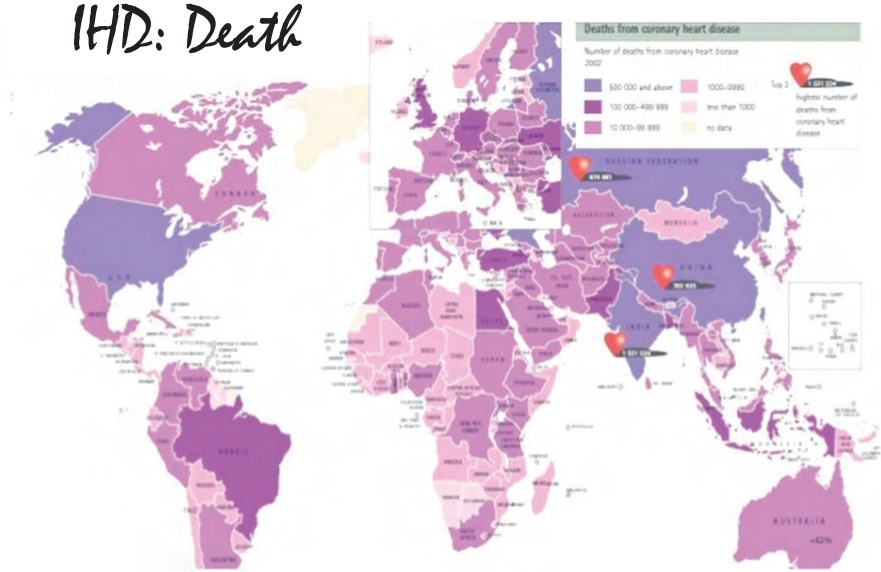


Coronary Remodeling

Cardiovascular pathophysiological continuum



IHD: Death



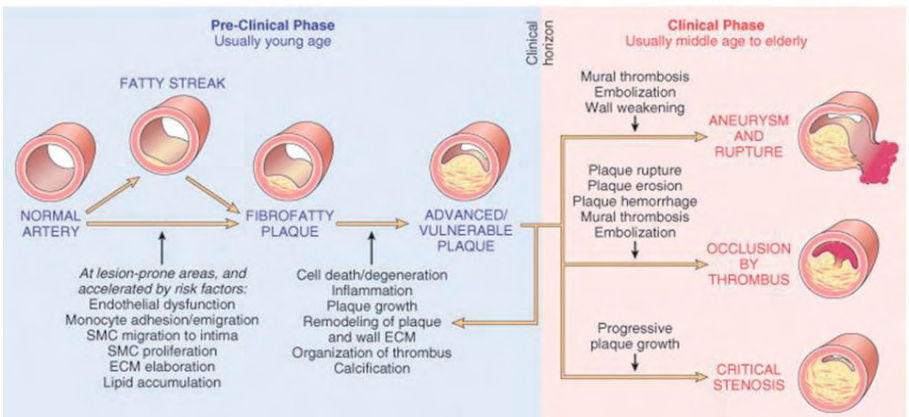
CAD/Ischemic Heart Disease: IHD

- Myocardial perfusion can't meet demand
- Usually caused by decreased coronary artery blood flow ("coronary artery disease")
- Ischemic heart disease is mostly due to coronary artery atherosclerosis
- Less frequently it is due to vasospasm and vasculitis
- A group of closely related syndromes caused by an imbalance between the myocardial oxygen demand and blood supply.
- Four syndromes:
  - ✓Angina pectoris (chest pain).
  - ✓Acute myocardial infarction.
  - ✓Sudden cardiac death.
  - ✓Chronic ischemic heart disease with congestive heart failure.

Pathogenesis of IHD

1) **Role of Critical stenosis or obstruction:**

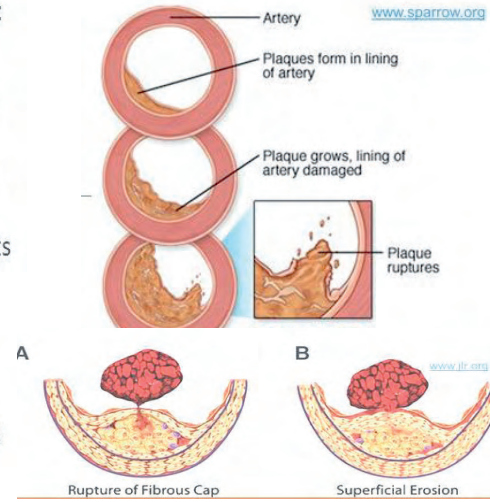
(>=75% of the lumen of one or more coronary arteries by atherosclerotic plaque).



Pathogenesis of IHD

2) **Role of Acute Plaque Change**:

- There is disruption of previously only partially stenosing plaques with rupture or ulceration, exposing the thrombogenic subendothelial basement membrane to blood.
- There is resultant hemorrhage into the atheroma, expanding its volume.
- It can cause the myocardial ischemia in unstable angina, acute MI, and (in many cases) sudden cardiac death.
- Abrupt plaque change followed by thrombosis.



Pathogenesis of IHD

3) **Role of Coronary Thrombus**:

- thrombus superimposed on a disrupted but previously only partially stenotic plaque converts it to a total occlusion. This can lead to acute transmural MI.
- When the extent of luminal obstruction by thrombosis is incomplete it usually leads to unstable angina, acute subendocardial infarction, or sudden cardiac death.
- Thrombus in coronary artery can also embolize.

Pathogenesis of IHD

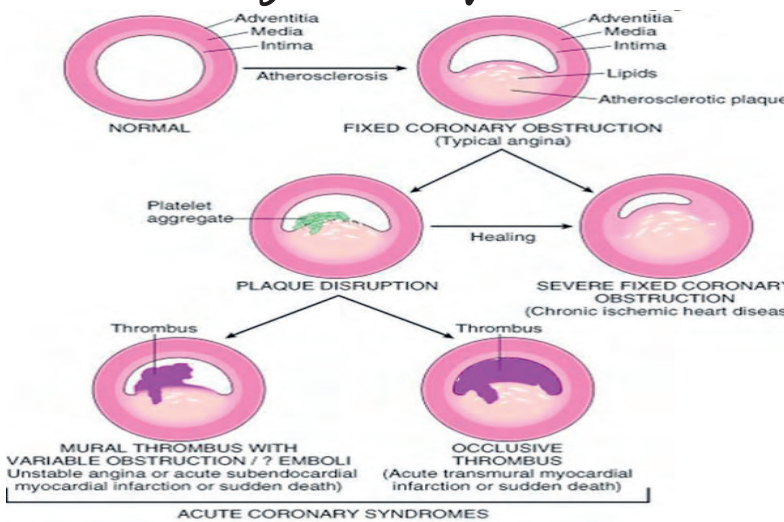
4) **Role of Vasoconstriction:**

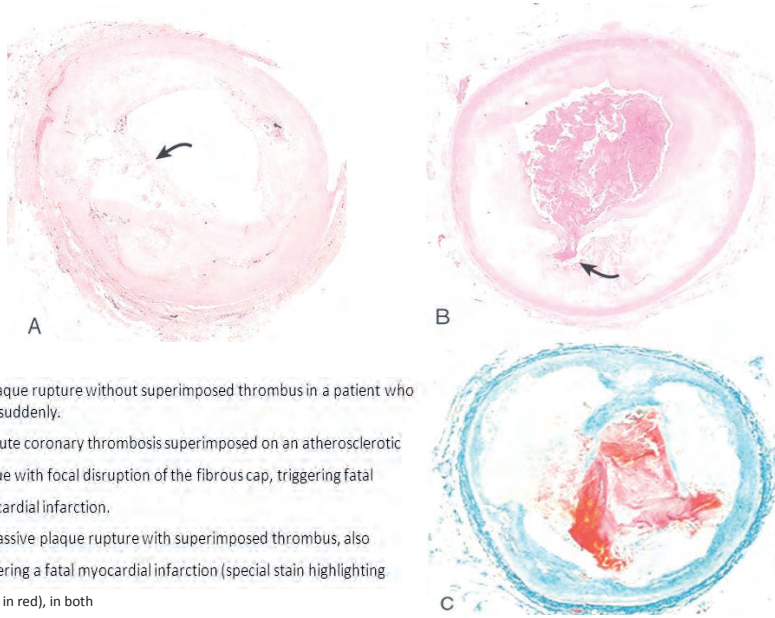
Vasoconstriction reduces lumen size and can therefore potentiate plaque disruption.

5) **Role of Inflammation:**

Inflammatory processes play important roles at all stages of atherosclerosis.

Pathogenesis of IHD



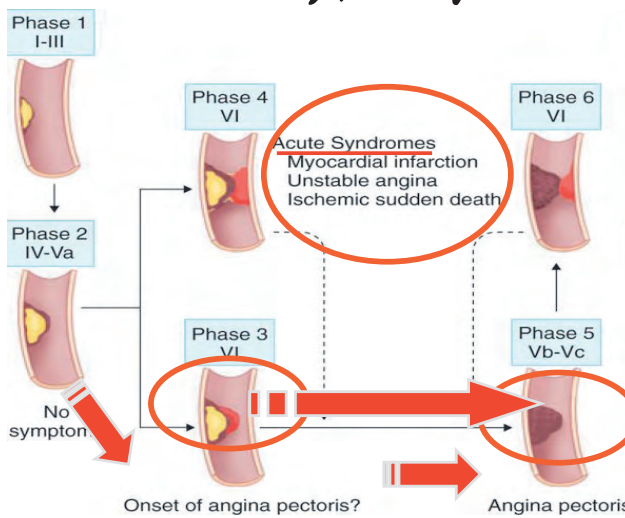


A. Plaque rupture without superimposed thrombus in a patient who died suddenly.

B. Acute coronary thrombosis superimposed on an atherosclerotic plaque with focal disruption of the fibrous cap, triggering fatal myocardial infarction.

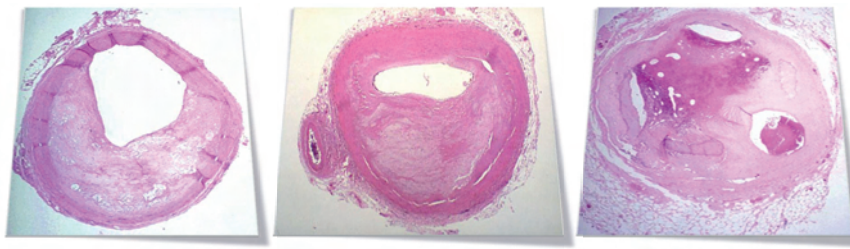
C. Massive plaque rupture with superimposed thrombus, also triggering a fatal myocardial infarction (special stain highlighting fibrin in red), in both

Clinical Types of CAD

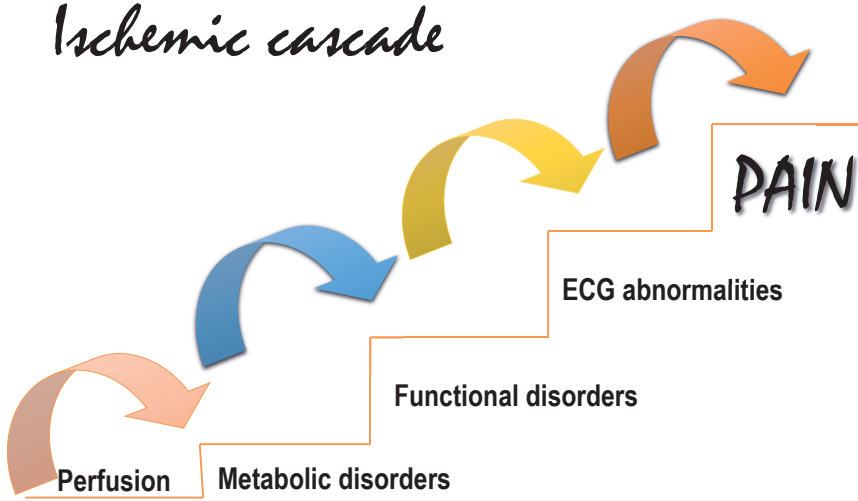


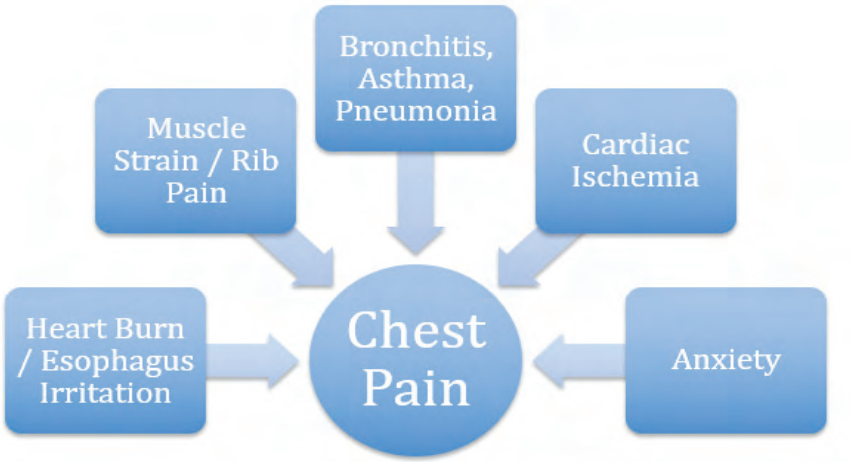
Atherosclerotic plaque

50% 75% MORE!



Ischemic cascade





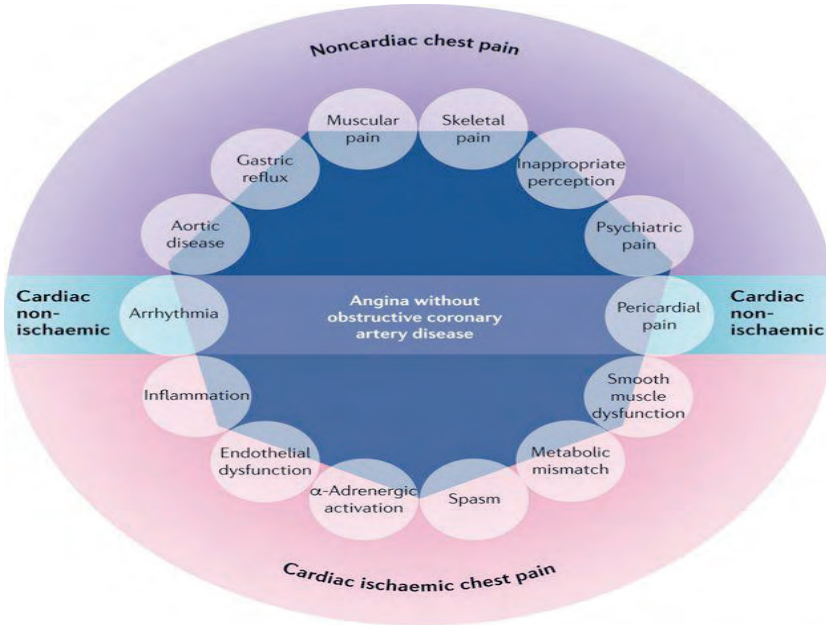
The causes of chest pain

- Recurrent, episodic chest discomfort may be noted with angina pectoris and with many cardiac and noncardiac causes

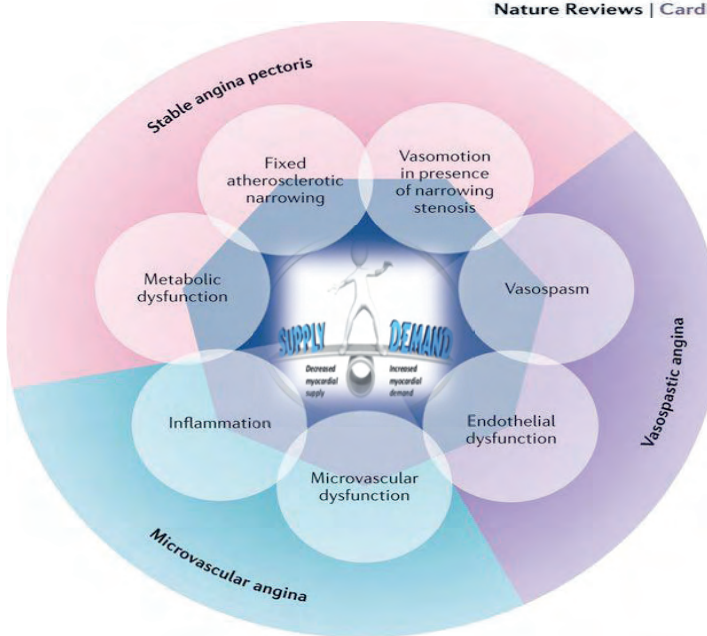
"A careful history remains the cornerstone of the diagnosis of chest pain"

CAUSES OF CHEST PAIN

Condition	Location	Quality	Duration	Aggravating or Relieving Factors	Associated Symptoms or Signs
CARDIOVASCULAR CAUSES					
Angina	Retrosternal region; radiates to or occasionally isolated to neck, jaw, epigastrium, shoulder, or arms (left common)	Pressure, burning, squeezing, heaviness, indigestion	**<2–15 min**	Precipitated by exercise, cold weather, or emotional stress; relieved by rest or nitroglycerin; atypical (Prinzmetal's) angina may be unrelated to activity, often early morning	S_3 or murmur of papillary muscle dysfunction during pain
Rest or unstable angina	Same as angina	Same as angina but may be more severe	**Usually <20 min**	Same as angina, with decreasing tolerance for exertion or at rest	Similar to stable angina, but may be pronounced; transient heart failure can occur
Myocardial infarction	Substernal and may radiate like angina	Heaviness, pressure, burning, constriction	**≥30 min but variable**	Unrelieved by rest or nitroglycerin	Shortness of breath, sweating, weakness, nausea, vomiting



Nature Reviews | Cardiology



Nature Reviews | Cardiology

Typical angina (Definite) 	*Meets all three of the following characteristics:* • *substernal chest discomfort of characteristic quality and duration;* • *provoked by exertion or emotional stress;* • *relieved by rest and/or nitrates within minutes.*
Atypical angina (probable)	*Meets two of these characteristics*
Non-anginal chest pain	*Lacks or meets only one or none of the characteristics*

Canadian Cardiovascular Society classification of stable angina

Class I	Ordinary activity does not cause angina such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.
Class II	Slight limitation of ordinary activity. Angina on walking or climbing stairs rapidly, walking or stair climbing after meals, or in cold, wind or under emotional stress, or only during the first few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
Class III	Marked limitation of ordinary physical activity. Angina on walking one to two blocks (~100–200 m)on the level or one flight of stairs in normal conditions and at a normal pace.
Class IV	Inability to carry on any physical activity without discomfort' – angina syndrome may be present at rest'.

Oxygen demand: cardiac work	
• Heart rate • BP • Myocardial contractility	• Left ventricular hypertrophy • Valve disease, e.g. aortic stenosis
Oxygen supply: coronary blood flow	
• Duration of diastole • Coronary perfusion pressure (aortic diastolic minus coronary sinus or right atrial diastolic pressure)	• Coronary vasomotor tone • Oxygenation Haemoglobin Oxygen saturation

N.B. Coronary blood flow occurs mainly in diastole.

Reduced myocardial perfusion, e.g.	*Increased myocardial oxygen demand, e.g.*

Common	
• Physical exertion • Cold exposure	• Heavy meals • Intense emotion
Uncommon	
• Lying flat (decubitus angina)	• Vivid dreams (nocturnal angina)

Angina pectoris

- Angina pectoris is a type of IHD characterized by paroxysmal and usually recurrent attacks of substernal or precordial chest discomfort (variously described as constricting, crushing, squeezing, choking, or knifelike). May radiate down the left arm or to the left jaw *(referred pain)* .
- It is due to inadequate perfusion and is caused by transient (15 seconds to 15 minutes) myocardial ischemia that falls short of inducing the cellular necrosis that defines infarction i.e. duration and severity is not sufficient for infarction
- There are three overlapping patterns of angina pectoris:

(1) Stable or typical angina

(2) Prinzmetal or variant angina

(3) Unstable or crescendo angina

Angina pectoris

Definition:

paroxysmal and usually recurrent attacks of substernal chest discomfort (variously described as constricting, crushing,squeezing, choking, or knifelike). May radiate down the left arm or to the left jaw *(referred pain)* .

Cause:

It is due to inadequate perfusion which is transient (15 seconds to 15 minutes) myocardial ischemia i.e. duration and severity is not sufficient for infarction

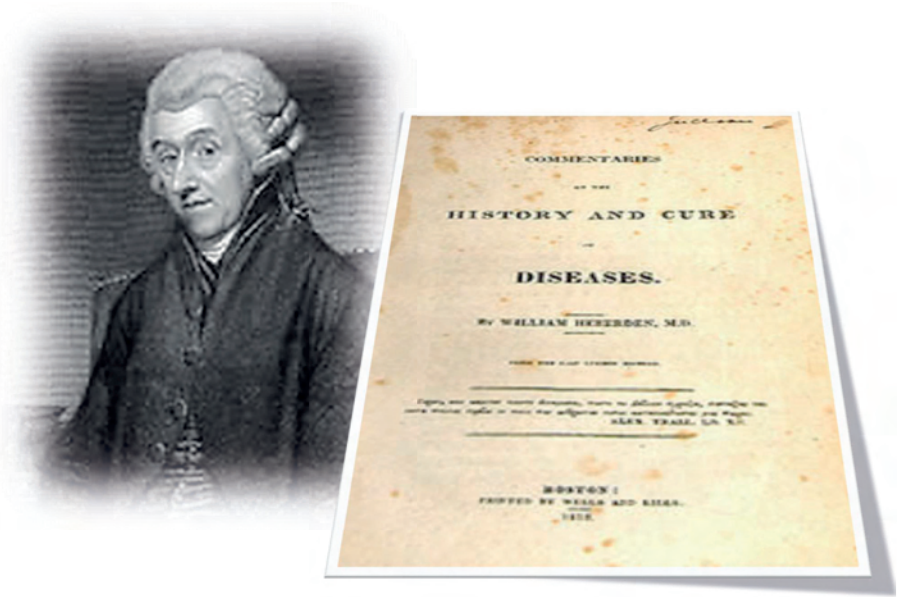
Clinical Manifestations

- **Typical clinical CASE….**

Angina pectoris.

Stable angina/ typical angina pectoris:

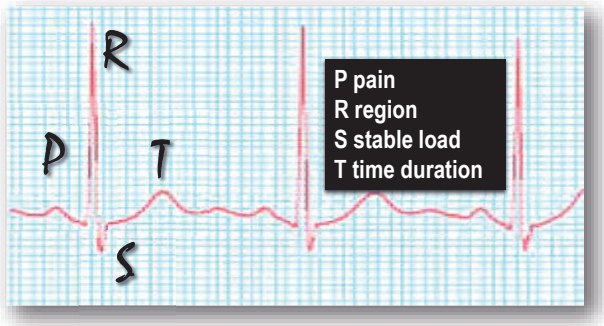
- the most common form of angina, caused by atherosclerotic disease with usually ≥75% narrowing of lumen i.e. (critical stenosis) fixed chronic stable stenosis.
- This significant reduction of coronary perfusion makes the heart vulnerable to further ischemia whenever there is increased demand, such as that produced by physical activity, emotional excitement, or any other cause of increased cardiac workload.
- Episodic chest pain associated with exertion or some other form of stress.
- Is usually relieved by rest (thereby decreasing demand) or nitroglycerin, a strong vasodilator.



"It seems ironic - I was prescribed
to take nitroglycerin. They call it
trinitrin so as not to upset
pharmacists and the public.

Your sincere friend
A. Nobel"

Angina pectoris: How to Diagnose?



NB!

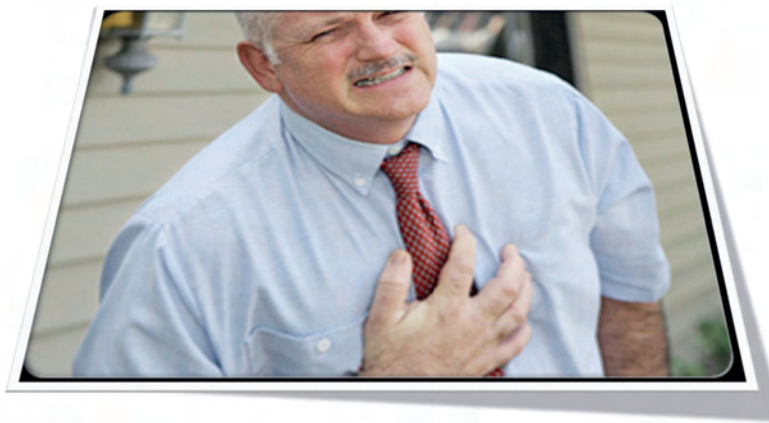
Angina pectoris.

Stable angina/ typical angina pectoris:

Definition : Episodic chest pain associated with exertion or some other form of stress.

- the most common form of angina, caused by atherosclerotic disease leading to fixed chronic stable stenosis.
- This significant reduction of coronary perfusion makes the heart vulnerable to further ischemia whenever there is increased demand, such as that produced by physical activity, emotional excitement, or any other cause of increased cardiac workload.
- It Is usually relieved by rest (thereby decreasing demand) or nitroglycerin, a strong vasodilator.

Typical ANGINA

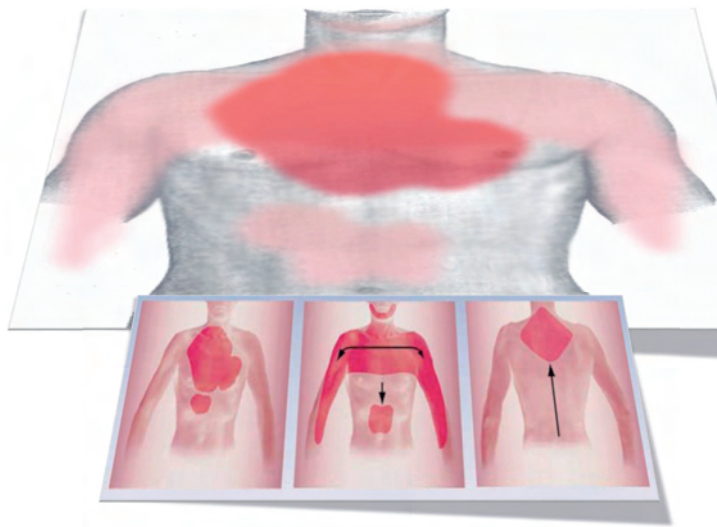


Fist sing by Levin

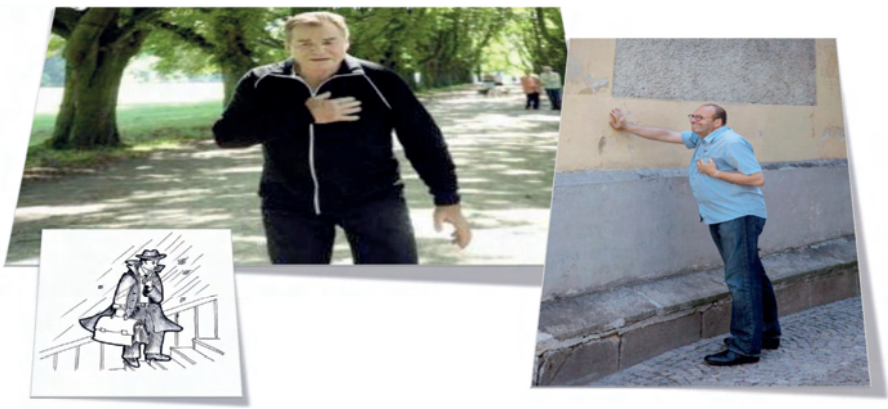
Typical ANGINA

Typical ANGINA

Typical radiation



Typical ANGINA on exertion



Atypical ANGINA

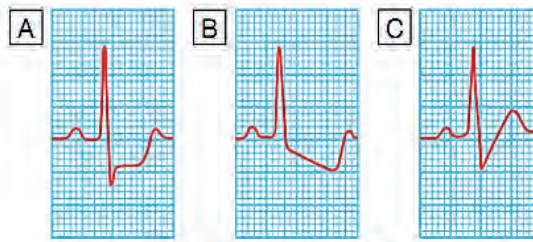
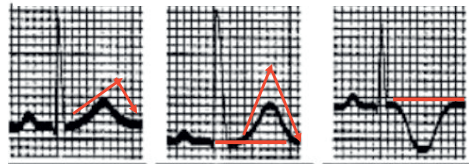
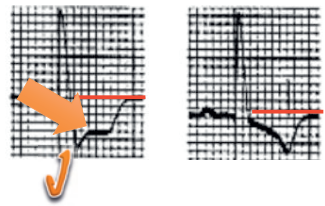


Fig. 18.63 Forms of exercise-induced ST depression. A Planar ST depression is usually indicative of myocardial ischaemia. B Down-sloping depression also usually indicates myocardial ischaemia. C Up-sloping depression may be a normal finding.

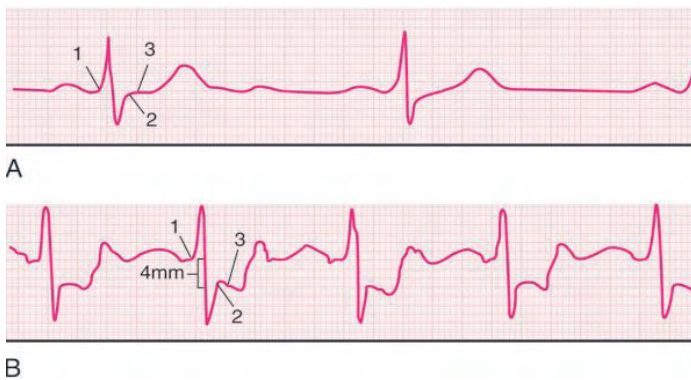
ECG sings of AP





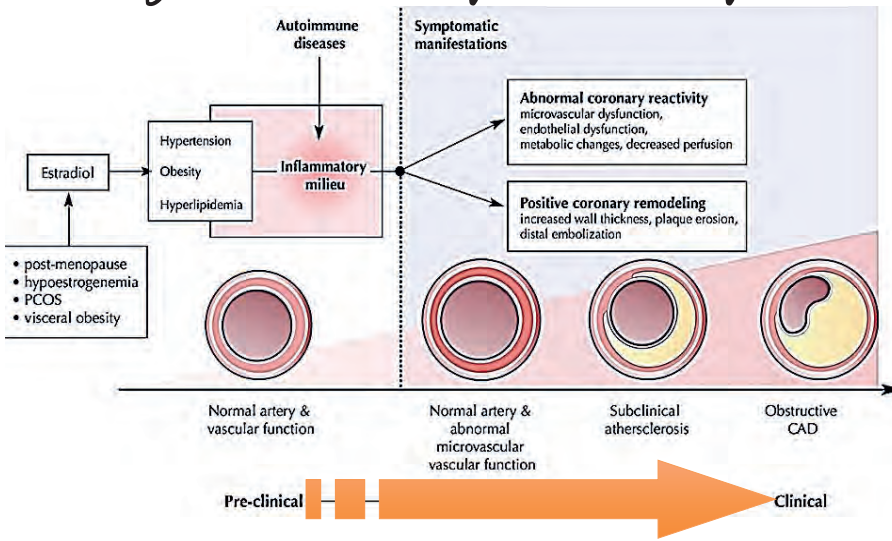
NB!

Typical electrocardiographic ST segment depression associated with myocardial ischemia



A, Lead V_5 at rest. B, Lead V_5 at peak exercise. The PQ junction (1) that serves as the baseline reference, the J point (2), and the ST segment at 80 msec past the J point (3) are represented. In this case, the amount of ST segment depression measured 80 msec past the J point is 0.4 mV or 4 mm, and the slope between the J point and 80 msec past the J point is nonexistent since the ST segment is horizontal and not upsloping.

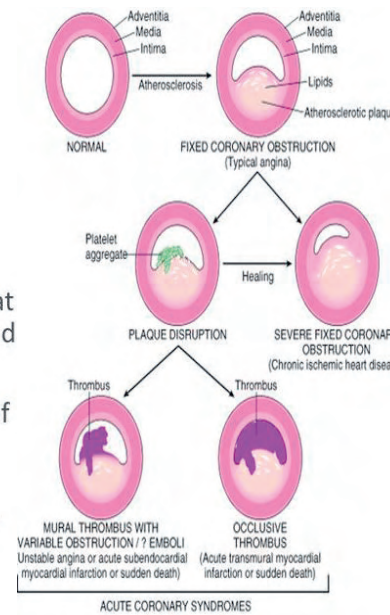
Progressive manifestation of IHD



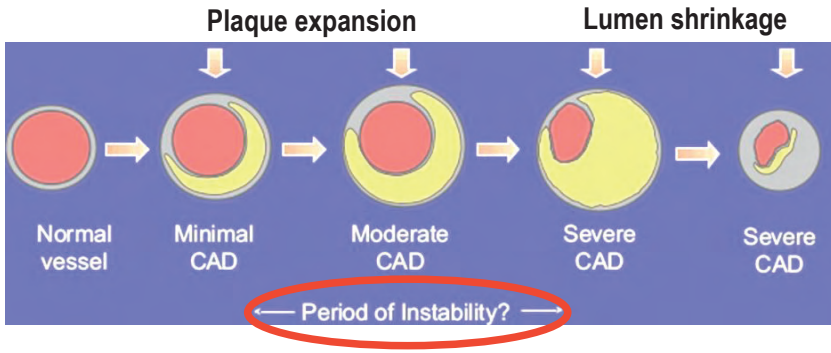
Angina pectoris.

Unstable or crescendo angina

- Unstable
- Pain occurs with progressively increasing frequency, is precipitated with progressively less exertion, even at rest, and tends to be of more prolonged duration.
- It is induced by disruption or rupture of an atherosclerotic plaque with superimposed partial thrombosis.
- Unstable angina is often the precursor of subsequent acute MI. Thus this referred to as preinfarction angina.

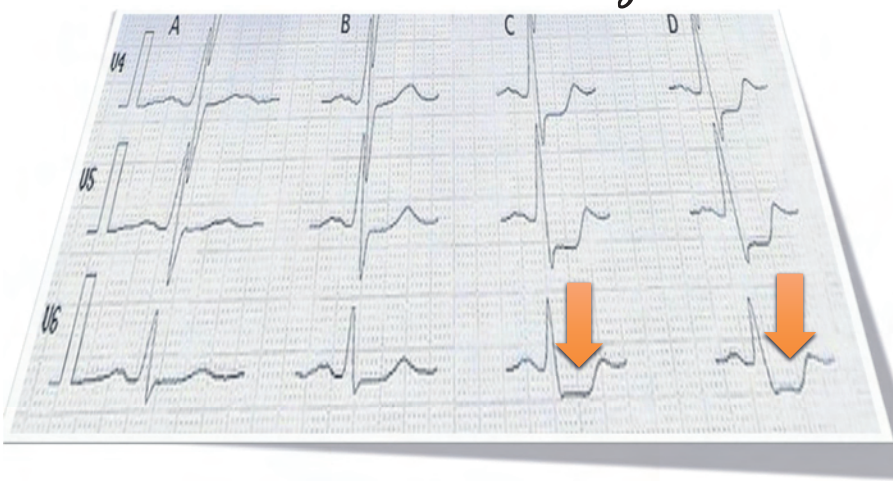


Coronary Remodeling



ACS

Unstable or crescendo angina



Angina pectoris.

Prinzmetal variant angina :

- is an uncommon pattern of episodic angina that occurs at rest and is due to coronary artery spasm.
- Prinzmetal angina generally responds promptly to vasodilators, such as nitroglycerin and calcium channel blockers.
- Not related to atherosclerotic disease
- The etiology is not clear.

Angina pectoris.

Summary

Intermittent chest pain caused by transient, reversible ischemia

Typical (stable) angina

- pain on exertion
- fixed narrowing of coronary artery

Unstable (pre-infarction) angina

- increasing pain with less exertion
- plaque disruption and thrombosis

Prinzmetal (variant) angina

- pain at rest
- coronary artery spasm of unknown etiology

Angina pectoris.

Summary

- Intermittent chest pain caused by transient, reversible ischemia
- Typical (stable) angina
  - pain on more exertion
  - fixed narrowing of coronary artery
- Unstable (pre-infarction) angina
  - increasing pain with less exertion
  - plaque disruption and thrombosis
- Prinzmetal (variant) angina
  - pain at rest
  - coronary artery spasm of unknown etiology

Silent ischemia

- Silent ischemia is diagnosed when no or minimal symptoms can be evoked despite objective documentation of myocardial ischemia, but in retrospect, subtle symptoms can often be elicited in these patients.

24-h monitoring of ECG

Nocturnal angina

- Nocturnal angina may occur soon after lying down in patients with subclinical heart failure because of an **increase in venous return**; in the early morning hours, at the time the **sympathetic tone is highest in patients with vasospastic disease**; or any time **in patients with sleep apnea**

Postprandial angina

- Postprandial angina develops during or soon after meals because of an **increased oxygen demand in the splanchnic vascular bed**

IHD: Investigations

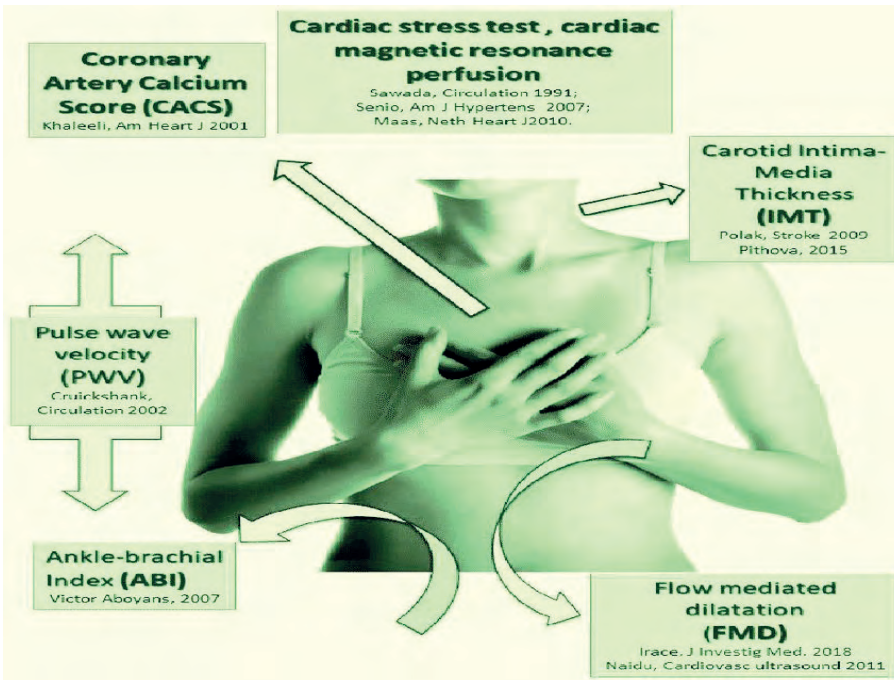
- ECG
- CARDIAC ENZYMES e.g. CK, LDH, TROPONIN etc.
- ECHOCARDIOGRAPHY
- TREADMILL EXERCISE TEST
- THALLIUM STRESS TEST
- CORONARY ANGIOGRAPHY

✓ **NOTE**:
- ECG CHANGES IN IHD:
  - ST DEPRESSION OCCURS IN ECG IN RESPECTIVE LEADS
- ECG CHANGES IN MI:
  - ST ELEVATION OCCURS IN ECG IN RESPECTIVE LEADS

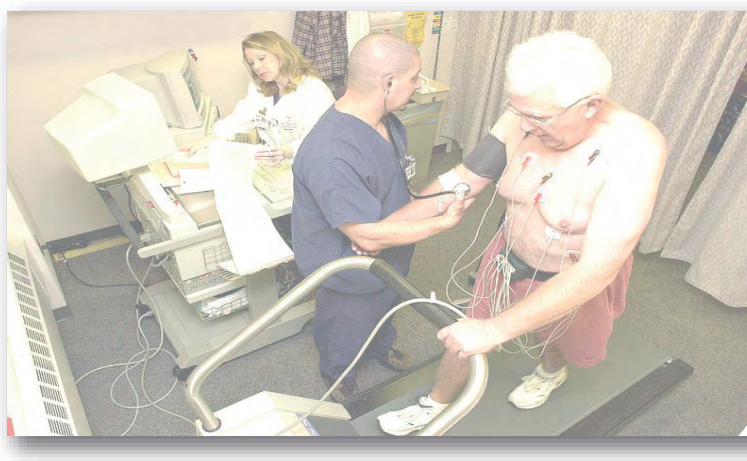
OTHER LABORATORY TESTS SUGGESTED IN PATIENTS WITH STABLE ANGINA

- LDL and HDL cholesterol levels (apolipoprotein B, apolipoprotein A-I)
- Triglyceride level
- Fasting glucose concentration
- Creatinine levels
- Homocysteine level in patients with strong family history, especially if not explained by other risk factors
- Hemoglobin, hematocrit
- Test of thyroid function (T_4 or TSH level)
- Consider C-reactive protein levels
- Troponin T or troponin I, CK-MB

CK-MB = creatine kinase MB; HDL = high-density lipoprotein; LDL = low-density lipoprotein; T_4 = thyroxine; TSH = thyroid-stimulating hormone



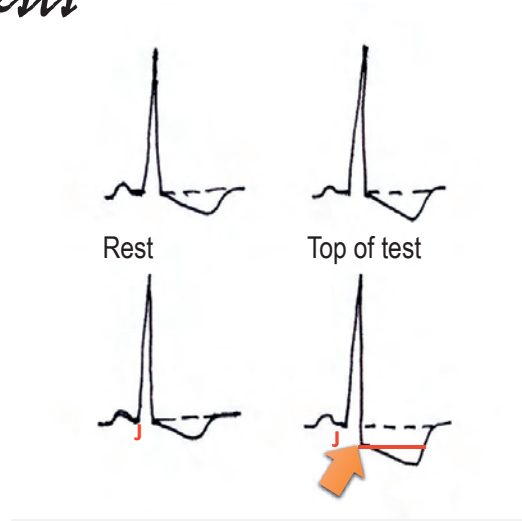
Physical exertion Examination



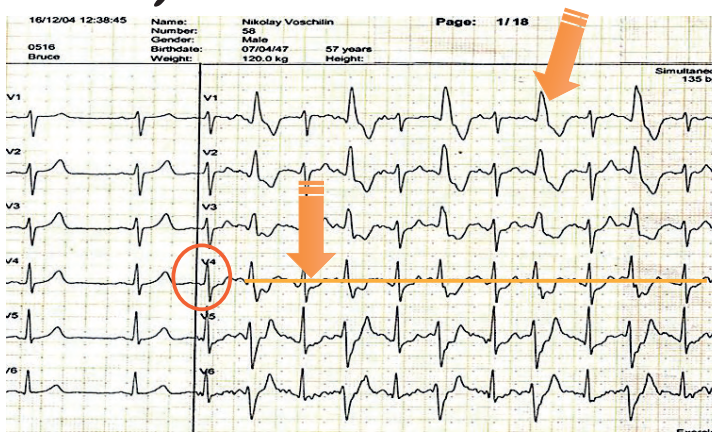
Physical tests

N

Ischemia

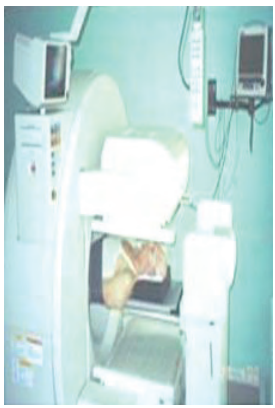


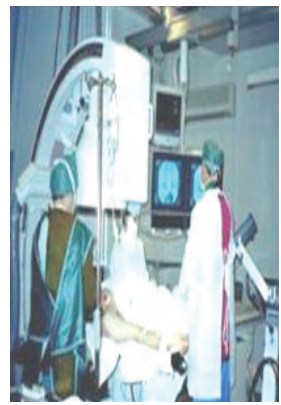
Physical exertion test

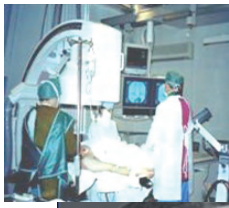


Rest Top of test

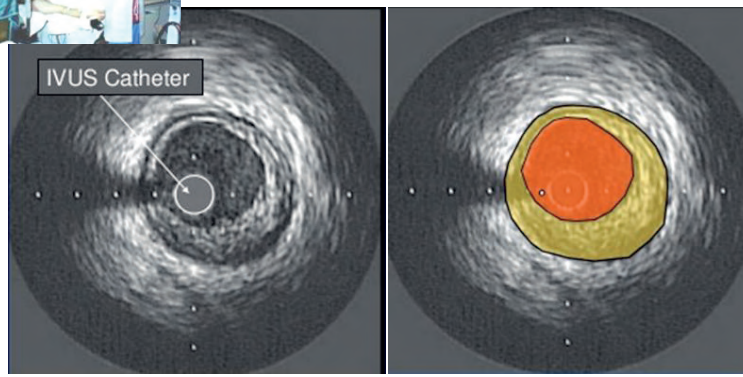
Other Instrumental Methods of examination







Atherosclerotic plaque



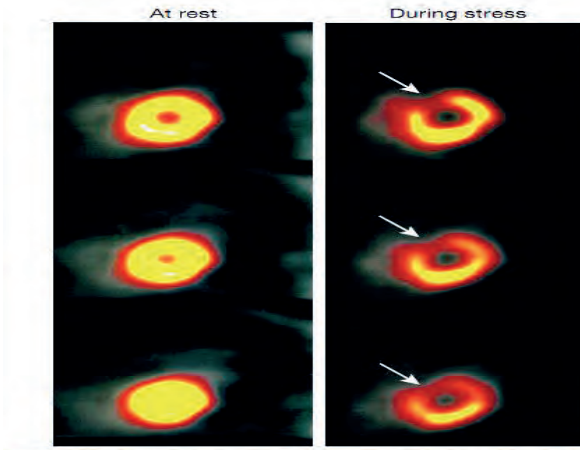
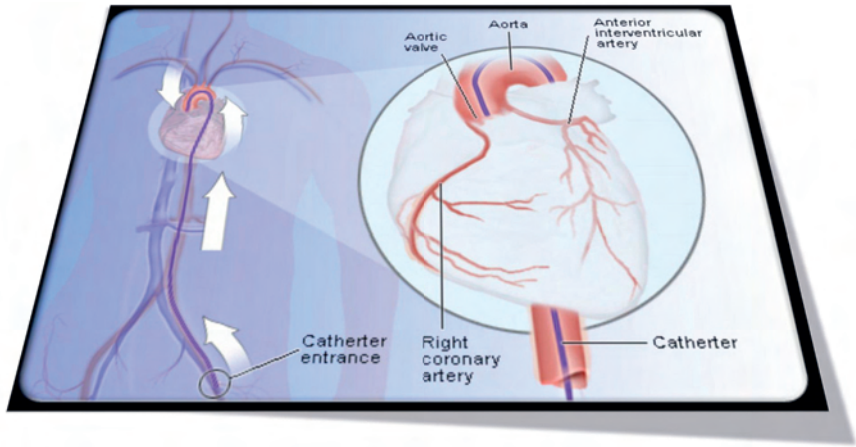
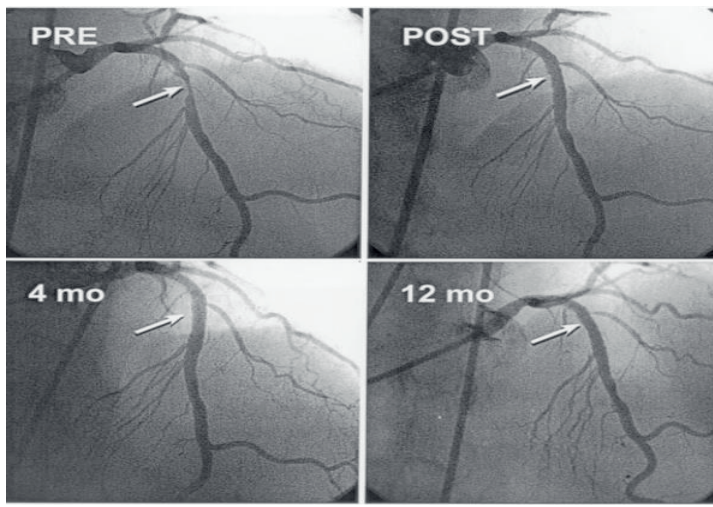


Fig. 18.65 A myocardial perfusion scan showing reversible anterior myocardial ischaemia. The images are cross-sectional tomograms of the LV. The resting scans (left) show even uptake of the ^{99}technetium-labelled tetrofosmin and look like doughnuts. During stress (e.g. a dobutamine infusion), there is reduced uptake of technetium, particularly along the anterior wall (arrows), and the scans look like crescents (right).

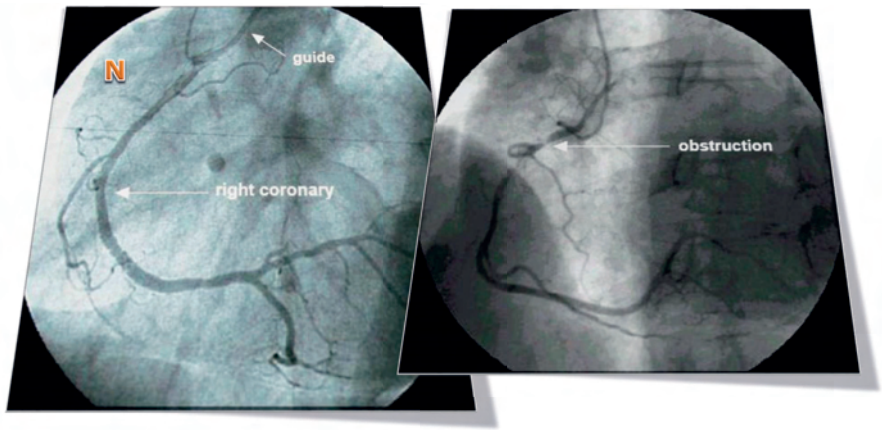
Coronary angiography

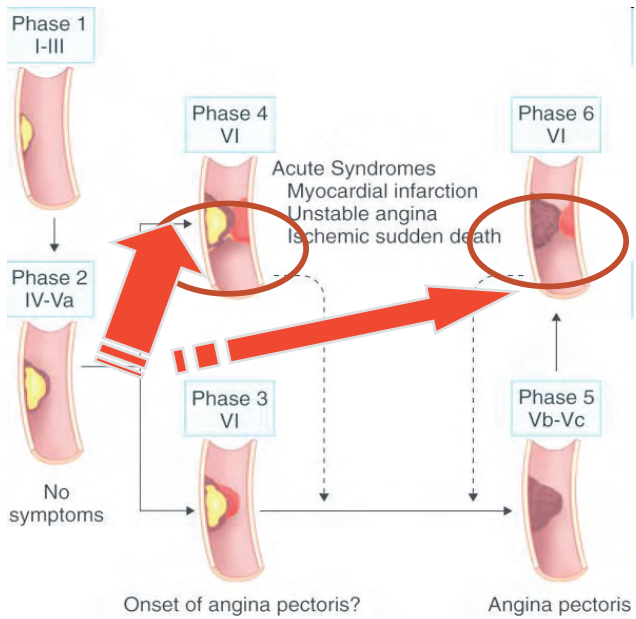


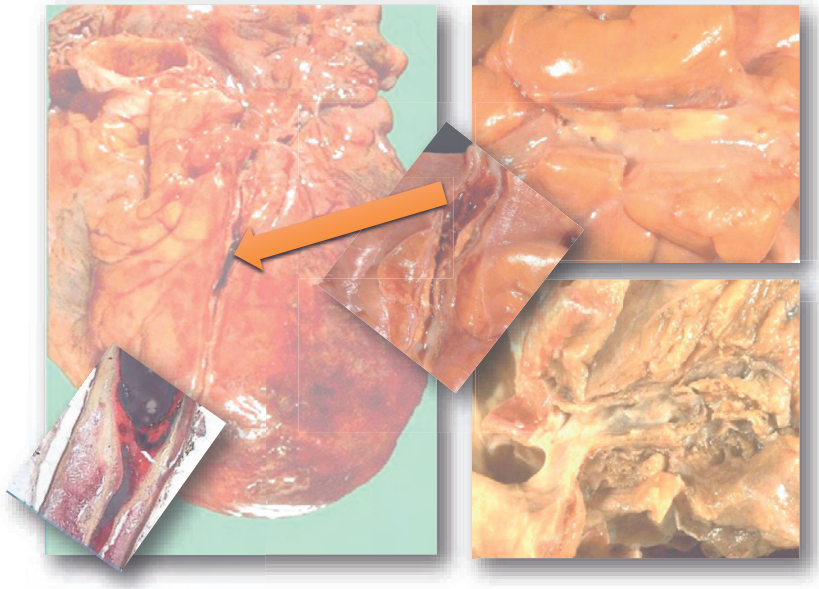
Coronary angiography



Coronary angiography

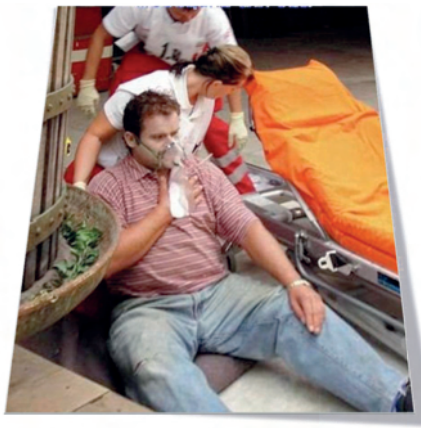






ACS: Chest pain

- **New, acute**, often ongoing **pain** may indicate an acute myocardial infarction, unstable angina, or aortic dissection; **a pulmonary cause**, such as acute pulmonary embolism or pleural irritation; **a musculoskeletal condition** of the chest wall, thorax, or shoulder; **or a gastrointestinal abnormality,** such as esophageal reflux or spasm, peptic ulcer disease, or cholecystitis



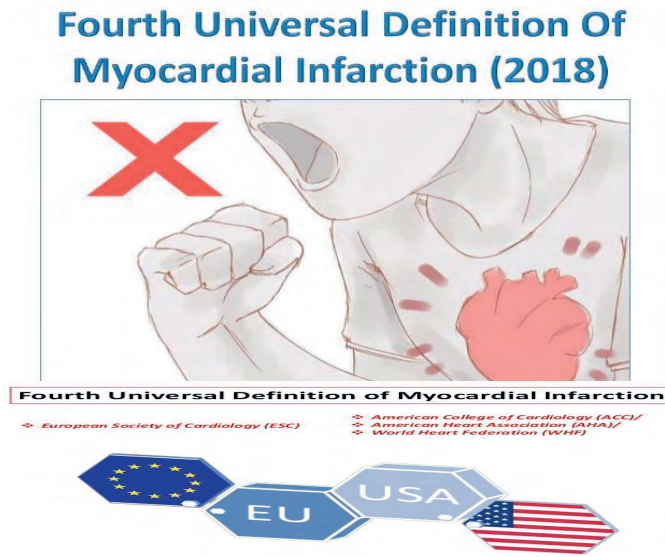
Arriving at a diagnosis of MI using the criteria in this document requires the integration of :

- *clinical findings,*
- *patterns on the ECG,*
- *laboratory data, and*
- *observations from imaging procedures,*

all viewed in the context of the time horizon over which the suspected event unfolds.

IHD: Laboratory evaluation

1. Troponins: **best marker**, TnT, TnI (more specific).
   - TnI and TnT are not normally detectable in the circulation
   - After acute MI both troponins become detectable after 2 to 4 hours, peaks at 48 hours. Their levels remain elevated for 7 to 10 days
2. CK-MB is the **second best mar**ker:
   - It begins to rise within 2 to 4 hours of MI, peaks at 24 to 48 hours and returns to normal within approximately 72 hours
3. Lactate dehydrogenase (LD)... LD1.
   - Rise 24 hrs, peaks 72 hrs, persists 72 hrs.



ESC European Society of Cardiology

European Heart Journal (2018) 00, 1–33 doi:10.1093/eurheartj/ehy462

EXPERT CONSENSUS DOCUMENT

Fourth universal definition of myocardial infarction (2018)

Kristian Thygesen* (Denmark), Joseph S. Alpert* (USA), Allan S. Jaffe (USA), Bernard R. Chaitman (USA), Jeroen J. Bax (The Netherlands), David A. Morrow (USA), Harvey D. White* (New Zealand): the Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/ American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction

Key points to remember

The following are key points to remember from this Expert Consensus Document on the Fourth Universal Definition of Myocardial Infarction

Types of MI

Type of MI	Characterization
Type 1	Spontaneous plaque rupture, ulceration, fissuring, erosion, or dissection with resultant intraluminal thrombus, cessation of myocardial blood flow, and acute myocyte necrosis
Type 2	Ischemic myocardial necrosis resulting from a marked increase in myocardial oxygen demand or a marked decrease in myocardial blood flow, occurring in the absence of acute plaque rupture or coronary thrombosis
Type 3	Sudden cardiac death related to coronary arterial thrombosis
Type 4	MI secondary to percutaneous coronary intervention • Myocardial infarction associated with percutaneous coronary intervention (type 4a) • Stent/scaffold thrombosis associated with percutaneous coronary intervention (type 4b) • Restenosis associated with percutaneous coronary intervention (type 4c)
Type 5	MI secondary to coronary artery bypass grafting

Reasons for the elevation of cardiac troponin values because of myocardial injury

1) Myocardial injury related to acute myocardial ischaemia

Atherosclerotic plaque disruption with thrombosis.

Reasons for the elevation of cardiac troponin values because of myocardial injury

2) Myocardial injury related to acute myocardial ischaemia because of oxygen supply/demand imbalance

Reduced myocardial perfusion, e.g.	Increased myocardial oxygen demand, e.g.
• Coronary artery spasm, microvascular dysfunction • Coronary embolism • Coronary artery dissection • Sustained bradyarrhythmia • Hypotension or shock • Respiratory failure • Severe anaemia	➢ Sustained tachyarrhythmia ➢ Severe hypertension with or without LVH

Reasons for the elevation of cardiac troponin values because of myocardial injury

3) Other causes of myocardial injury

Cardiac conditions, e.g.

- Heart failure
- Myocarditis
- Cardiomyopathy (any type)
- Takotsubo syndrome
- Coronary revascularization procedure
- Cardiac procedure other than revascularization
- Catheter ablation
- Defibrillator shocks
- Cardiac contusion

Systemic conditions, e.g.

- Sepsis, infectious disease
- Chronic kidney disease
- Stroke, subarachnoid haemorrhage
- Pulmonary embolism, pulmonary hypertension
- Infiltrative diseases, e.g. amyloidosis, sarcoidosis
- Chemotherapeutic agents
- Critically ill patients
- Strenuous exercise

Criteria For MI

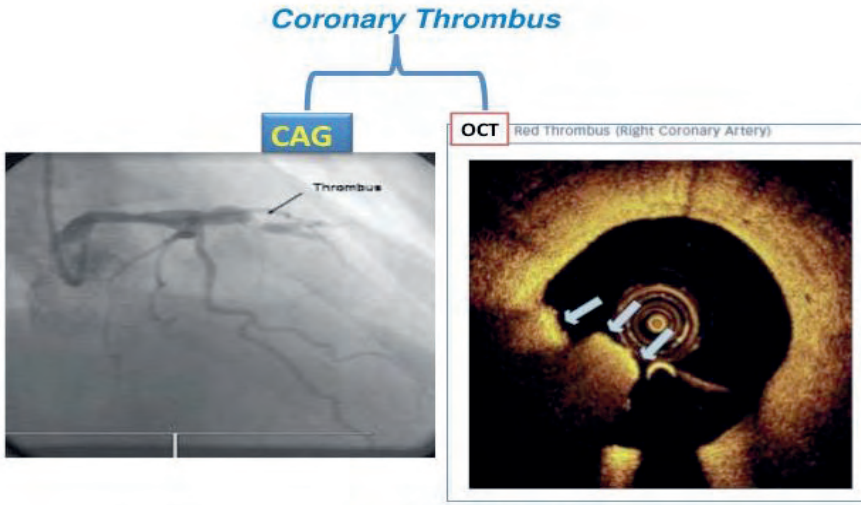
Biomarkers :
Detection of a rise and/or fall of cTn with at least one value above the 99th percentile

& with at least one of the following

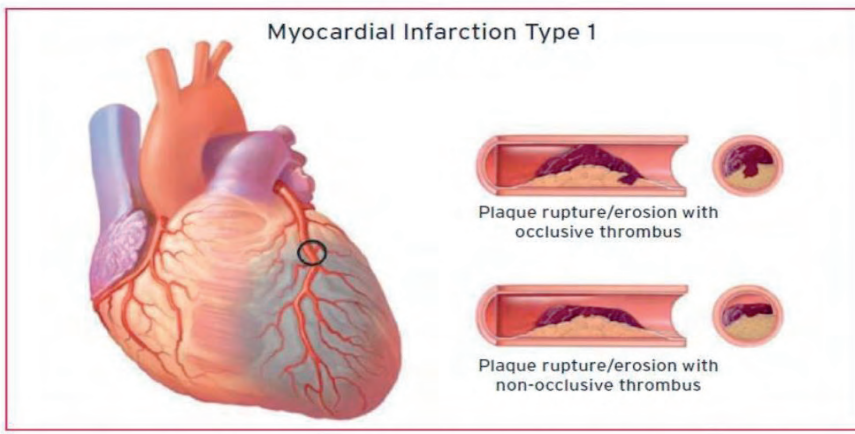
Symptoms :
Symptoms of acute myocardial ischemia

ECG :
New ischemic ECG changes;
Development of pathological Q waves

Imaging
evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology



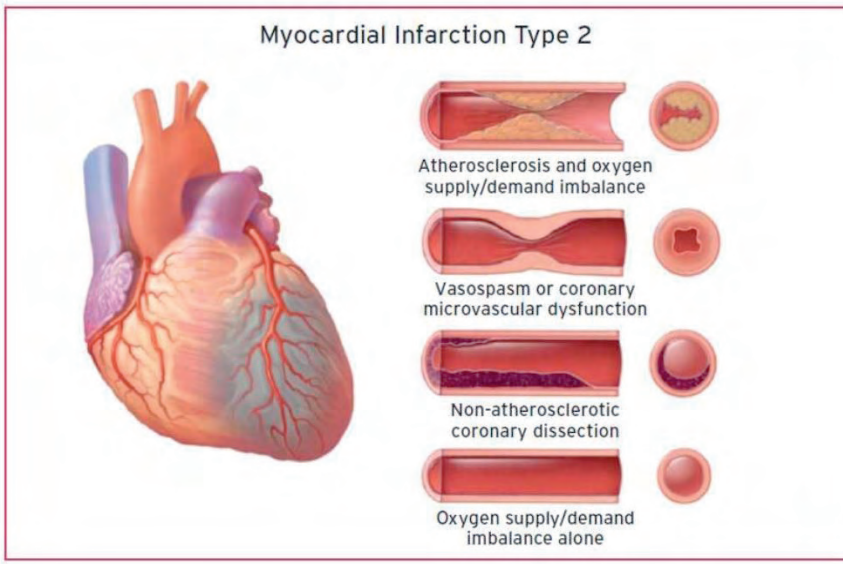
Type 1 MI



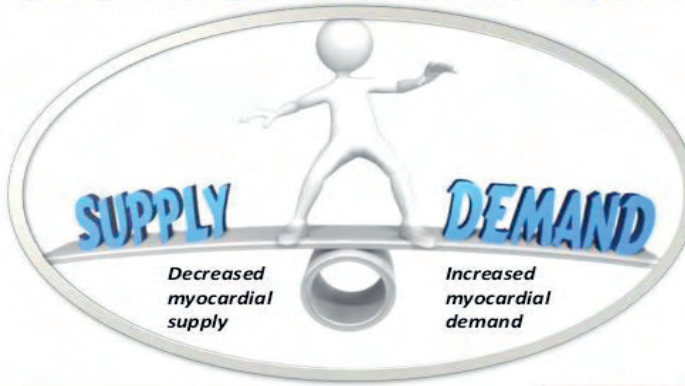
It is essential to integrate the ECG findings with the aim of classifying type 1 MI into **STEMI** or **NSTEMI** in order to establish the appropriate treatment according to current Guidelines

The criteria for type 1 MI includes detection of a rise and/or fall of cTn with at least one value above the 99th percentile and with at least one of the following:

- ***Symptoms of acute myocardial ischemia;***
- ***New ischemic electrocardiographic (ECG) changes;***
- ***Development of pathological Q waves;***
- ***Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology;***
- ***Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.***



Instigating Factors for Type 2 Myocardial Infarction



- Hypotension
- Anemia
- Hypoxia
- Coronary vasospasm

- Hypotension
- Sepsis
- Tachyarrhythmia
- Hypertension
- Thyrotoxicosis

The criteria for type 2 MI includes detection of a rise and/or fall of cTn with at least one value above the 99th percentile and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following:

- **Symptoms of acute myocardial ischemia;**
- **New ischemic ECG changes;**
- **Development of pathological Q waves;**
- **Imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.**

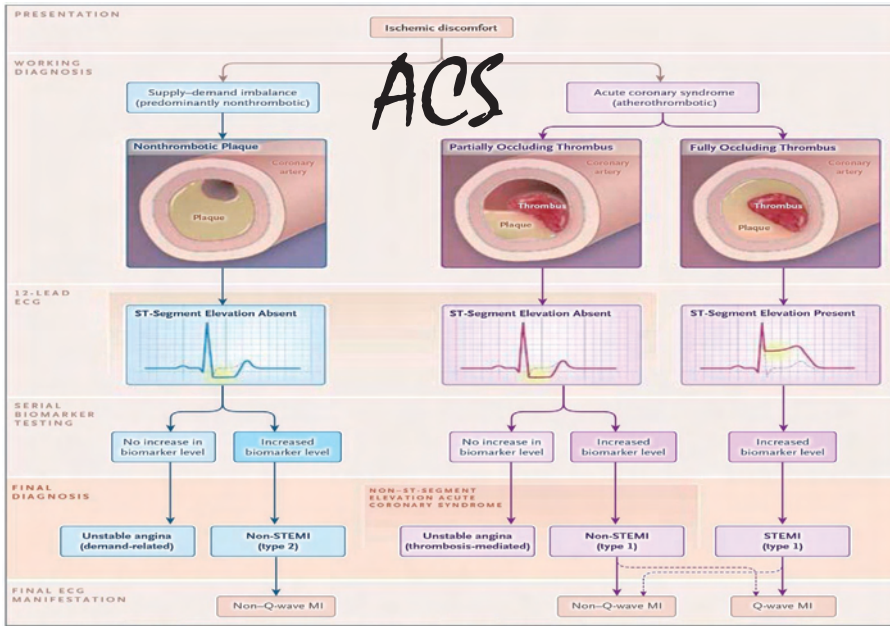
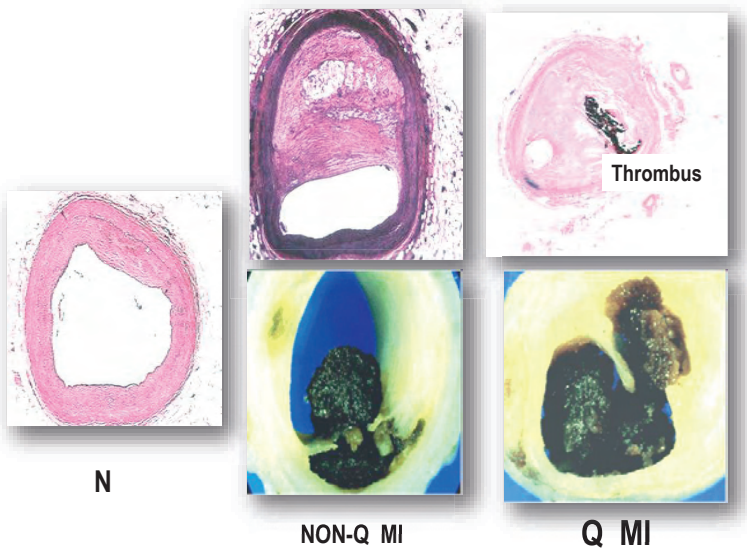


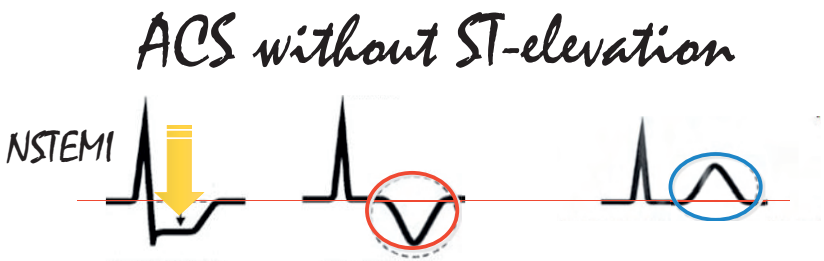
Figure 1. Spectrum of Pathologic and Clinical ST-Segment Elevation Acute Myocardial Infarction (STEMI) and Non-STEMI Acute Coronary Syndromes.
Adapted from Morrow.[10] ECG denotes electrocardiogram, and MI myocardial infarction.

Evaluation

10 min !

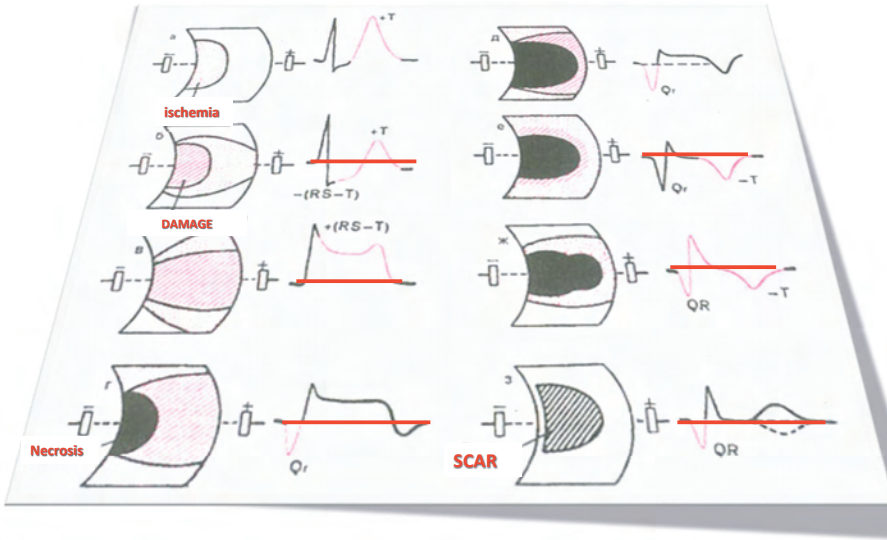
- In general, **evaluation begins** with ambulatory electrocardiography (ECG)


Thrombus
N
NON-Q MI
Q MI


ACS without ST-elevation
NSTEMI


ACS with ST-elevation
STEMI
Q!

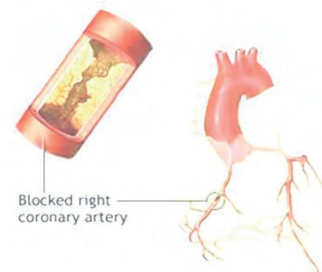
MI, ECG-evolution



Myocardial Infarction

Definition: MI, also known as "heart attack," is the death of cardiac muscle resulting from ischemia.

Risks are the same as those of coronary atherosclerosis.



Pathogenesis of MI

Most common cause is thrombosis on a preexisting disrupted atherosclerotic plaque. In the typical case of MI, the following sequence of events can be proposed:

1. The initial event is a sudden change in the structure of an atheromatous plaque, that is, disruption as intraplaque hemorrhage, ulceration, or rupture.
2. Exposure of the thrombogenic subendothelial basement membrane and necrotic plaque contents resulting in thrombus formation.
3. Frequently within minutes, the thrombus evolves to completely occlude the lumen of the coronary vessel.

MI: common location in the right dominent coronary artery heart (90% of population)

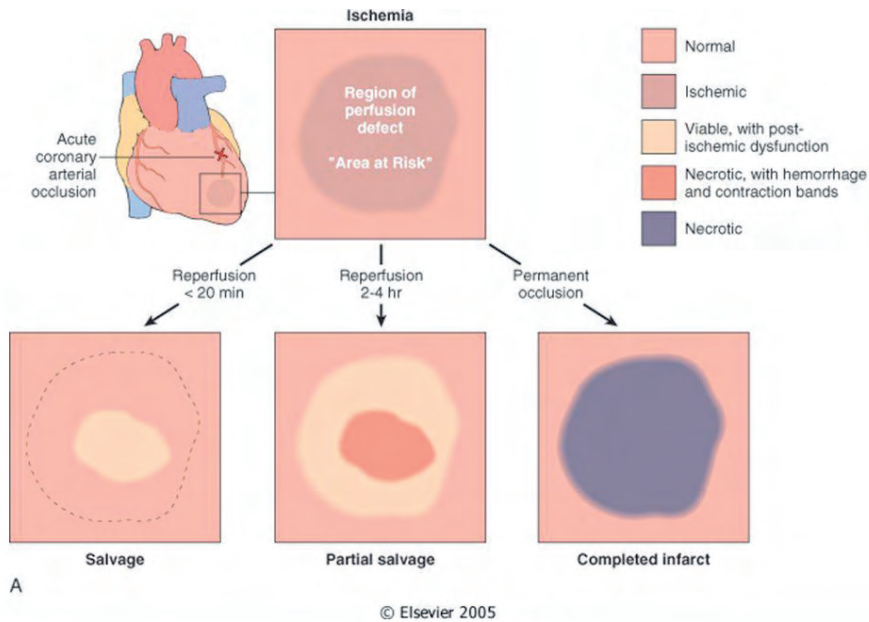
- **Left anterior descending(40-50%):** it supplies the anterior left ventricle, apex and anterior two thirds of interventricular septum.
- **Right coronary artery(30-40%):** it supplies the posterior wall of the left ventricle, posterior one third of interventricular septum.
- **Left circumflex (about 20%)**: it supplies the lateral wall of left ventricle.

Pathogenesis of MI

Myocardial necrosis begins within 20-30 minutes, mostly starting at the subendocardial region (less perfused, high intramural pressure).

Infarct reaches its full size within 3-6 hrs., during this period, lysis of the thrombus by streptokinase or tissue plasminogen activator, may limit the size of the infarct.

Irreversible cell injury: 20-40 min



Pathogenesis of MI

The precise location, size, and specific morphologic features of an acute myocardial infarct depend on:

1. The location, severity, and rate of development of coronary atherosclerotic obstructions
2. The size of the area supplied by the obstructed vessels
3. The duration of the occlusion
4. The oxygen needs of the myocardium at risk
5. The extent of collateral blood vessels
6. Other factors, such as blood vessel spasm, alterations in blood pressure, heart rate, and cardiac rhythm.
7. In addition reperfusion may limit the size of the infarct.

IHD: MI types

Transmural

- Full thickness (>50% of the wall)

Subendocardial

- Inner 1/3 of myocardium

Myocardial Infarction: Morphology

Coagulative necrosis and inflammation.

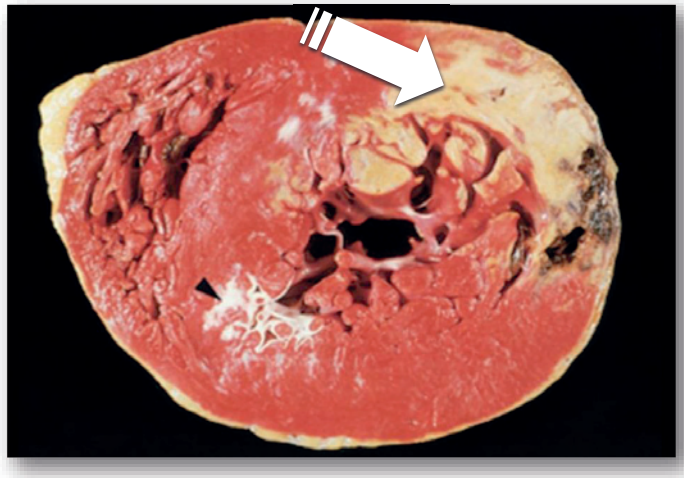
Formation of granulation tissue.

Organization of the necrotic tissue to form a fibrous scar.

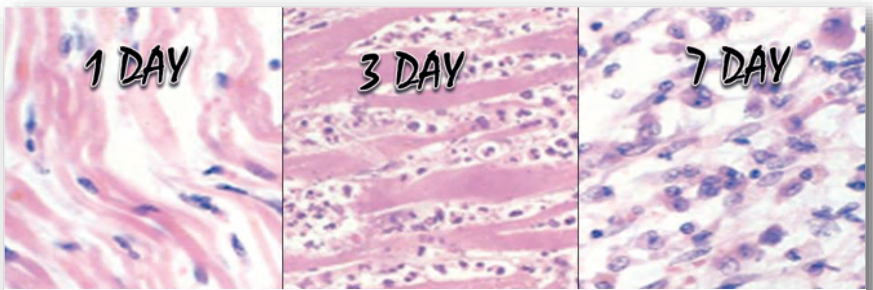
Myocardial Infarction: Morphology

Time	Gross changes	Microscopic changes
0-4h	None	None
4-12h	Mottling	Coagulation necrosis
12-24h	Mottling	More coagulation necrosis; neutrophils come in
1-7 d	Yellow infarct center	Neutrophils die, macrophages come to eat dead cells
1-2 w	Yellow center, red borders	Granulation tissue
2-8 w	Scar	Collagen

Acute myocardium infarction



Myocardial Infarction:

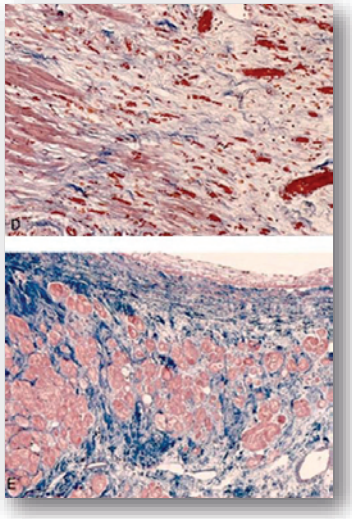


A. One-day-old infarct showing coagulative necrosis, wavy fibers with elongation, and narrowing, compared with adjacent normal fibers (lower right). Widened spaces between the dead fibers contain edema fluid and scattered neutrophils.

B. Dense polymorphonuclear leukocytic infiltrate in an area of acute myocardial infarction of 3 to 4 days' duration.

C. Nearly complete removal of necrotic myocytes by phagocytosis (approximately 7 to 10 days).

Myocardial Infarction:



D. Granulation tissue with a rich vascular network and early collagen deposition, approximately 3 weeks after infarction.

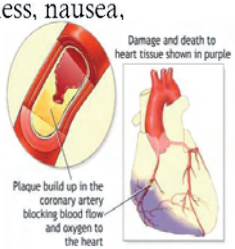
E. Well-healed myocardial infarct with replacement of the necrotic fibers by dense collagenous scar. A few residual cardiac muscle cells are present. (In D and E, collagen is highlighted as blue in this Masson trichrome stain.)

Myocardial Infarction: Clinical Features

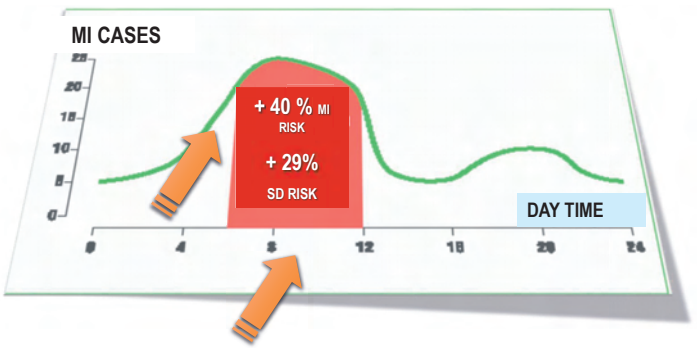
- Pain:
  - Severe crushing sub-sternal chest pain, which may radiate to the neck, jaw, epigastrium, shoulder or left arm.
  - Pain lasts for hours to days and is not relieved by nitroglycerin.
  - Absent in 20-30% of patients (diabetics, hypertensive, elderly).
- Pulse is rapid and weak.
- Diaphoresis (sweating)
- Dyspnea.
- Cardiogenic shock in massive MI(>40%of lt. ventricle).
- ECG shows typical findings of ischemia.

MI: Symptoms

- Major symptom = chest pain
  - Tight band around chest, bad indigestion, something heavy sitting on chest, squeezing or heavy pressure
- Other symptoms include:
  - Anxiety, cough, fainting, light headedness, dizziness, nausea, vomiting, palpitations and sweating.
- "Silent" heart attacks have no symptoms

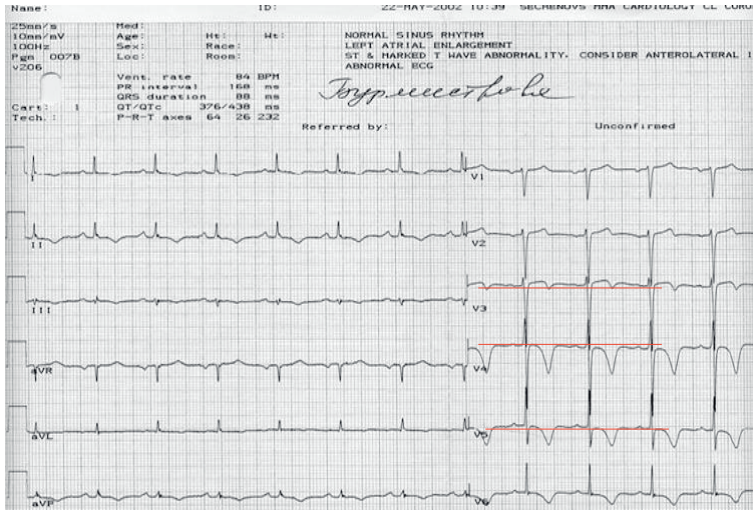


«TIME of EVENTS»

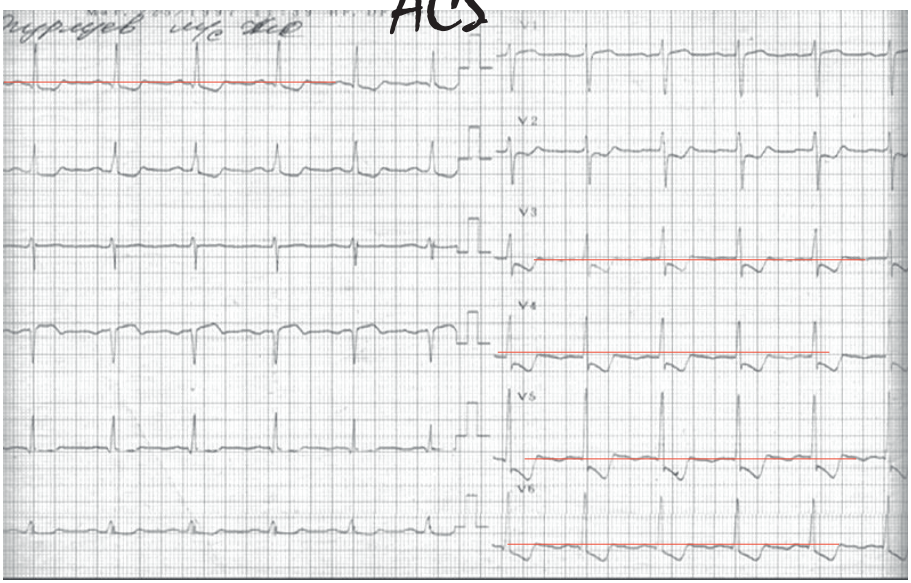


Elliot WJ. Cyclic and circadian variations in cardiovascular events. Am J Hypertens.2001,14:291S-295S

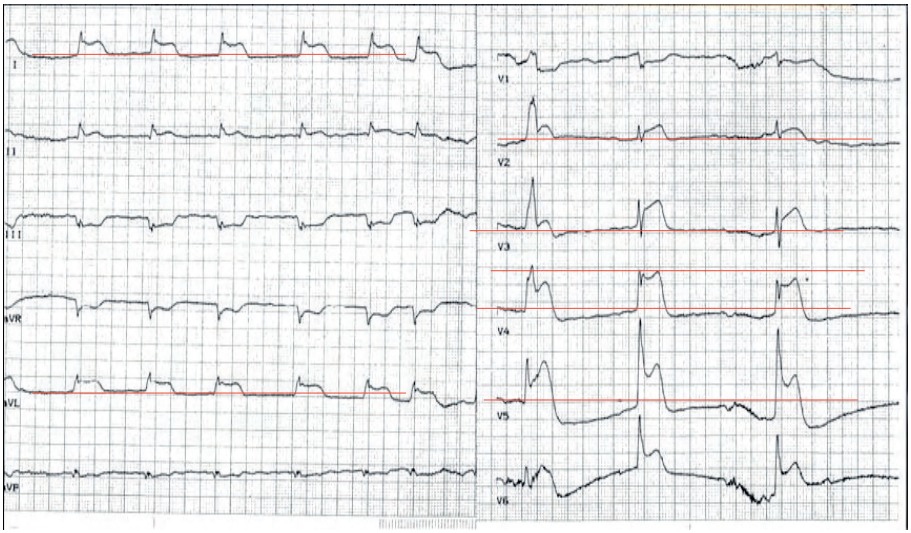
ACS


Name:
ID:
25mm/s
10mm/mV
100Hz
Pge 007B
v206
Med:
Age:
Sex:
Loc:
Ht:
Wt:
Race:
Room:
Vent. rate 84 BPM
PR interval 168 ms
QRS duration 88 ms
QT/QTc 376/438 ms
P-R-T axes 64 26 232
NORMAL SINUS RHYTHM
LEFT ATRIAL ENLARGEMENT
ST & MARKED T WAVE ABNORMALITY. CONSIDER ANTEROLATERAL I
ABNORMAL ECG
Referred by:
Unconfirmed
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6

ACS


V1
V2
V3
V4
V5
V6

ACS



MI: Outcomes or complications

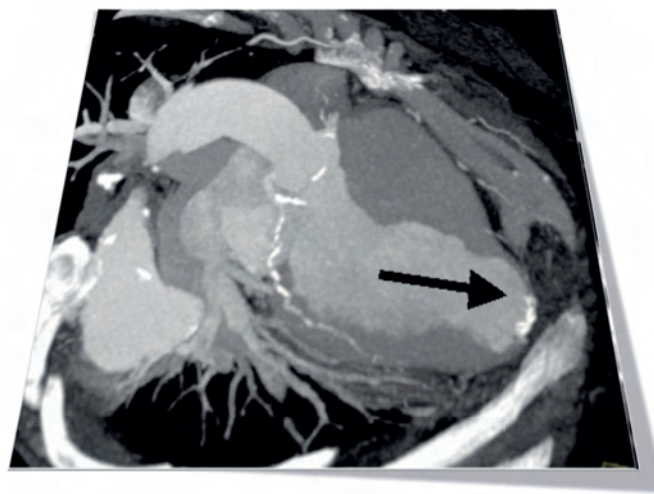
No complications in 10-20%.

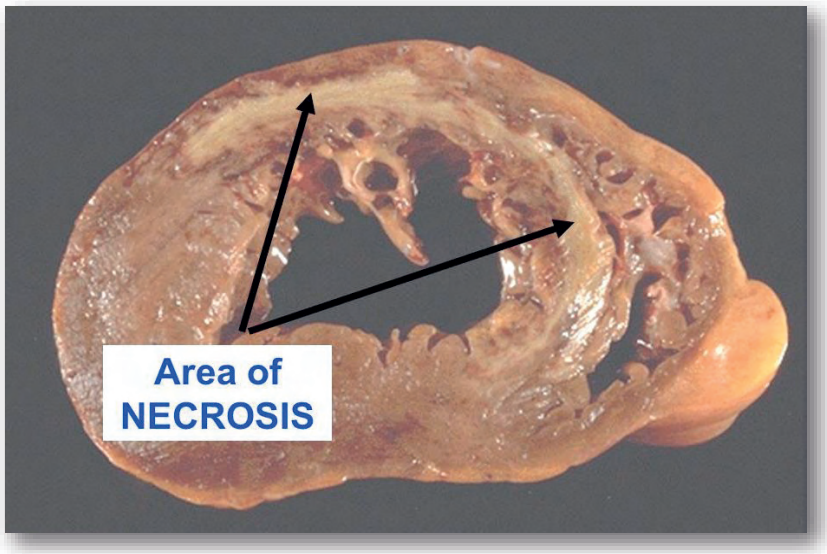
80-90% experience one or more of the following complications:

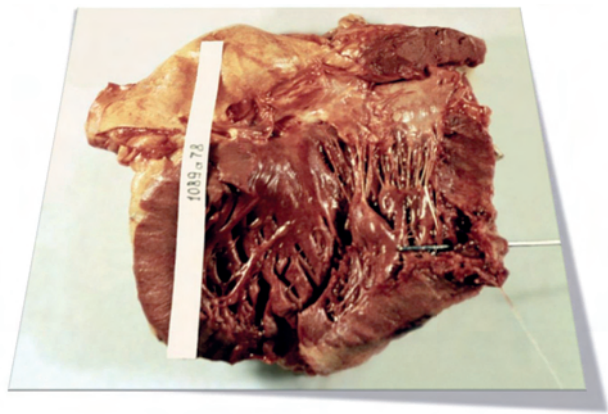
1. Cardiac arrhythmia (75-90%). Many patients have conduction disturbances and myocardial irritability following MI, which undoubtedly are responsible for many of the sudden deaths. Sudden coronary death can occur due to ventricular arrhythmia.
2. Left ventricular failure with mild to severe pulmonary edema (60%).
3. Cardiogenic shock (10%).

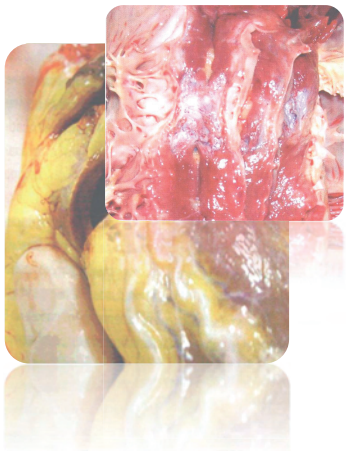
MI: complications

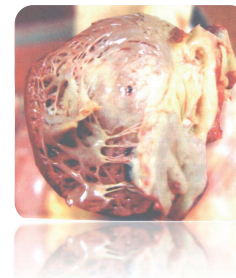
4. Myocardial rupture: Rupture of free wall, septum, papillary muscle (leading to papillary muscle dysfunction)
5. Thromboembolism (15-49%). the combination of a local myocardial abnormality in contractility (causing stasis) with endocardial damage (causing a thrombogenic surface) can foster mural thrombosis and, potentially, thromboembolism
6. Pericarditis
7. Infarct extension and expansion
8. Ventricular aneurysm in which the ventricle is dilated and the wall is thinned out.
9. External rupture of the infarct with associated bleeding into the pericardial space (hemopericardium).
10. Progressive late heart failure in the form of chronic IHD.




Area of
NECROSIS







MI: SUMMERY

Necrosis of heart muscle caused by ischemia

Most due to acute coronary artery thrombosis

- sudden plaque disruption
- platelets adhere
- coagulation cascade activated
- thrombus occludes lumen within minutes
- irreversible injury/cell death in 20-40 minutes

Prompt reperfusion can salvage myocardium

MI: SUMMERY

Clinical features
- Severe, crushing chest pain ± radiation
- Not relieved by nitroglycerin, rest
- Sweating, nausea, dyspnea
- Sometimes no symptoms

Laboratory evaluation
- Troponins increase within 2-4 hours, remain elevated for a week.
- CK-MB increases within 2-4 hours, returns to normal within 72 hours.

Complications
- contractile dysfunction
- arrhythmias
- rupture
- chronic progressive heart failure

Prognosis
- depends on remaining function and perfusion
- overall 1 year mortality: 30%
- 3-4% mortality per year thereafter

Chronic Ischemic Heart Disease

- Progressive heart failure due to ischemic injury, either from:
  - prior infarction(s) (most common)
  - chronic low-grade ischemia
- Unexpected death from cardiac causes either without symptoms or within 1 to 24 hours of symptom onset
- Results from a fatal arrhythmia, most commonly in patients with severe coronary artery disease

BE HEALTHY!!!

REFERENCES

Kovalyova O.N., Ashcheulova T.V. Propedeutics to Internal Medicine. Part 2. – Vinnytsya: NOVA KNYHA, 2017. – 264 p.

Kovalyova O.N., Asheulova T.V. General inspection: manual for students. – Kharkov: "Turbo". – 2004. – 60p.

Khomazjuk V.A., Ostashevska T.G., Krasyuk I.V. Propaedeutics of Internal Medicine and Patient Care: Study guide for the practical classes. Part I. – Kyiv: NMU, 2005. – 44 p.

KovalyovaO.N., AsheulovaT.V., ShapovalovaS.A. Instrumental methods examination of cardiovascular system: manual for students. – Kharkov: KSMU. – 2004. – 147p.

Bickley, Lynn S.; Szilagyi, Peter G. Bates' Guide to Physical Examination and History Taking, 10th Edition. – 934 p. Copyright ©2009 Lippincott Williams & Wilkins
The Point online resources, http://thepoint.lww.com

LECTURE # 13

HEART FAILURE SYNDROME

THE PLAN

- Definition
- Prevalence of HF
- "Therapeutic" Phenotypes
- Risk factors
- Pathophysiology of heart failure - Venn diagram
- Heart failure types
- Low cardiac output
- High-output failure
- Diastolic and systolic dysfunction
- EF
- ACC&AHA classification of HF
- New York Heart Association
- Acute and chronic heart failure. Definition. Types
- Investigations
- References

Definition

Heart failure is a serious condition in which the heart is unable to pump enough blood to meet the needs of the body. Although often life threatening, the typical symptoms of heart failure (breathlessness, swollen limbs and fatigue) are usually less dramatic than those associated with a heart attack. In economically developed countries, up to one person in five is expected to develop heart failure at some point in their life,[1] and even more people will be affected as family members, friends or healthcare professionals.

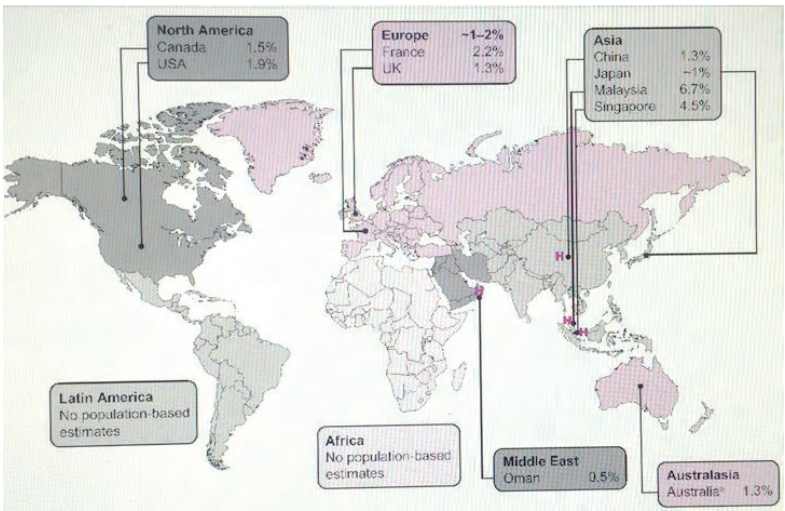
Patient perspective[4]

"When you have heart problems, you always worry [that] the next breath is your last one. That's something you never know."

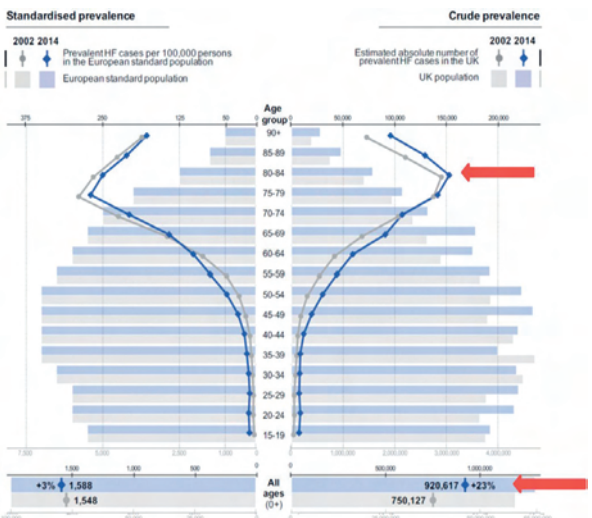
Heart failure survival rates remain poor across the globe

Across the globe, 17–45% of patients admitted to hospital with heart failure die within 1 year of admission and the majority die within 5 years of admission (Figure 2).[3–24]

Proportion of the population living with HF across the globe



Changing prevalence of heart failure in the United Kingdom between 2002 and 2014 obtained from a primary-care ...



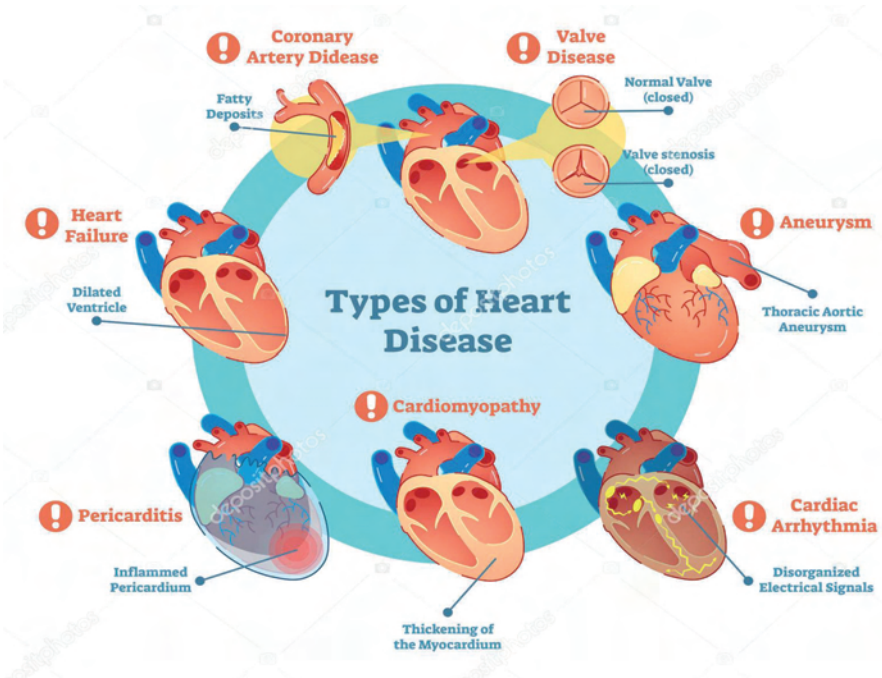
European Heart Journal, Volume 40, Issue 8, 21 February 2019, Pages 651–661, https://doi.org/10.1093/eurheartj/ehz010

Almost all forms of heart disease can lead to HF.

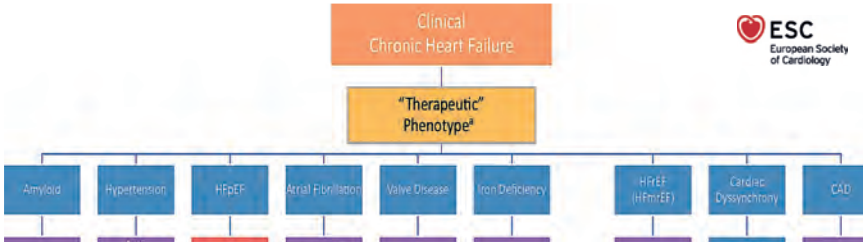
An accurate etiological diagnosis is important

because in some situations a specific remedy

may be available



Take home figure Heart failure, classified by 'therapeutic' phenotypes

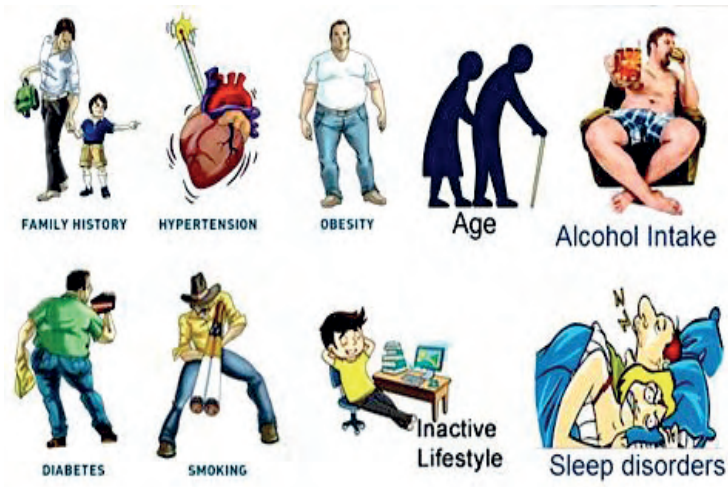


"Therapeutic" Phenotypes

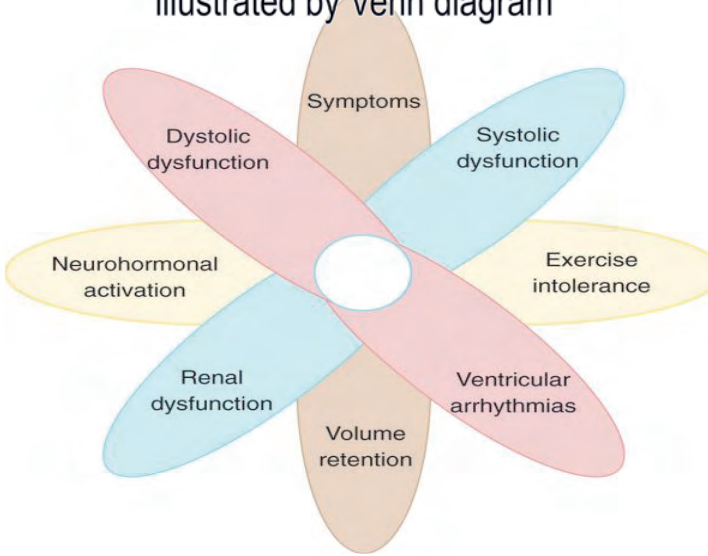
European Heart Journal, Volume 40, Issue 8, 21 February 2019, Pages 651–661, https://doi.org/10.1093/eurheartj/ehz010

OXFORD UNIVERSITY PRESS

Risk factors

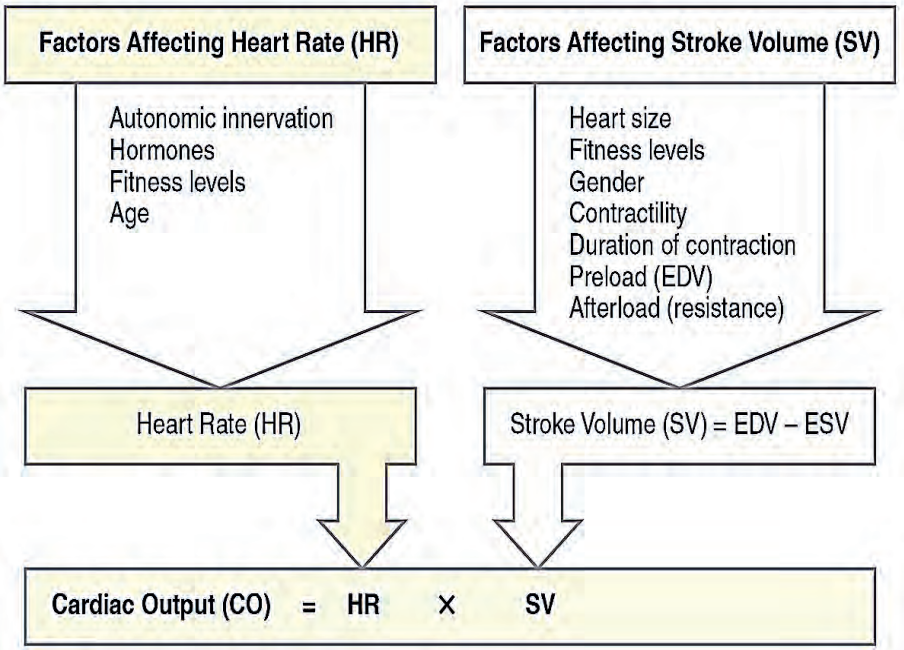


Pathophysiology of heart failure, illustrated by Venn diagram



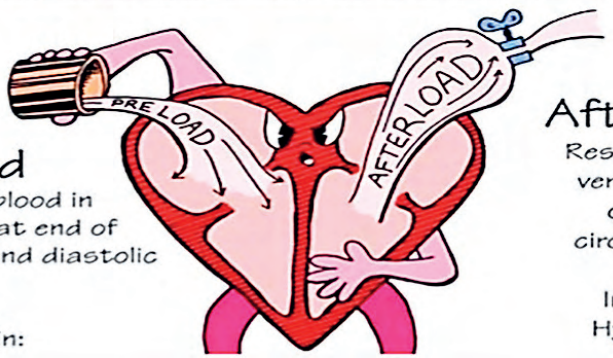
Heart failure is divided into the following types:

- Left-sided heart failure
- Right-sided heart failure
- Global heart failure
- Systolic heart failure
- Diastolic heart failure
- Chronic heart failure
- Acute heart failure



NB!

PRELOAD AND AFTERLOAD



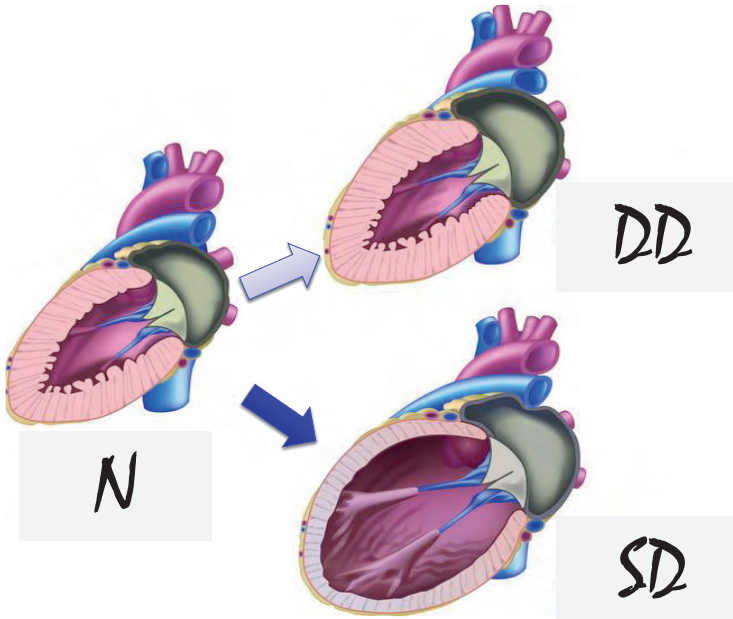
Preload
Volume of blood in ventricles at end of diastole (end diastolic pressure)

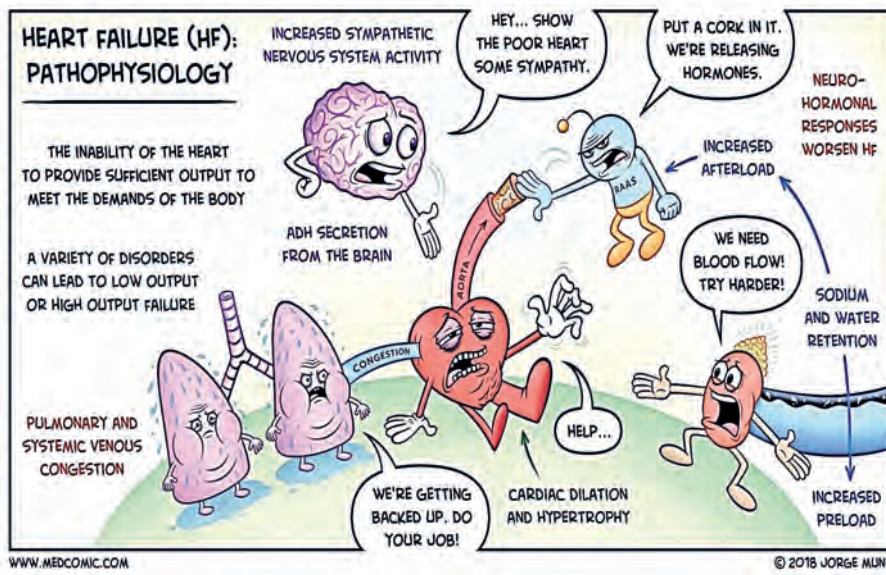
Increased in:

Afterload
Resistance left ventricle must overcome to circulate blood

Increased in:
Hypertension

this is the basis of Starling's law


DD
N
SD


HEART FAILURE (HF): PATHOPHYSIOLOGY
THE INABILITY OF THE HEART TO PROVIDE SUFFICIENT OUTPUT TO MEET THE DEMANDS OF THE BODY
A VARIETY OF DISORDERS CAN LEAD TO LOW OUTPUT OR HIGH OUTPUT FAILURE
INCREASED SYMPATHETIC NERVOUS SYSTEM ACTIVITY
ADH SECRETION FROM THE BRAIN
HEY... SHOW THE POOR HEART SOME SYMPATHY.
PUT A CORK IN IT. WE'RE RELEASING HORMONES.
NEURO-HORMONAL RESPONSES WORSEN HF
INCREASED AFTERLOAD
WE NEED BLOOD FLOW! TRY HARDER!
SODIUM AND WATER RETENTION
INCREASED PRELOAD
CONGESTION
PULMONARY AND SYSTEMIC VENOUS CONGESTION
HELP...
CARDIAC DILATION AND HYPERTROPHY
WE'RE GETTING BACKED UP. DO YOUR JOB!
WWW.MEDCOMIC.COM
© 2018 JORGE MUNIZ

Low cardiac output

A low cardiac output causes

- fatigue,
- listlessness,
- and a poor effort tolerance,
- the peripheries are cold and the BP is low.

- To maintain perfusion of vital organs, blood flow is diverted away from skeletal muscle and this may contribute to fatigue and weakness.
- Poor renal perfusion leads to oliguria and uraemia

High-output failure

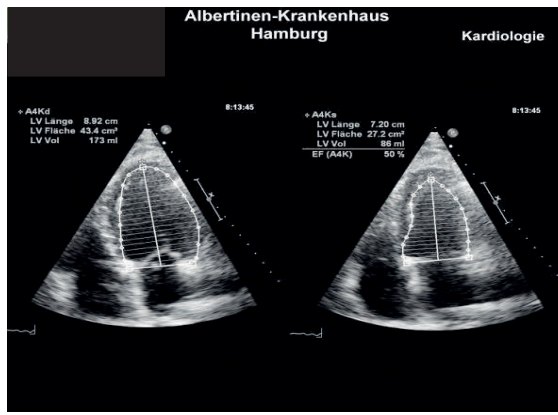
Conditions such as large arteriovenous shunt, beri-beri, severe anaemia or thyrotoxicosis can occasionally cause heart failure due to an excessively high cardiac output

Diastolic and systolic dysfunction

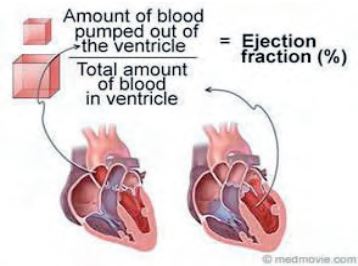
EF?

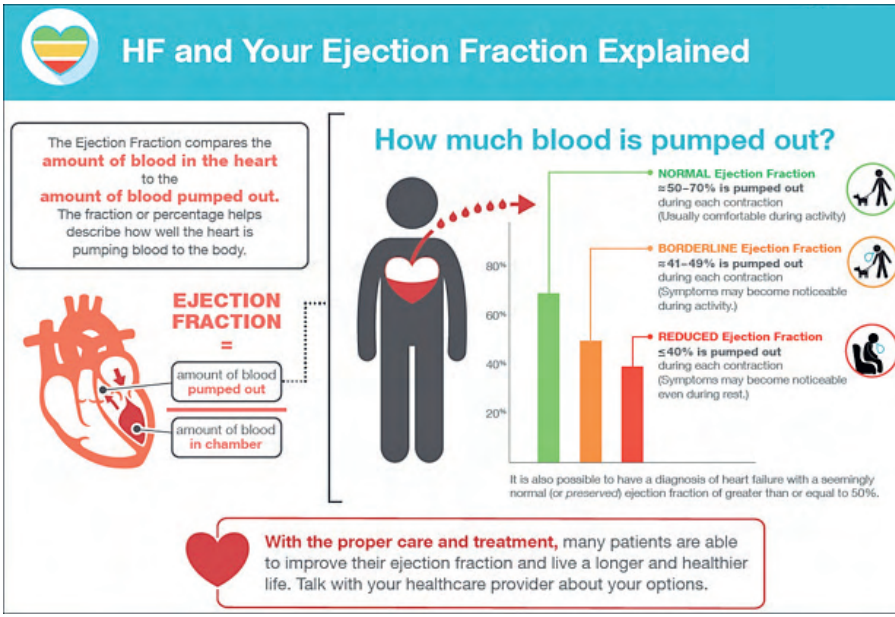
- Heart failure may develop as a result of impaired myocardial contraction (**systolic dysfunction**) but can also be due to poor ventricular filling and high filling pressures caused by abnormal ventricular relaxation (**diastolic dysfunction**). The latter is caused by a stiff non-compliant ventricle and is commonly found in patients with left ventricular hypertrophy

- Systolic and diastolic dysfunction often coexist, particularly in patients with coronary artery disease



EF?

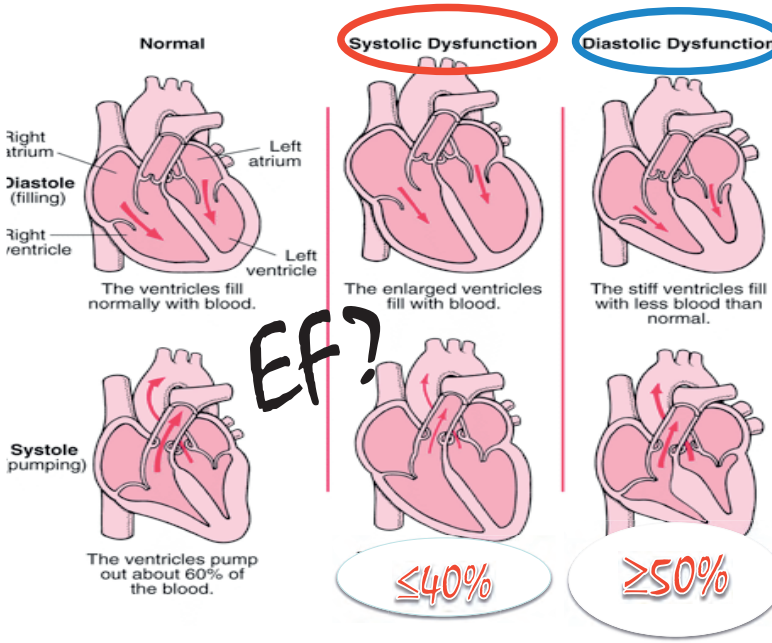




ESC and AHA guideline definitions of heart failure

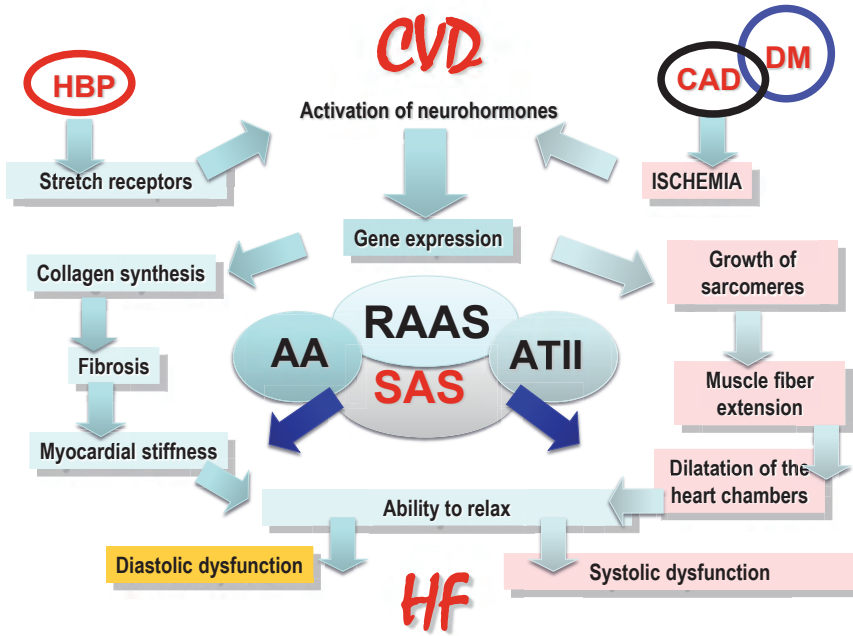
Type of HF	HFrEF	HFmrEF	HFpEF
ESC criteria (Ponikowski et al. 2016)	• LVEF <40% • Symptoms ± signs EF?	• LVEF 40–49% • Symptoms ± signs • Elevated levels of natriuretic peptides; BNP >35 or NT-proBNP ≥125 • Relevant structural heart disease (LVH and/or LAE) or diastolic dysfunction	• LVEF ≥50% • Symptoms ± signs • Elevated levels of natriuretic peptides; BNP >35 or NT-proBNP ≥125 • Relevant structural heart disease (LVH and/or LAE) or diastolic dysfunction
AHA/ ACCFCriteria (Writing Committee et al. 2013)	• LVEF ≤40%	• 41–49%[a]	• LVEF ≥50%

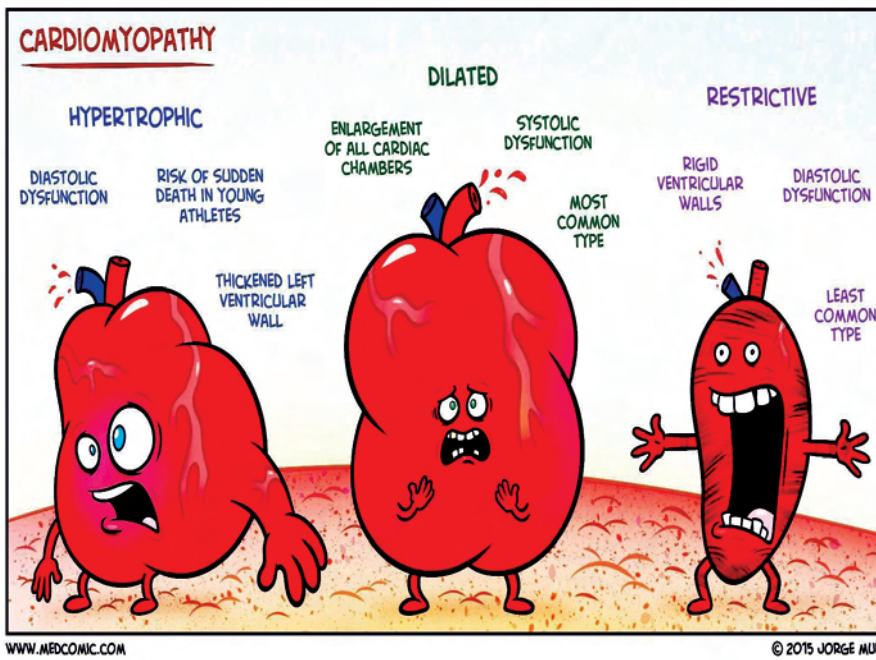
ACC American College of Cardiology, *AHA* American Heart Association, *BNP* B-type Natriuretic Peptide, *ESC* European Society of Cardiology, *HFmrEF* heart failure with mid-range ejection



Systolic versus Diastolic

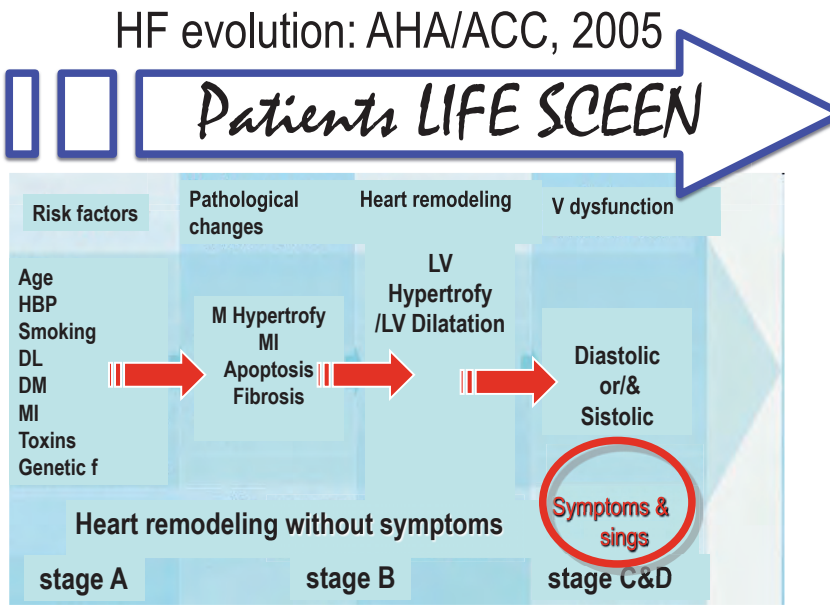
- Systolic – can't pump
- Diastolic – can't fill


CVD
HBP
CAD
DM
Activation of neurohormones
Stretch receptors
ISCHEMIA
Gene expression
Collagen synthesis
Growth of sarcomeres
RAAS
AA
ATII
SAS
Fibrosis
Muscle fiber extension
Myocardial stiffness
Dilatation of the heart chambers
Ability to relax
Diastolic dysfunction
Systolic dysfunction
HF


CARDIOMYOPATHY
HYPERTROPHIC
DILATED
RESTRICTIVE
DIASTOLIC DYSFUNCTION
RISK OF SUDDEN DEATH IN YOUNG ATHLETES
ENLARGEMENT OF ALL CARDIAC CHAMBERS
SYSTOLIC DYSFUNCTION
MOST COMMON TYPE
RIGID VENTRICULAR WALLS
DIASTOLIC DYSFUNCTION
THICKENED LEFT VENTRICULAR WALL
LEAST COMMON TYPE
WWW.MEDCOMIC.COM
© 2015 JORGE MUNIZ

ACC&AHA classification of heart failure

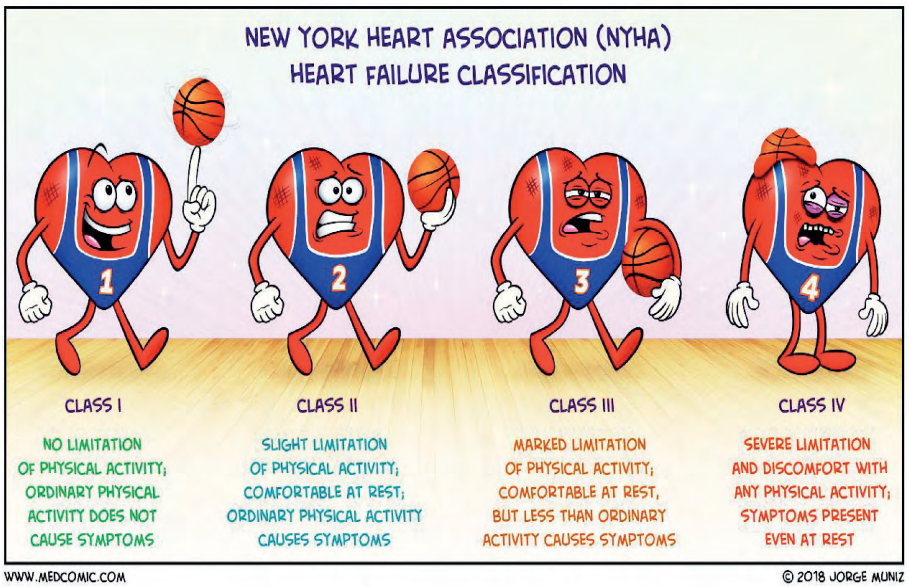
- **Stage A:** Patients at risk for heart failure who have not yet developed structural heart changes (i.e. those with diabetes, those with coronary disease without prior infarct)
- **Stage B:** Patients with structural heart disease (i.e. reduced ejection fraction, left ventricular hypertrophy, chamber enlargement) who have not yet developed symptoms of heart failure
- **Stage C:** Patients who have developed clinical heart failure
- **Stage D:** Patients with refractory heart failure requiring advanced intervention (i.e. biventricular pacemakers, left ventricular assist device, transplantation



New York Heart Association

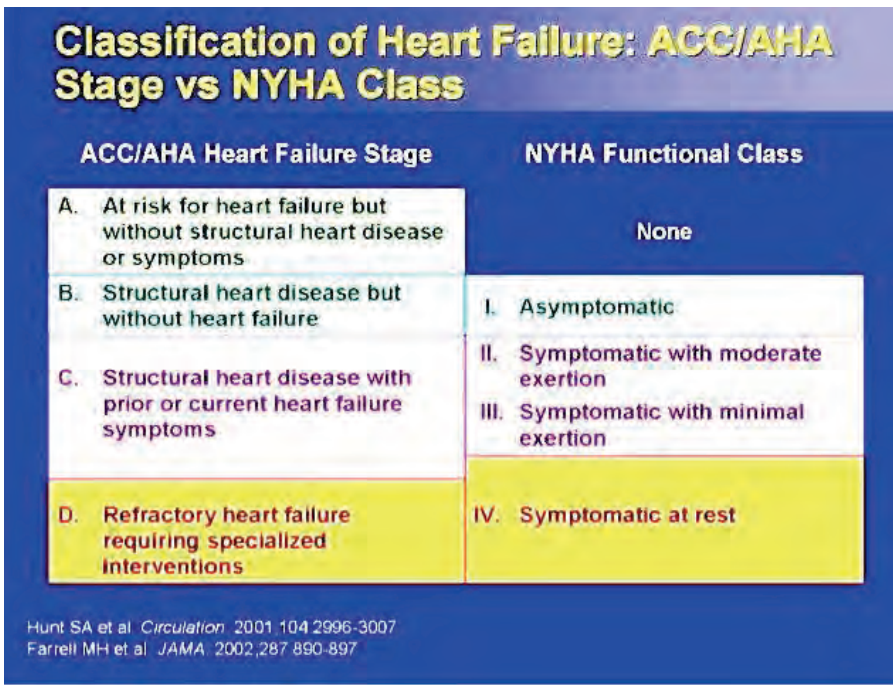
helps to categorize HF

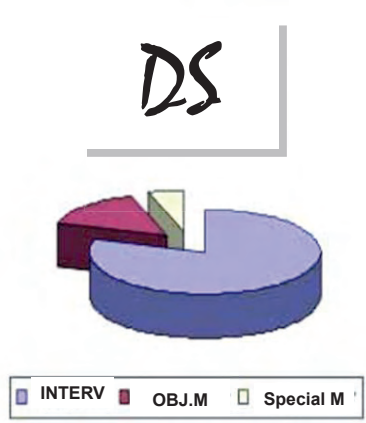
- **Class I:** No symptoms of heart failure
- **Class II:** Symptoms of heart failure with moderate exertion such as ambulating two blocks or two flights of stairs
- **Class III:** Symptoms of heart failure with minimal exertion such as ambulating one block or one flight of stairs, but no symptoms at rest
- **Class IV:** Symptoms of heart failure at rest

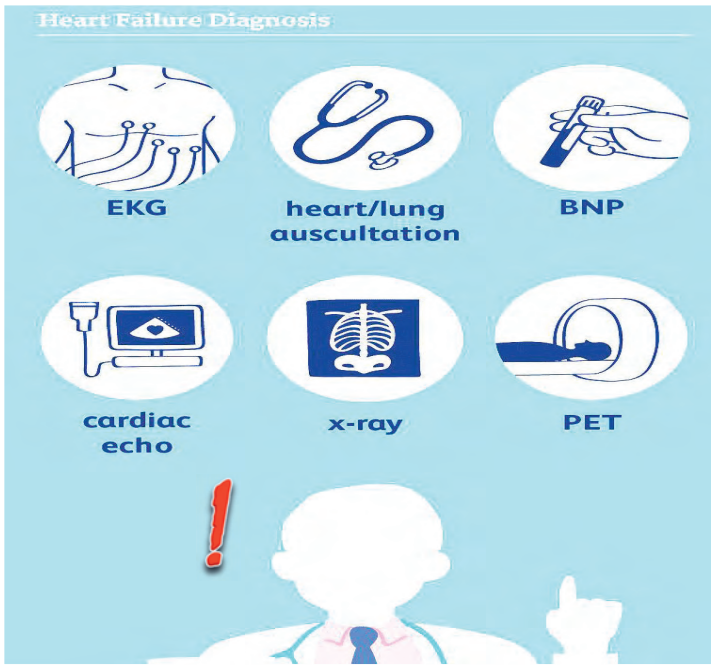


NYHA Class	Physical Activity	2-Year Mortality (%) on ACE-I
I	Asymptomatic (no limitation of physical activity; there is no shortness of breath, fatigue, or palpitations with ordinary physical activity)	10
II	Slight limitation (shortness of breath, fatigue, or palpitations with ordinary physical activity)	20
III	Marked limitation (shortness of breath, fatigue, or palpitations with activities of daily living)	30—40
IV	Symptoms at rest (shortness of breath, fatigue, or palpitations at rest)	40—50

ACE-I, angiotensin-converting enzyme inhibitors; NYHA, New York Heart Association.



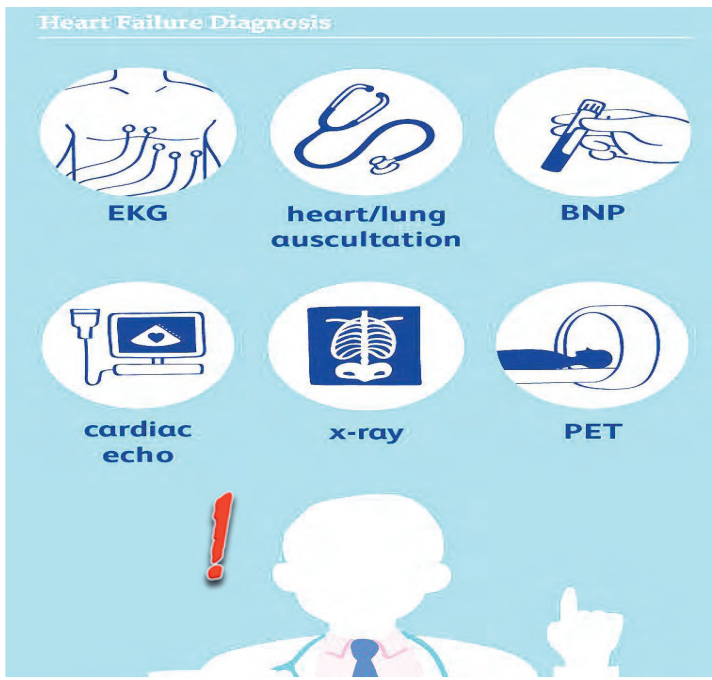

DS
INTERV
OBJ.M
Special M

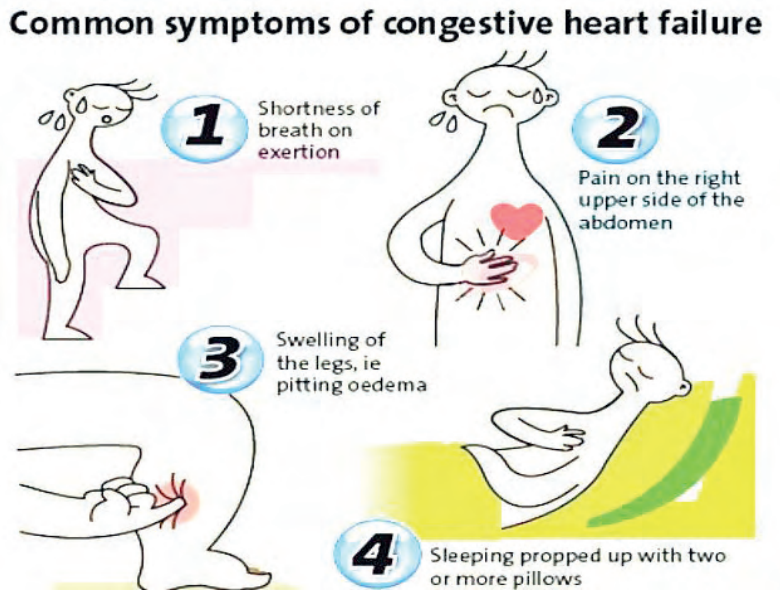

Heart Failure Diagnosis
EKG
heart/lung auscultation
BNP
cardiac echo
x-ray
PET

Acute and chronic heart failure

Heart failure may develop **suddenly**, as in MI, or **gradually**, as in progressive valvular heart disease. When there is gradual impairment of cardiac function, a variety of compensatory changes may take place

Chronic heart failure




Common symptoms of congestive heart failure
1
Shortness of breath on exertion
2
Pain on the right upper side of the abdomen
3
Swelling of the legs, ie pitting oedema
4
Sleeping propped up with two or more pillows


Shortness of breath
Swelling of feet & legs
Chronic lack of energy
Difficulty sleeping at night due to breathing problems
Swollen or tender abdomen with loss of appetite
Cough with frothy Sputum
Increased urination at night
Confusion and/or impaired memory

Chronic heart failure

Chronic heart failure is the most common cardiac cause of chronic dyspnoea.

Symptoms may first present on moderate exertion, such as walking up a steep hill, and may be described as a difficulty in **'catching my breath'**.

As heart failure progresses, the dyspnoea is **provoked by less exertion** and ultimately the patient may be *breathless walking from room to room, washing, dressing or trying to hold a conversation*

Breathlessness (dyspnea)

Dyspnoea of cardiac origin may vary in severity from an uncomfortable awareness of breathing to a frightening sensation of **'fighting for breath'.**

The sensation of dyspnoea originates in the cerebral cortex

Breathlessness (dyspnea)

There are several causes of cardiac dyspnea:

- **acute left heart failure,**
- **chronic heart failure,**
- **arrhythmia and**
- **angina equivalent**

Chronic heart failure

Other symptoms may include:

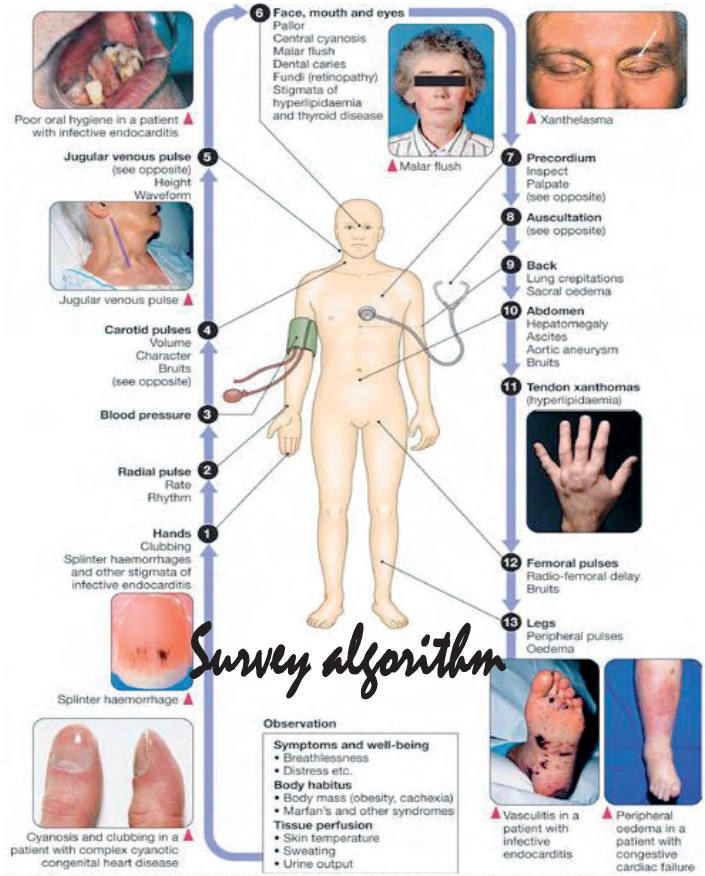
Orthopnea. Lying down increases the venous return to the heart and provokes breathlessness. Patients may prop themselves up with pillows to prevent this

Paroxysmal nocturnal dyspnea. In patients with severe heart failure, fluid shifts from the interstitial tissues of the peripheries into the circulation within 1-2 hours of lying down. Pulmonary edema supervenes, causing the patient to wake and sit upright, profoundly breathless

Cheyne-Stokes respiration. This cyclical pattern of respiration is due to impaired responsiveness of the respiratory centre to carbon dioxide and occurs in severe left ventricular failure. The pattern of slowly diminishing respiration, leading to apnea, followed by progressively increasing respiration and hyperventilation, may be accompanied by a sensation of breathlessness and panic during the period of hyperventilation. The Cheyne-Stokes cycle length is a function of the circulation time. The condition can also occur in diffuse cerebral atherosclerosis, stroke or head injury, and may be exaggerated by sleep, barbiturates and opiates

Arrhythmia

Any arrhythmia may cause breathlessness but usually does so only if the heart is structurally abnormal, such as with the onset of atrial fibrillation in a patient with mitral stenosis



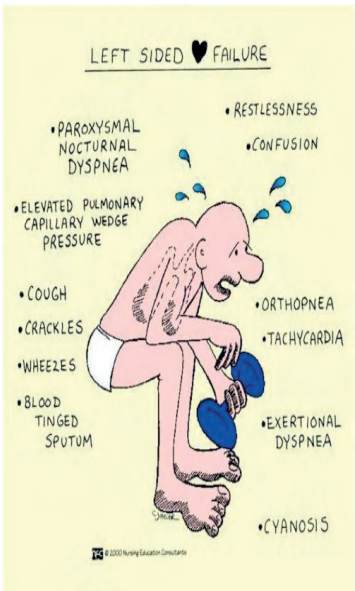
Left versus Right Failure

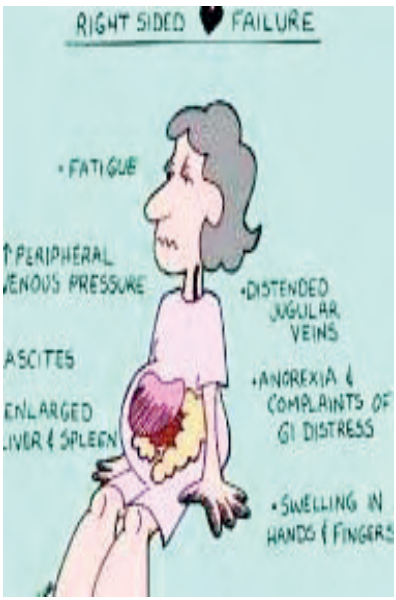
Left Heart Failure

- Dyspnea
- Decrease exercise tolerance
- Cough
- Orthopnea
- Pink, frothy sputum

Right Heart Failure

- Decrease exercise tolerance
- Edema
- Hepatomegaly
- Ascites





Definition

1. **Left-sided heart failure:** Fluid collects in the lungs makes it more difficult for the airways to expand as a person inhales. Breathing becomes more difficult and the person may feel short of breath, particularly with activity or when lying down.
2. **Right-sided heart failure:** Fluid begins to collect in the feet and lower legs (pitting edema). With pitting edema, a finger pressed on the swollen leg leaves an imprint. Non-pitting edema is not caused by heart failure. As the right heart failure worsens, the upper legs swell and eventually the abdomen collects fluid (ascites). Weight gain accompanies the fluid retention.

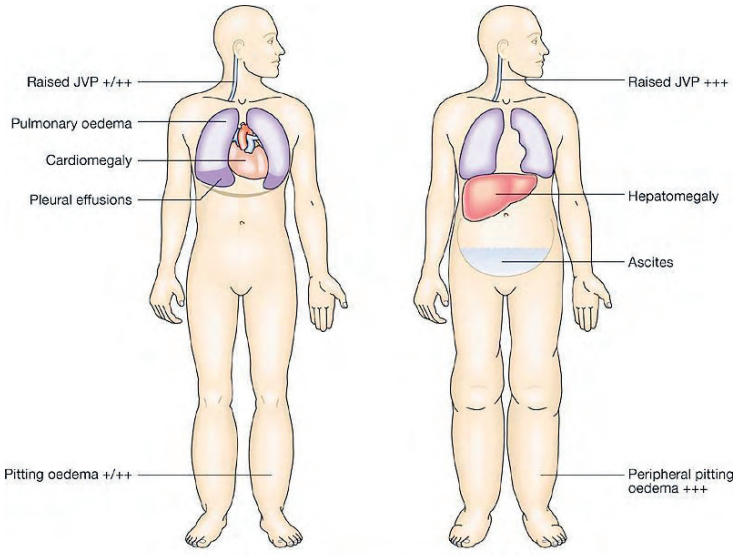
Definition

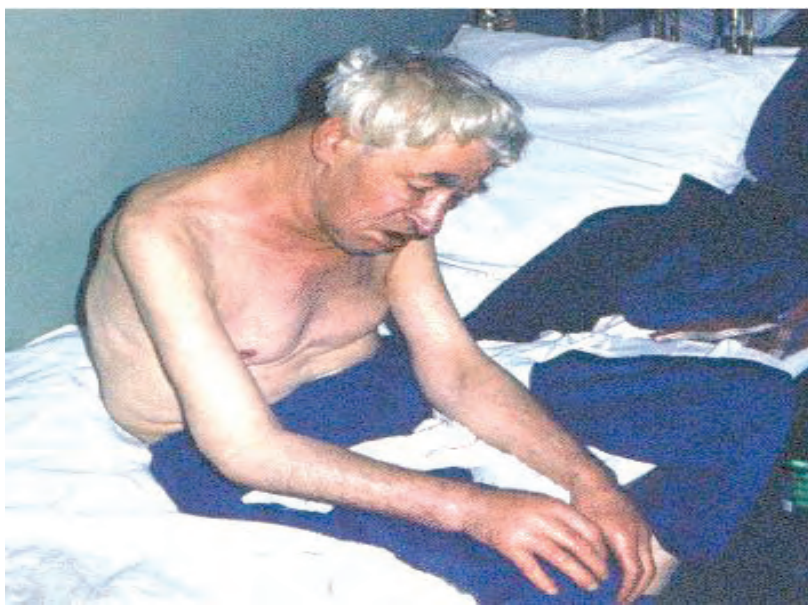
Pulmonary edema due to left-sided HF presents as described above and with inspiratory crepitations over the lung bases.

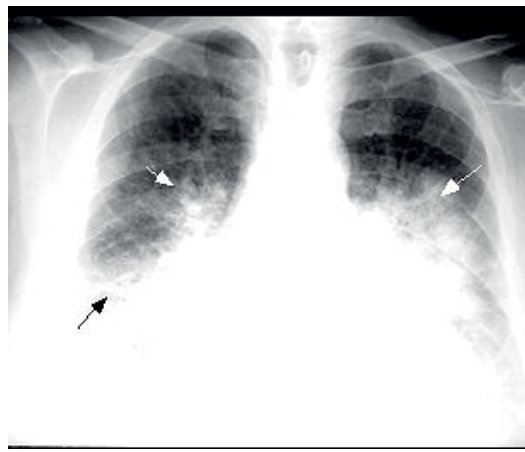
In contrast, right-sided HF produces a high JVP with hepatic congestion and dependent peripheral edema. In ambulant patients, the edema affects the ankles, whereas in bed-bound patients it collects around the thighs and sacrum. Ascites or pleural effusion occurs in some cases. Heart failure is not the only cause of edema

Clinical features of left and right heart failure

(JVP = jugular venous pressure)

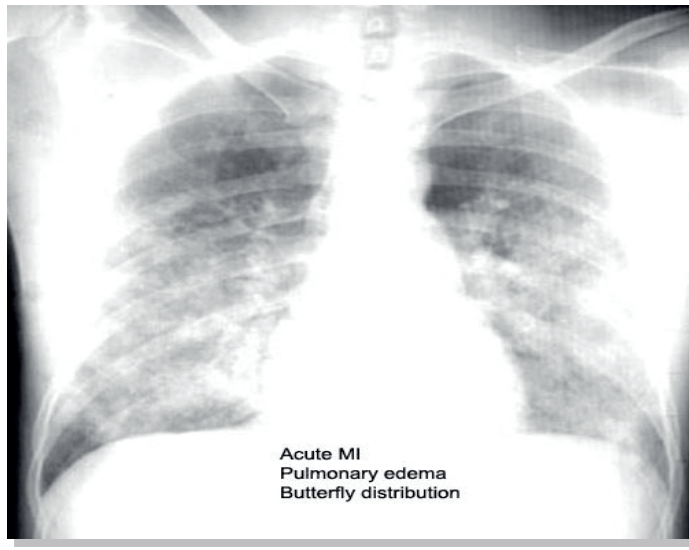






Severe heart failure This chest radiography shows severe heart failure with cardiomegaly, pulmonary vascular congestion with infiltrates in the mid lung fields (white arrow), and a small pleural effusion (black arrow). Courtesy of Jonathan Kruskal, MD.

Acute Left sided heart failure



Right sided heart failure

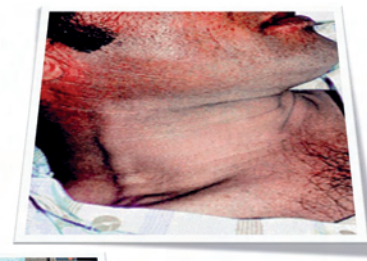
Right heart failure occurs when the cardiac output from the right ventricle is not able to meet the demands of the body

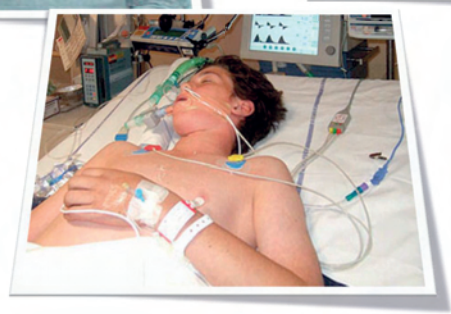
The most common cause of right sided HF is left sided HF

- **Ventricle fails, the pressures increase and transmit to the left atrium, the pulmonary veins, the pulmonary arterial system and eventually into the right heart. This can cause right heart failure. There are multiple causes of left heart failure as described in the systolic congestive heart failure review**

- **Causes of isolated right heart failure include severe lung disease (resulting in severe pulmonary hypertension), pulmonic/tricuspid valve disease, primary pulmonary hypertension, chronic pulmonary embolism, sleep related breathing disorders (obstructive sleep apnea) or right ventricular infarction**

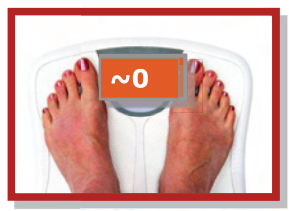
Acute Right sided heart failure



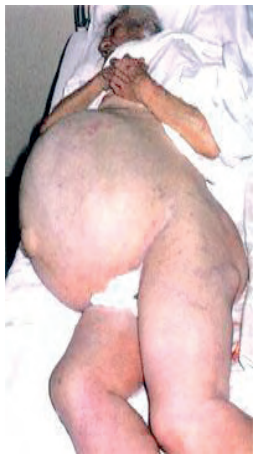


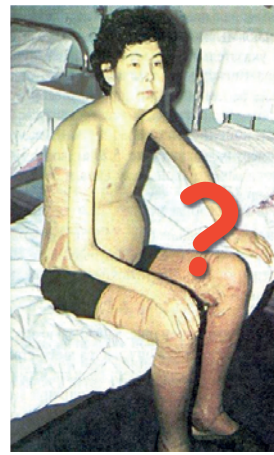
MONITORING ALGORITHM

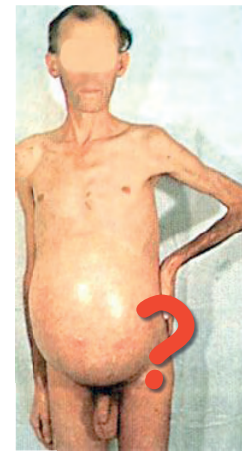
N



of water balance study

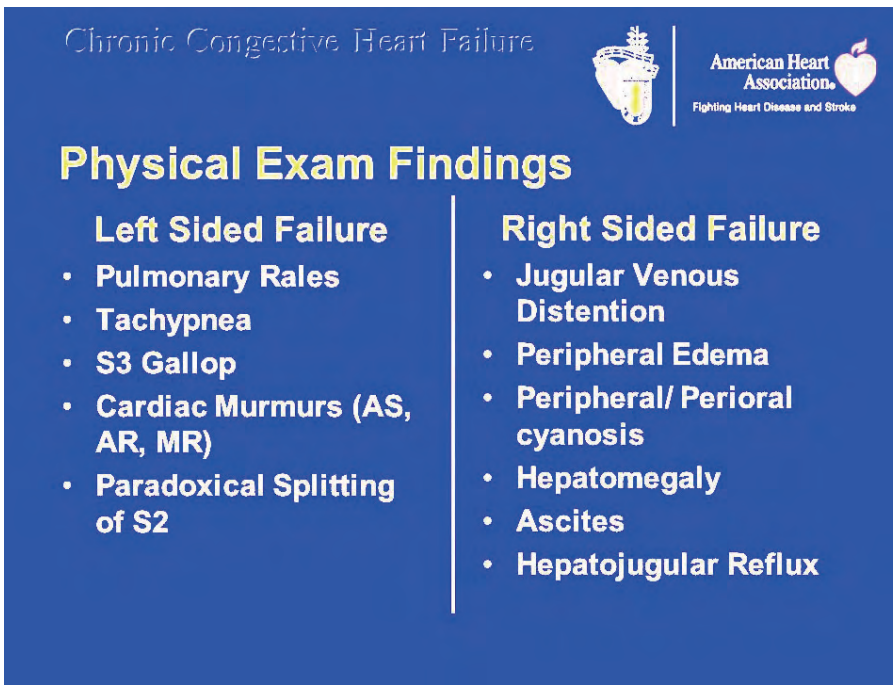






Chronic heart failure

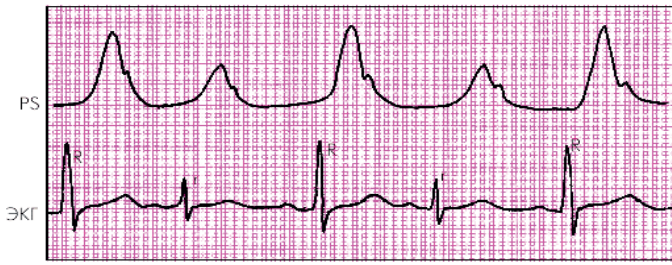
Chronic heart failure is sometimes associated with marked weight loss (cardiac cachexia) caused by a combination of anorexia and impaired absorption due to gastrointestinal congestion, poor tissue perfusion due to a low cardiac output, and skeletal muscle atrophy due to immobility



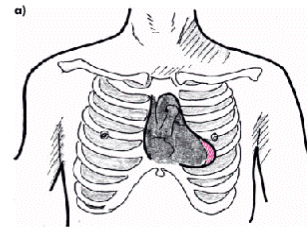
ARTERIAL PULS

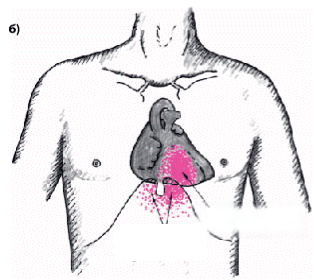
- Pulsus frequens
- Pulsus irregularis
- Pulsus parvus et vacuus
- Pulses alternans
- Pulsus deficiens

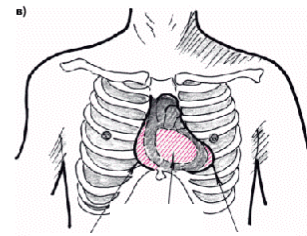
Pulsus alternans

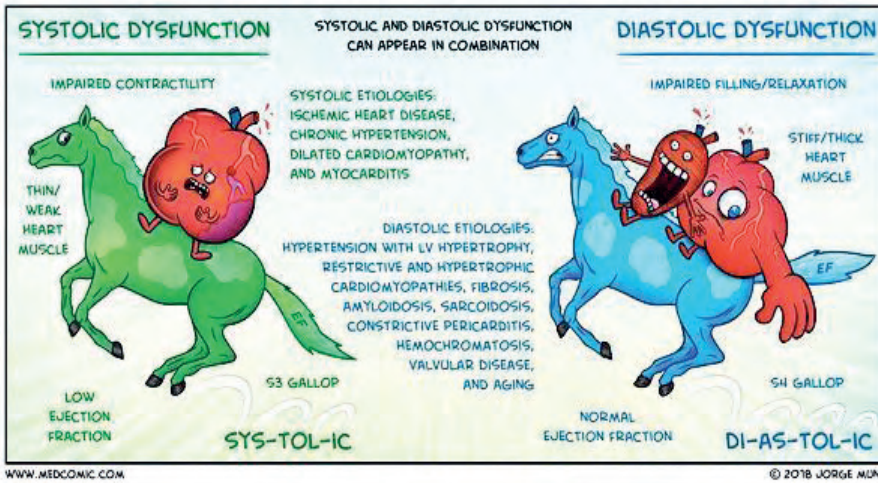


Types of Cardiomegaly



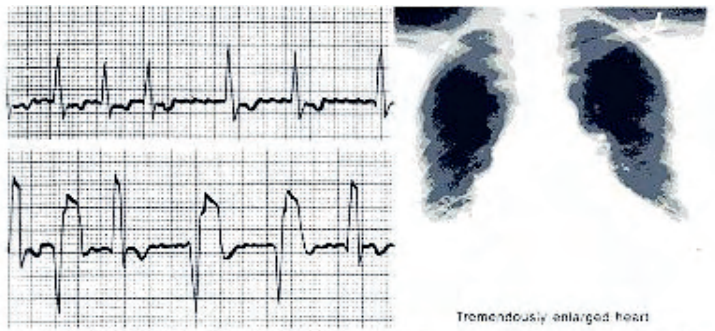


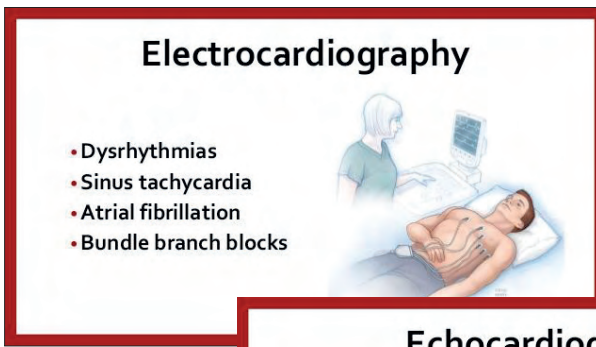


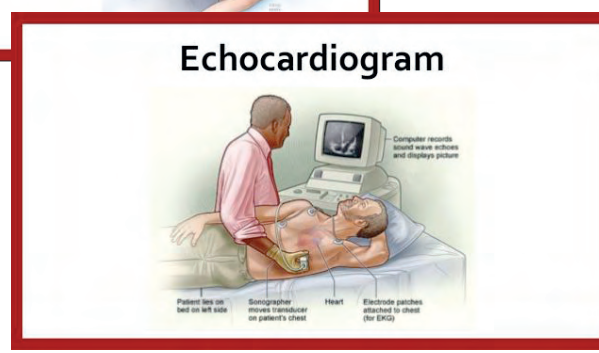


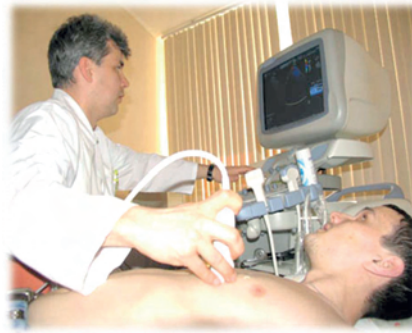
Investigations

- Serum urea and
- electrolytes,
- haemoglobin,
- thyroid function,
- ECG and
- chest X-ray may help to establish the nature and severity of the underlying heart disease and detect any complications.
- Brain natriuretic peptide (BNP) is elevated in heart failure and is a marker of risk;
- it is useful in the investigation of patients with breathlessness or peripheral edema


Tremendously enlarged heart
Multiple varying, bizarre arrhythmias, including atrial fibrillation, multifocal PVCs and episodes of ventricular tachycardia


Electrocardiography
• Dysrhythmias
• Sinus tachycardia
• Atrial fibrillation
• Bundle branch blocks


Echocardiogram
Computer records sound wave echoes and displays picture
Patient lies on bed on left side
Sonographer moves transducer on patient's chest
Heart
Electrode patches attached to chest (for EKG)



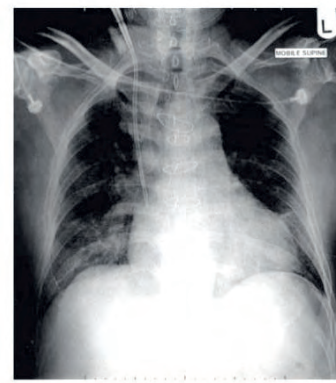
Echocardiography

is very useful and should be considered in all patients with heart failure in order to:

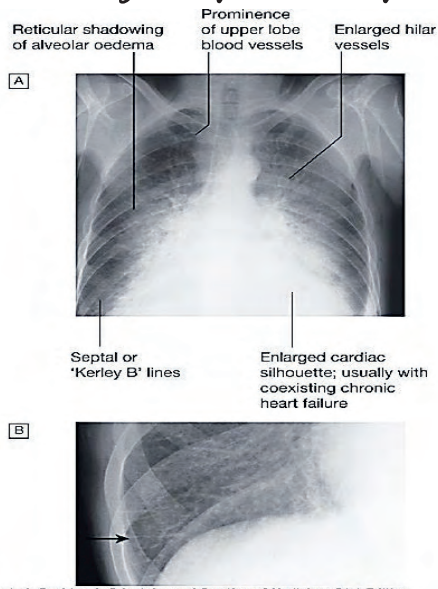
- ❑ **determine the etiology**
- ❑ **detect hitherto unsuspected valvular heart disease, such as occult mitral stenosis, and other conditions that may be amenable to specific remedies**

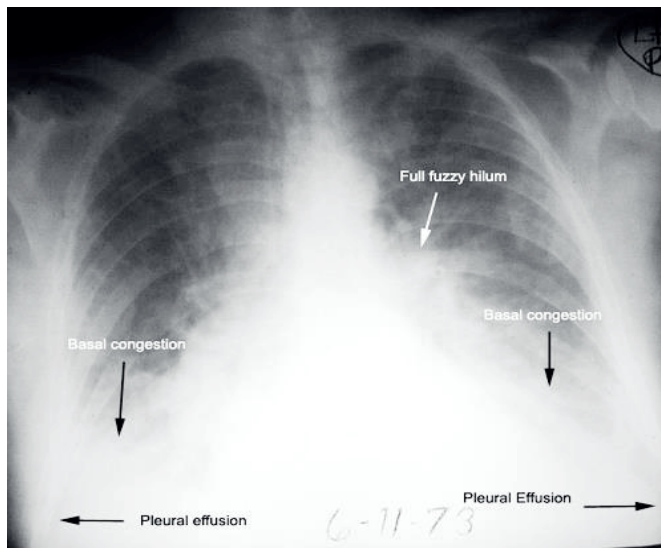
Chest X-Ray

- Cardiomegaly
- Cephalization of blood flow
- Kerley's A lines [1- to 2-cm lines of interstitial edema out from the hilum]
- Kerley's B lines [short, thin, flattened streaks of interstitial edema outlining the subsegmental lymphatics that extend from the pleural surface]



Radiological features of HF





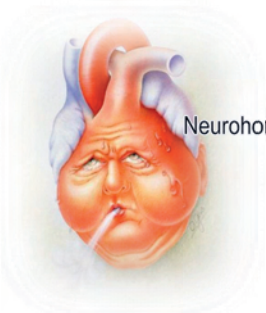
Laboratory Studies

- ↑ Hematocrit (Hct)
- ↑ Hemoglobin (Hb) concentration
- ↑ Erythrocyte count
- Hyponatremia
- Hypokalemia
- ↑ Atrial natriuretic peptide (ANP)
- ↑ Brain natriuretic peptide (BNP)

Arterial Blood Gases

Useful for determining:

- The degree of gas exchange derangement
- The trend in the patient's pulmonary status



Heart - endocrine gland

Neurohormones that may be increased in chronic heart failure

Norepinephrine
Epinphrine
Angiotensin II
Aldosterone
Vasopressin
Natriuretic peptides: A, B, C

SCREENING!!!

BNP / pro-BNP

<100 pg/ml CHF - NO !!!

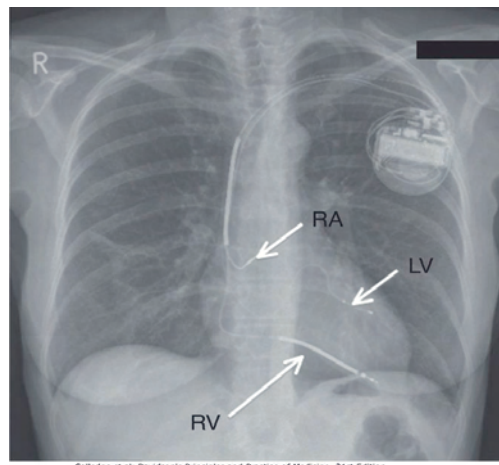
> 400 pg/ml CHF - YES !!!

Chest X-ray

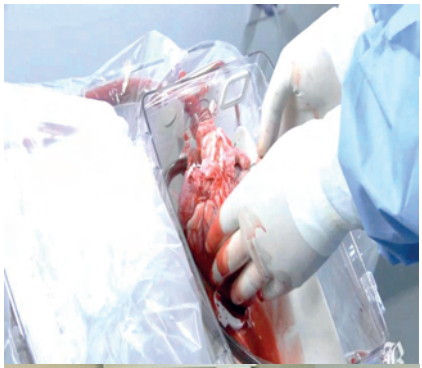
- A rise in pulmonary venous pressure from left-sided heart failure first shows on the chest X-ray as an abnormal distension of the upper lobe pulmonary veins (with the patient in the erect position). The vascularity of the lung fields becomes more prominent, and the right and left pulmonary arteries dilate
- Subsequently, interstitial edema causes thickened interlobular septa and dilated lymphatics. These are evident as horizontal lines in the costophrenic angles (septal or 'Kerley B' lines)
- More advanced changes due to alveolar edema cause a hazy pacification spreading from the hilar regions, and pleural effusions

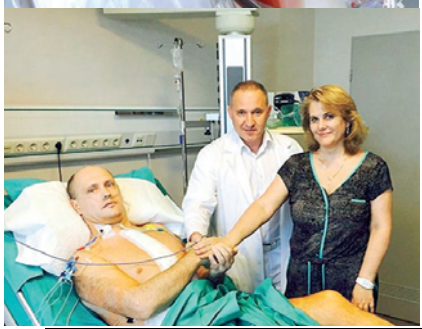
Ventricular assist devices

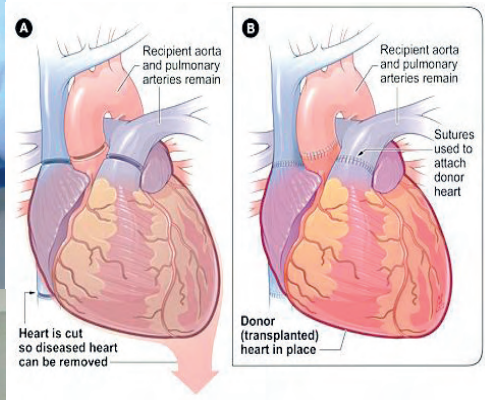
Chest X-ray of a biventricular pacemaker and defibrillator



The right ventricular lead (RV) is in position in the ventricular apex and is used for both pacing and defibrillation. The left ventricular lead (LV) is placed via the coronary sinus and the right atrial lead (RA) is placed in the right atrial appendage; both are used for pacing only.







Heart transplantation.
Heart Center, Kiev, Ukraine.
Professor Boris Todurov with his first patient

Home massages

- Heart failure is one of the professional killer diseases.
- Heart failure is malignant than malignancy.
- The most common cause of heart failure complication is poor compliance to treatment.
- Asymptomatic patient with no heart damage but have risk factors for heart failure is consider to be Stage A.
- Main role of family physician is prevention.

REFERENCES

Kovalyova O.N., Ashcheulova T.V. Propedeutics to Internal Medicine. Part 2. – Vinnytsya: NOVA KNYHA, 2017. – 264 p.

Kovalyova O.N., Asheulova T.V. General inspection: manual for students. – Kharkov: "Turbo". – 2004. – 60 p.

Khomazjuk V.A., Ostashevska T.G., Krasyuk I.V. Propaedeutics of Internal Medicine and Patient Care: Study guide for the practical classes. Part I. – Kyiv: NMU, 2005. – 44 p.

KovalyovaO.N., AsheulovaT.V., ShapovalovaS.A. Instrumental methods examination of cardiovascular system: manual for students. – Kharkov: KSMU. – 2004. – 147 p.

Bickley, Lynn S.; Szilagyi, Peter G. Bates' Guide to Physical Examination and History Taking, 10th Edition. – 934 p. Copyright ©2009 Lippincott Williams & Wilkins

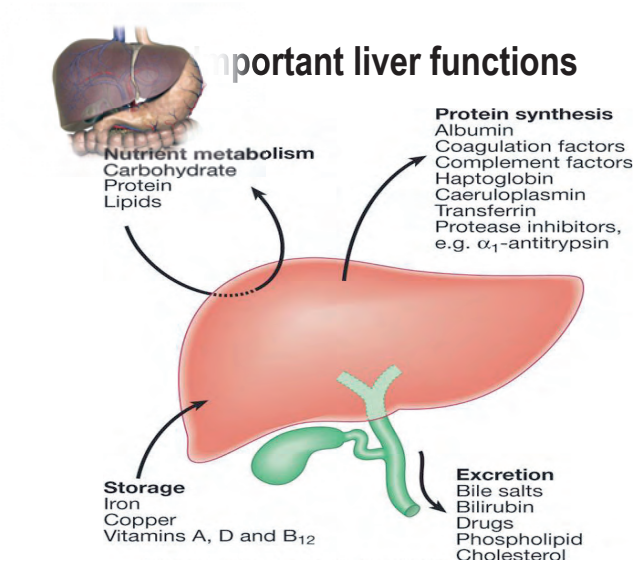
The Point online resources, http://thepoint.lww.com

LECTURE # 14

THE MAIN SYNDROMES OF LIVER DISEASES

THE PLAN

- Important liver functions
- Causes of acute and chronic liver injury
- Key history points Symptoms
- FAMILY HISTORY
- Causes of acute liver failure
- The diagnosis of acute drug-induced liver disease
- The diagnosis of acute drug-induced liver disease
- PAST MEDICAL AND SURGICAL HISTORY
- PAST MEDICAL AND SURGICAL HISTORY
- Aims of investigations in patients with suspected liver disease
- SYMPTOMS & SINGS OF LIVER DISEASE
- THE PHYSICAL EXAMINATION SINGS SMALL & MAJOR LIVER SINGS
- Syndromes
- Assessment of encephalopathy
- Jaundice
- Abdomen examination
- Portal hypertension
- INVESTIGATIONS – instrumental, Liver function tests
- Features of chronic liver failure
- Percutaneous liver biopsy
- References



A liver is executed by more than 500 different vitally important functions, at its delete death comes during 1-2 days."

Causes of acute and chronic liver injury

Acute liver injury	Chronic liver injury
Viral hepatitis (A, B, E)	Chronic viral hepatitis (B + C)
Alcoholic liver disease*	
Drugs	NAFLD Haemochromatosis Wilson's disease α_1-antitrypsin deficiency Cryptogenic (unknown)
Autoimmune hepatitis*	
	PBC PSC

*Although there is often evidence of chronic liver disease at presentation, may present acutely with jaundice. In alcoholic liver disease this is due to superimposed alcoholic hepatitis (NAFLD = non-alcoholic fatty liver disease; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis).

APPROACH TO THE PATIENT WITH LIVER DISEASE

- Identification of a chief complaint, a complete medical history, and a thorough physical examination form the basis for the approach to a patient with liver disease. Identification of risk factors for liver disease is particularly important

- Patients with liver disease may have subtle symptoms, recognition of which will alert the clinician to hepatic pathology. Other times, the quality of life of patients may be markedly impaired. Often, however, the first suggestion of liver disease is from laboratory data obtained as part of routine health maintenance, for nonspecific symptoms, or for other medical reasons

- The range of liver injury varies from inflammation to fibrosis and cirrhosis.
- Liver failure, which is characterized by impaired function, can be acute and fulminant, but most liver conditions that lead to long-term complications tend to be chronic and progress slowly, so accurate diagnosis may provide an opportunity for successful treatment

Key history points Symptoms

• Key history points Symptoms*

- **Itching preceding jaundice**
- **Abdominal pain (suggests stones)**
- **Weight loss (chronic liver disease and malignancy)**
- **Dark urine and pale stools**
- **Fever ± rigors**
- **Dry eyes/dry mouth**
- **Fatigue**

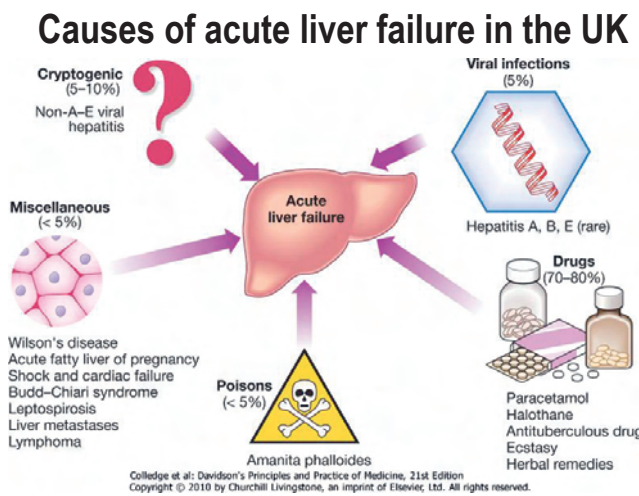
• Recent drug history Other

- **Exposure to intravenous drug or blood transfusions**
- **Travel history and country of birth**
- **Family history of liver disease**
- **Autoimmune disease history**
- **Alcohol history**
- **Inflammatory bowel disease**
- **Metabolic syndrome (increased body mass index ± type 2 diabetes/hypertension)**

FAMILY HISTORY

- **A history of liver disease in family members is relevant for the diagnosis of hereditary liver diseases, including primary hemochromatosis , α_1-antitrypsin deficiency, and Wilson's disease**

- **A history of viral hepatitis B in the mother may suggest perinatally acquired hepatitis in the patient**



The relative frequency of the different causes varies according to geographical area

The diagnosis of acute drug-induced liver disease

- Tabulate drugs taken
  - Prescribed
  - Self-administered
- Establish if reported hepatotoxicity in the literature
- Relate time drugs taken to onset of illness
  - 4 days-8 weeks (usual)
- Effect of stopping drugs on normalisation of liver biochemistry
  - Hepatitic LFTs (2 months)
  - Cholestatic/mixed LFTs (6 months)
- Exclude other causes
  - Viral hepatitis
  - Biliary disease
- Consider liver biopsy

PAST MEDICAL AND SURGICAL HISTORY

- A history of jaundice or abnormal serum liver profile may suggest prior hepatitis or the passage of a gallstone

- A history of gallbladder surgery, including laparoscopic cholecystectomy, in a patient with cholestasis should trigger a search for postsurgical biliary strictures, which must be repaired to prevent biliary cirrhosis

- Biliary strictures can also be a complication of chronic pancreatitis

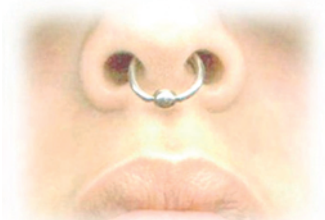
PAST MEDICAL AND SURGICAL HISTORY

- Activities that involve **contact with blood** and **body fluids** are risks for acquiring viral hepatitis

- In the United States, individuals are at risk for contracting viral hepatitis (e.g., hepatitis C and B and delta hepatitis) **from transfusion of blood**, especially before 1992, and other **blood products** (e.g., clotting factors), especially before 1987, **intravenous injection** of illicit drugs, and **chronic hemodialysis**

- **Body piercings** and **tattoos** with contaminated tools and certain sexual behavior (e.g., **multiple sexual partners**) are risk factors for viral hepatitis

RISK FACTORS FOR LIVER DISEASE

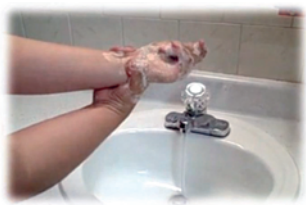


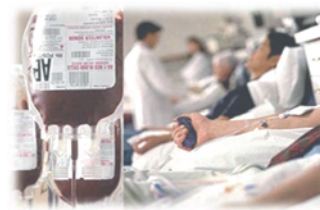
Body piercings and **tattoos**

Multiple sexual partners

RISK FACTORS FOR LIVER DISEASE

RISK FACTORS FOR LIVER DISEASE





IDENTIFICATION OF RISK FACTORS FOR LIVER DISEASES

- **Alcohol abuse** is an important cause of cirrhosis of the liver, and many medications or dietary supplements, by prescription or over the counter, can cause liver disease
- The drinking of **"bush tea"** in some Caribbean islands (e.g., Jamaica) can be associated with veno-occlusive disease, which can present dramatically as ascites and hepatic insufficiency
- Hepatic vascular thrombosis and hepatic adenomas are complications of **estrogens** and **anabolic steroids**
- Malignant tumors of the liver have been associated with exposure to certain compounds used in industry (e.g., vinyl chloride, inorganic arsenicals) and to aflatoxin B_1, which can result from the ingestion of food products (e.g., grains) contaminated with the mold ***Aspergillus flavus***
- Travel to endemic areas may expose individuals to infectious diseases that may involve the liver, including **leptospirosis, malaria, Q fever, amebiasis, echinococcosis, and schistosomiasis**

Aims of investigations in patients with suspected liver disease

- Detect hepatic abnormality
- Measure the severity of liver damage
- Detect the pattern of liver function test abnormality: hepatitic or obstructive/cholestatic
- Identify the specific cause
- Investigate possible complications

SYMPTOMS OF LIVER DISEASE

Acute liver disease

This may be asymptomatic and anicteric. Symptomatic disease, which is often viral, produces generalized symptoms of malaise, anorexia and fever. Jaundice may appear as the illness progresses

Chronic liver disease

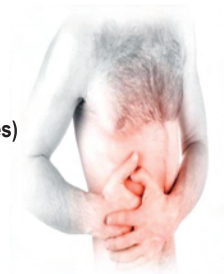
Patients may be asymptomatic or complain of non-specific symptoms, particularly fatigue

Specific symptoms include:

- right hypochondrial pain due to liver distension
- abdominal distension due to ascites
- ankle swelling due to fluid retention
- hematemesis and melena from gastrointestinal hemorrhage
- pruritus due to cholestasis – this is often an early symptom of primary biliary cirrhosis
- breast swelling (gynecomastia), loss of libido and amenorrhea due to endocrine dysfunction
- confusion and drowsiness due to neuropsychiatric complications (portosystemic encephalopathy)

Complains…

Abdominal pain (suggests stones)



Nausea

Weight under the right costal arch

Flatulence, diarrhea

Pain

- Patients with liver disease can report more abdominal pain than other individuals do, and the pain is worse after meals. Biliary colic and acute cholecystitis must also be considered in patients with liver disease because the prevalence of gallstones is increased in patients with cirrhosis

- Peripheral neuropathy manifested by localized neurologic deficits and pain can be a symptom in patients with liver disease secondary to cholestasis, primarily in children. Xanthomatous neuropathy can be caused by lipid deposition on peripheral nerves in patients with hyperlipidemia as a result of profound cholestasis

Fetor Hepaticus

- A **sweet odor** emanating from the breath can be perceived in patients with advanced liver disease, including those with extensive portosystemic shunting

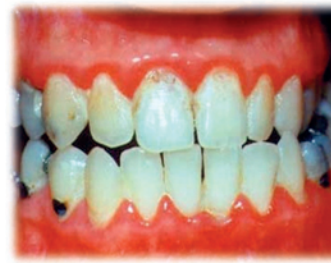
Alterations in the Senses of Taste and Smell

- Taste abnormalities (e.g., **hypogeusia** and **dysgeusia**) are recognized complications of liver disease
- Smokers with acute hepatitis B and perhaps other acute liver diseases may lose interest in cigarettes because of a perverted sense of taste from liver inflammation
- **Impaired gustatory function** with decreased sensitivity to or recognition of bitter, salt, sweet, and sour taste has been reported in patients with cirrhosis
- Serum concentrations of certain elements, including magnesium, zinc, and vitamin A, are decreased in some patients with liver disease and an altered sense of taste. A central mediation of taste abnormalities in patients with liver disease has been proposed
- **Hyposmia** can be associated with cirrhosis and may resolve after liver transplantation

Bleeding

- History of **hematemesis, melena** or **hematochezia** may identify patients with portal hypertension

Nasal bleeding



Bleeding from the gums during tooth brushing

Irritability

Fatigue, decreased performance

Depression

Sleep disorders

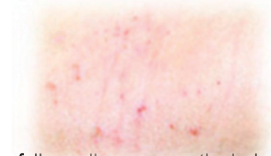
Fatigue

- Lack of energy or fatigue, which may be the most common symptom of liver disease, is sometimes associated with acute liver injury (e.g., acute viral hepatitis; or a chronic condition (e.g., primary biliary cirrhosis and chronic hepatitis C infection. The pathogenesis of fatigue in liver disease is unknown, and it does not appear to be related to abnormal **musculoskeletal function or neurologic impairment**. Fatigue has been associated with poor-quality sleep and with depression, perhaps via the opioid and serotoninergic systems. When fatigue is prominent, conditions other than liver disease, including hypothyroidism, anemia, and depression, should be excluded

Personality Changes and Sleep Disturbances

- **One of the most dramatic manifestations of decompensated liver disease is hepatic encephalopathy, which is characterized by inhibitory neurotransmission. Its manifestation can be subtle or florid. Reversal of the sleep pattern is well recognized, with patients reporting both insomnia and an inability to stay awake during the day. Family members may report confusion, cognitive deficiencies, and changes in personality, including combativeness**

Pruritus



- Pruritus, or itching, can be a manifestation of liver disease, particularly diseases characterized by **cholestasis** (i.e., impaired secretion of bile, presumably because of the accumulation of substances that are normally excreted in bile and that as a result of cholestasis accumulate in tissues)
- However, the nature of the pruritogen or pruritogens is unknown, and there is no specific evidence indicating a role of bile acids in this symptom. It has been hypothesized that the pruritus of cholestasis is mediated, at least in part, by increased opioidergic neurotransmission; amelioration of the pruritus by opiate antagonists (e.g., naloxone, 0.4 mg by intravenous push, followed by a continuous infusion of 0.02 μg/kg/min) supports this hypothesis
- It is important to appreciate that pruritus and fatigue can precede the diagnosis of liver disease by years

Poor Appetite and Weight Loss

- Poor appetite may accompany the onset of acute liver disease. Patients with advanced liver disease may also have chronic poor appetite, weight loss, or muscle wasting

- In advanced liver disease, weight loss may not be a reliable indicator of liver disease because fluid retention may compensate for the lost dry weight

Dyspnea

- Decreased exercise tolerance and shortness of breath in patients with liver disease may be caused by the **hepatopulmonary syndrome,** portopulmonary hypertension, and cardiomyopathy, the latter traditionally associated with alcohol abuse and recently also being recognized as a complication of chronic hepatitis C infection
-
- Dyspnea can also result from impaired diaphragmatic excursion **secondary to ascites**

Stool Characteristics

Discolored feces

- Jaundice associated with **acholic** (e.g., pale) stools, which result from decreased bile pigments in feces, **suggests biliary obstruction**
- In liver diseases characterized by profound cholestasis, the critical micellar concentration of bile acids is decreased in the small intestine; hence, diarrhea from fat malabsorption and, in some cases, from maldigestion may ensue
- Diarrhea is also a cardinal manifestation of inflammatory bowel disease, which can be associated with primary sclerosing cholangitis and cholestasis

Dark Urine

- Dark brown urine suggests bilirubinuria, which is a reflection of hyperbilirubinemia. This finding can precede jaundice

Vision Disturbances

- **Deficiency of vitamin A** is usually manifested as impaired visual adaptation to darkness, of which patients may not be aware

- Patients with liver disease may be deficient in vitamin A because of malabsorption and decreased availability of retinol binding protein. In addition, there may be impaired release of vitamin A from liver stores

Bone Pain and Fractures

- Pain in the long bones (e.g., tibia) and joints, sometimes associated with clubbing, is suggestive of hypertrophic osteoarthropathy, a complication of cirrhosis. A dramatic manifestation of liver disease of the cholestatic type can be bone fractures from osteopenia, the etiology of which is uncertain but may relate to osteomalacia from decreased bowel absorption of vitamin D

Presenting features of liver disease represent combined effects of:

Impairment of liver function and metabolic sequela of this
- Jaundice (failure of bilirubin clearance)
- Encephalopathy (failure of clearance of by-products of metabolism)
- Bleeding (impaired liver synthesis of clotting factors)
- Hypoglycemia

Ongoing presence of etiological factors (e.g. alcohol)
- Effects of etiological agent, e.g. intoxication, withdrawal, cognitive impairment

versus
- Effects of liver injury from agent, e.g. encephalopathy

Effects of chronic liver injury (> 6 moths)

Catabolic status (± poor nutrition)
- Skin thinning ('paper-money skin')
- Loss of muscle bulk
- Leuconychia

Impaired albumin synthesis
- Reduced oncotic pressure (contributes to ascites)

Reduced aldosterone clearance
- Na+ retention (contributes to ascites)

Reduced oestrogen clearance
- Mild feminization of males (loss of body hair, gynecomastia)

Chills and Rigors

- Chills and rigors are **manifestations of infection.** Examples that can complicate the course of liver disease are spontaneous bacterial peritonitis in patients with ascites, an infected biliary tree in patients with primary sclerosing cholangitis, and pneumonia or meningitis in an immunocompromised patient with alcoholic liver disease

Sexual Dysfunction and Disinterest

- **Decreased libido** and impotence are manifestations of cirrhosis in men. **Decreased serum levels of testosterone** and increased serum levels of gonadotropins are known complications of alcoholic cirrhosis
- **Hypogonadism** may also result from the toxic effect of alcohol and its metabolites on the gonads and from the systemic effect of estrogens on the hypothalamic-pituitary-gonadal axis
- In women, the most relevant factors in lack of interest in sexual activities have been reported to be depression and fatigue

Muscle Cramps

- Mostly nocturnal, muscle cramps affecting the calves, toes, and fingers can complicate cirrhosis of the liver and have a marked negative impact on quality of life. The pathogenesis is unknown

THE PHYSICAL EXAMINATION

- Signs of liver disease may be overt, subtle, or absent
- **Fever** in a patient with liver disease should trigger the exclusion of infections, including bacterial peritonitis in patients with ascites and cholangitis in patients with biliary obstruction
- In patients with decompensated liver disease, **blood pressure tends to be lower** than average because of systemic arterial vasodilation

SMALL LIVER SINGS

- appearance on the skin of overhead half of trunk of «vascular asterisks» - teleangiektazija **as spiders;**
- **angiomas** at the edge of nose, in the corner of eyes (they can bleed);
- erythema of hands is the bright red huckleberry colouring of warm hands poured out or in area of thenar or hypothenar, and also in area of pillows of fingers **(«hepatic hands», «hands of beer lovers»)** (Weber);
- rarer similar erythema is on feet;
- tongue of cowberry-red color lacquered, oedematous, unassessed;
- **carmine-red coloring of mucous membrane of cavity of mouth and lips**
- disruption of the menstrual cycle in women;
- **gynecomastia, testicular atrophy, feminization aspect, impotence, hair loss in men;**
- hypertrophy of the parotid salivary glands (symptom of **"hamster"**);
- enhanced capillary network on the face (a symptom **of "dollar banknote"**);
- Dupuytrens contracture;
- Rhinophyma;
- Leykonihii;
- symptom of clubbing

MAJOR LIVER SINGS

- Jaundice s.
- Hepatomegaly s.
- Splenomegaly s.
- The syndrome of portal hypertension

Syndromes

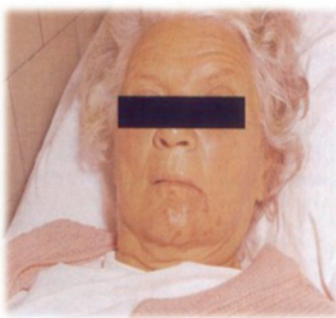
- Asthenic syndrome
- Paine s.
- Jaundice s.
- Cholestatic s.
- Lymphadenopathy s.
- Syndrome of hepatocellular failure
- The syndrome of portal hypertension
- Hepatolienal s.
- Mesenchymal-inflammatory s.

Clinical features of hepatic cirrhosis

- Hepatomegaly (although liver may also be small)
- Jaundice
- Ascites
- Circulatory changes: spider telangiectasia, palmar erythema, cyanosis
- Endocrine changes: loss of libido, hair loss

  Men: gynecomastia, testicular atrophy, impotence

  Women: breast atrophy, irregular menses, amenorrhea
- Haemorrhagic tendency: bruises, purpura, epistaxis
- Portal hypertension: splenomegaly, collateral vessels, variceal bleeding
- Hepatic (portosystemic) encephalopathy
- Other features: pigmentation, digital clubbing, Dupuytren's contracture

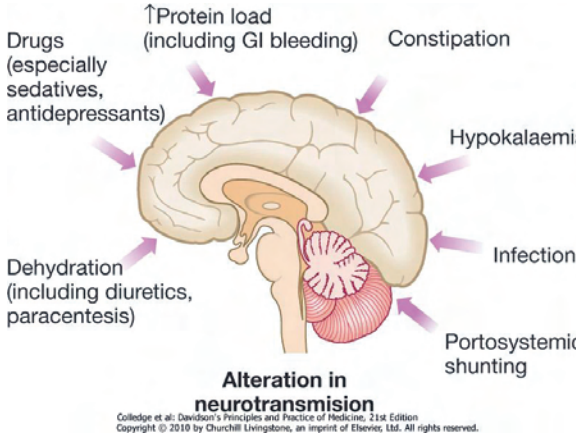


Coma

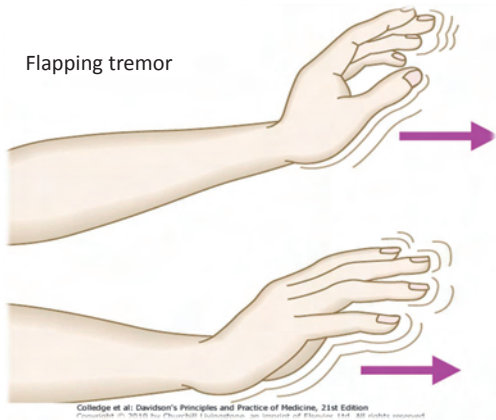
Depression, disorientation

Alteration in nervous status

Factors precipitating hepatic encephalopathy



Assessment of encephalopathy



Jerky forward movements every 2-3 minutes when arms are outstretched and hands are dorsiflexed suggest hepatic encephalopathy.

Neuropsychiatric Alterations

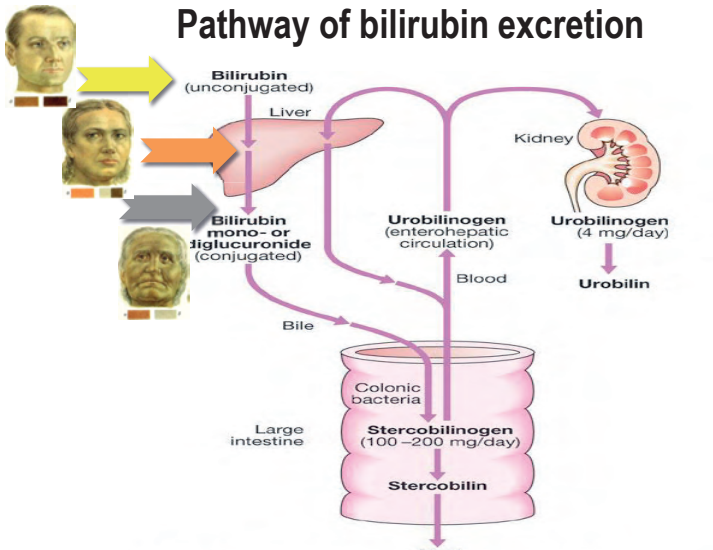
- Subtle alterations in personality can be reported by family members
- **Constructional apraxia** (e.g., inability to draw a five-pointed star or to write legibly) in a fully conscious patient is a typical finding of hepatic encephalopathy
- **Asterixis,** a sign of encephalopathy, can be appreciated by having the patient extend the arms, with the palms down, and then dorsiflex the wrists while separating the fingers for at least 15 seconds; a positive test is characterized by a series of extension and flexion movements at the level of the wrist
- Electromyography of the contracted muscles reveals lapses of electrical input that coincide with asterixis
- **Tremors** can also be noted

SYMPTOMS AND SIGNS OF LIVER DISEASE

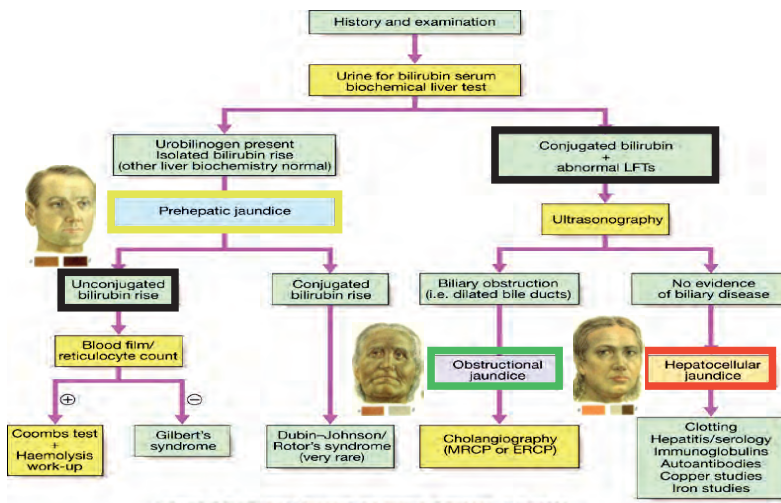
Jaundice

- Classically recognized as a sign of liver disease, jaundice may be identified by the patient and hence be part of the chief complaint as "yellow eyes". In general, jaundice is a good indication that some aspect of bilirubin metabolism is altered (e.g., bilirubin availability, uptake, conjugation, or excretion)

Pathway of bilirubin excretion



Investigation of jaundice



Key history points in patients with jaundice

Symptoms*

- Itching preceding jaundice
- Abdominal pain (suggests stones)
- Weight loss (chronic liver disease and malignancy)
- Dark urine and pale stools
- Fever ± rigors
- Dry eyes/dry mouth
- Fatigue

Recent drug history
Other

- Exposure to intravenous drug or blood transfusions
- Travel history and country of birth
- Metabolic syndrome (increased body mass index ± type 2 diabetes/hypertension)
- Autoimmune disease history
- Alcohol history
- Inflammatory bowel disease
- Family history of liver disease, autoimmune disease or the metabolic syndrome

Pre-hepatic jaundice

- This is caused either by hemolysis or by congenital hyperbilirubinaemia, and is characterized by an isolated raised bilirubin level. In hemolysis, destruction of red blood cells or their precursors in the marrow causes increased bilirubin production

- Jaundice due to hemolysis is usually mild because a healthy liver can excrete a 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 metabolize bilirubin

- The most common form of non-hemolytic hyperbilirubinemia is Gilbert's syndrome, an inherited disorder of bilirubin metabolism. Other inherited disorders of bilirubin metabolism also exist but they are very rare

Clinical features and complications of cholestatic jaundice

- **Cholestasis**

Early features

- Jaundice
- Dark urine
- Pale stools
- Pruritus

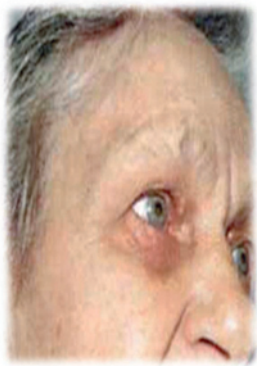
• Late features

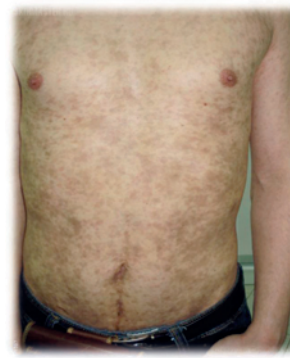
- Malabsorption (vitamins A, D, E and K)
  - Weight loss
  - Steatorrhoea
  - Osteomalacia
  - Bleeding tendency
  - Xanthelasma and xanthomas

• Cholangitis

- **Fever**
- Rigors
- Pain (if gallstones are present)

Hyperpigmentation





- Hyperpigmentation is a complication of liver disease, mostly of the cholestatic type. Its pathogenesis is unknown, but increased availability of α-melanocyte–stimulating hormone has been proposed as a contributing factor

The Skin, Mucous Membranes, and Nails

- Scleral icterus may be subtle or obvious. A yellow discoloration of the skin and mucous membranes defines jaundice, which may be secondary to biliary tract obstruction, acute hepatitis, hepatocellular failure, or excess bilirubin production from hemolysis

- Kayser-Fleischer rings, a brown rim on the periphery of the cornea secondary to copper accumulation in Descemet's membrane, is a classic finding of Wilson's disease that is often seen only by slit lamp examination. In prolonged cholestasis not related to Wilson's disease, Kayser-Fleischer rings may also be seen

The Skin, Mucous Membranes, and Nails

- In advanced liver disease, the skin is warm from a hyperdynamic circulation.
- Spider telangiectasia, which are characterized by vascular arborizations that blanch on pressure, are found on the face, upper part of the back, thorax, and upper part of the arms. The pathogenesis of spider angiomas is thought to be a systemic excess of estrogen combined with portosystemic shunting from cirrhosis.
- Skin hyperpigmentation is common in patients with cholestasis and especially in those with primary biliary cirrhosis, who may display what has been named the "butterfly sign," an area of relative hypopigmentation between the scapulae as compared with the surrounding skin.
- A gray to brown discoloration of the skin and mucous membranes from the accumulation of hemosiderin and hemofuscin (gray hue) and melanin (brown hue) suggests hereditary hemochromatosis .

Parotid Glands, Breasts, and Genitalia

- **Parotid gland enlargement** can be detected in 20% of patients with cirrhosis secondary to alcohol abuse

- **Testicular atrophy and feminization,** including **gynecomastia**, which is a classic finding in men with cirrhosis, may result from increased peripheral conversion of androgens; tender gynecomastia is also a side effect of spironolactone, a diuretic used to treat ascites

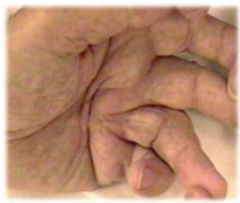
The Skin, Mucous Membranes, and Nails

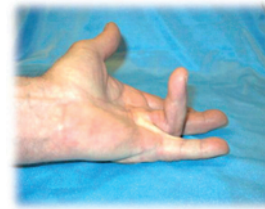
- **Xanthomatosis,** which is accumulation of lipids in the skin, is a manifestation of hyperlipidemia in cholestasis (e.g., primary biliary cirrhosis). It is associated with **xanthomas** on the palms, soles, trunk, and flexor surfaces; tuberous xanthomas over the joints; and **xanthelasmas** on the eyelids and under the eyes
- **Lichen planus** is also associated with primary biliary cirrhosis
- **"Paper money" skin,** characterized by telangiectases on the cheeks, can be a sign of cirrhosis
- **Purpura** is a manifestation of **vasculitis,** which can be associated with chronic hepatitis C and B infections
- **Telangiectasia** on mucous membranes (e.g., lips) suggest CREST syndrome or hereditary hemorrhagic telangiectasia , in which vascular malformations can occur in the liver
- **The distribution of body hair** in men with cirrhosis is in a feminine pattern
- **Excoriations and prurigo** nodularis result from chronic scratching in patients who suffer from pruritus
- Nails can display white **horizontal (Muehrcke's) lines,** indicative of hypoalbuminemia. Azure lunula (**sky blue moon**) of the nails and a green hue on the skin from the accumulation of copper are described in Wilson's disease .

Extremities

- **Red palms,** especially on the thenar and hypothenar eminences, can be seen in patients with cirrhosis. Retraction of the palmar fascia with subsequent contracture of the palms and fingers is known as **Dupuytren's contracture,** a condition that is more prevalent in patients with liver disease. Acquired finger **clubbing** can be seen in patients with cirrhosis and in those with hepatopulmonary syndrome

- Lower extremity edema complicates fluid retention in liver disease. The edema is usually pitting, but when chronic or complicated by venous insufficiency, the appearance can resemble elephantiasis





Dupuytren's contracture, which is a thickening of the palmar fascia, occurs mostly in alcoholic cirrhosis

Cardiovascular System

- **Heart failure** from any cause may result in hepatomegaly; clues include cardiomegaly, cardiac gallops, and distended neck veins

- **Constrictive pericarditis** is classically manifested as distended neck veins, a pericardial knock, hepatomegaly, and ascites

- **Pulmonary hypertension** associated with portal hypertension or liver disease (i.e., portopulmonary hypertension) is suggested by an accentuated pulmonary component of the second heart sound or the presence of a systolic murmur consistent with tricuspid insufficiency, or both

- **Pounding pulses** are characteristic of patients with decompensated liver disease and are caused by systemic vasodilation and increased cardiac output

Respiratory System

- **Decreased breath sounds** at the lung bases, usually at the right base, suggest hydrothorax in a patient with decompensated liver disease and, usually, ascites

- **Hepatopulmonary syndrome**, which is associated with intrapulmonary vascular dilation, is characterized by orthodeoxia (i.e., arterial deoxygenation when moving from the supine to the upright position) and platypnea (i.e., dyspnea on moving from the supine to the upright position). These phenomena result from an increase in intrapulmonary shunting of blood to the lower lobes

Abdomen

- **The liver is dull to percussion.** To feel the liver, the abdomen is examined with the patient in the supine position, arms parallel to the sides of the body, and the knees bent to relax the abdominal muscles. It is useful to start palpating from the right lower quadrant of the abdomen toward the rib cage so that the liver edge is encountered on the way up

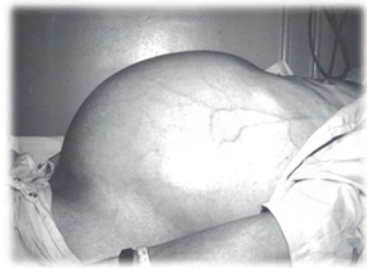
- **The liver edge is smooth and sometimes slightly tender when palpated.** In general, a liver that is felt up **to 2 cm below** the right costal margin is considered normal. A normal-sized liver can be displaced downward by emphysematous lungs. In thin subjects, the liver edge can be felt on deep inspiration, even in the absence of hepatic pathology.

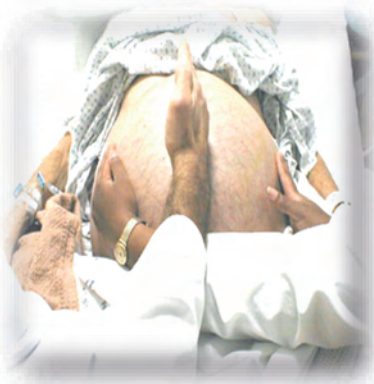
- **Hepatomegaly** may indicate cirrhosis, infiltrative disease, or space-occupying lesions (e.g., tumors). **A liver with a firm or hard consistency is consistent with cirrhosis**

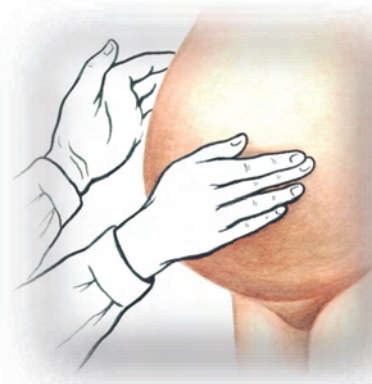
- The liver can extend across the midline, and the left lobe can be felt in the epigastrium. When the presence or absence of hepatomegaly is uncertain, the scratch test, which is conducted by placing the bell of the stethoscope on the right upper quadrant over the rib cage and scratching the surface of the abdominal wall from the midabdomen towards the liver, may demonstrate amplification of the sound of the scratch on an area under which the liver lies. In the presence of ascites, the liver edge can be made to bounce by exerting quick pressure with the fingertips below the rib cage

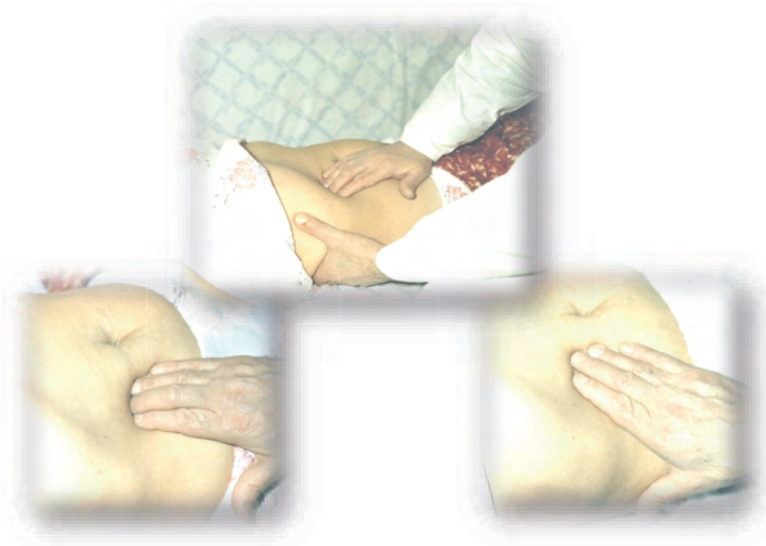
- **Splenomegaly** suggests portal hypertension

Ascites



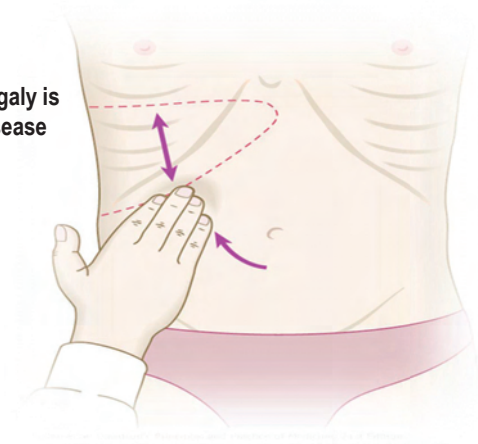




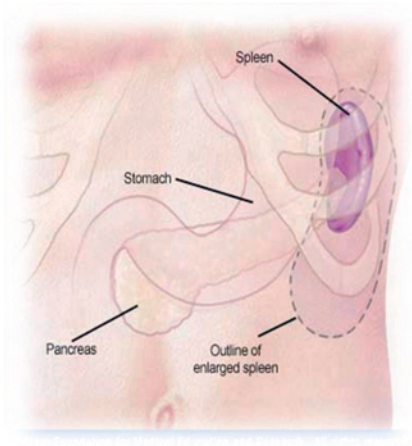


Clinical assessment of hepatomegaly is important in diagnosing liver disease

- 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
- Detect if smooth or irregular, tender or non-tender; ascertain shape
- Identify the upper border by percussion

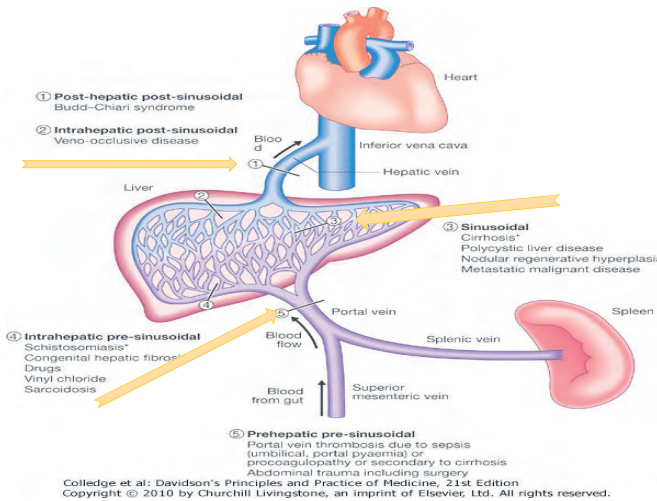


Hepatomegaly



Splenomegaly is indicative of portal hypertension

Classification of portal hypertension according to site of vascular obstruction

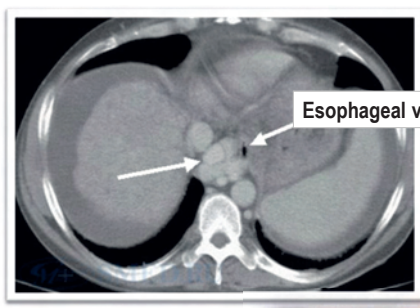


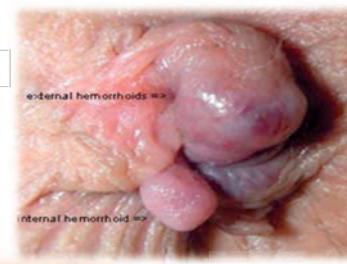
*Most common cause. Note that splenic vein occlusion can also follow pancreatitis leading to gastric varices.

Complications of portal hypertension

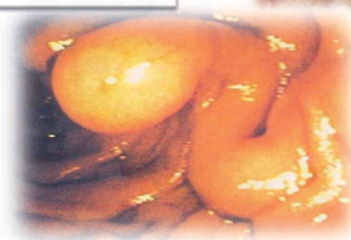
- Variceal bleeding: oesophageal, gastric, other (rare)
- Congestive gastropathy
- Hypersplenism
- Ascites
- Iron deficiency anaemia
- Renal failure
- Hepatic encephalopathy

Complications of portal hypertension





Rectum varices



The small intestine varices

INVESTIGATIONS

Investigative tests can be divided into:

- **Blood tests**

(a) Liver 'function' tests:

(i) serum albumin and bilirubin
(ii) prothrombin time

(b) Liver biochemistry:

(i) serum aspartate and alanine aminotransferases – reflecting hepatocellular damage
(ii) serum alkaline phosphatase, γ-glutamyl transpeptidase – reflecting cholestasis
(iii) total protein

(c) Viral markers

(d) Additional blood investigations; haematological, biochemical, immunological, markers of liver fibrosis and genetic analysis.

- **Urine tests – for bilirubin and urobilinogen**
- **Imaging techniques – to define gross anatomy**
- **Liver biopsy – for histology**

Liver function tests

'Hepatitic' and 'cholestatic'/'obstructive' liver function tests

Pattern	AST/ALT	GGT	ALP
Biliary obstruction	↑	↑↑	↑↑↑
Hepatitis	↑↑↑	↑	↑
Alcohol/enzyme-inducing drugs	N/↑	↑↑	N

N = normal;
↑ mild elevation (< twice normal);
↑↑ moderate elevation(2–5 times normal);
↑↑↑ marked elevation (> 5 times normal).
ALT = alanine aminotransferase;
ALP = alkaline phosphatase;
AST = aspartate aminotransferase;
GGT = gamma-glutamyltransferase

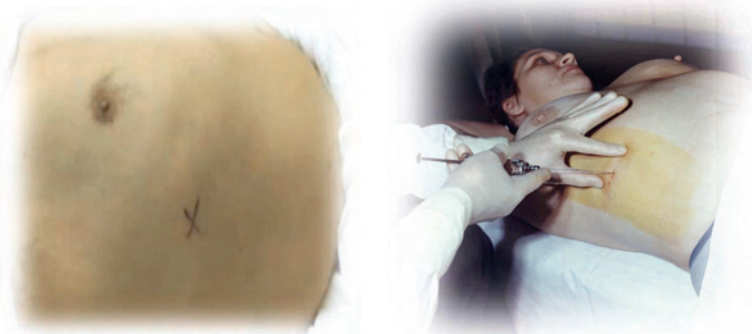
Features of chronic liver failure

- **Worsening synthetic liver function**

  - **Prolonged PT**
  - **Low albumin**

  - **Jaundice**
  - **Portal hypertension**
  - **Variceal bleeding**
  - **Hepatic encephalopathy**
  - **Ascites**
  - **Spontaneous bacterial peritonitis**
  - **Hepatorenal failure**

Percutaneous liver biopsy



- Examination of liver histology provides the opportunity to diagnose or confirm a particular disease, determine the degree of liver injury (e.g., the presence of cirrhosis), and assess response to treatment. The decision to perform a liver biopsy must be individualized by weighing the risks versus the benefits

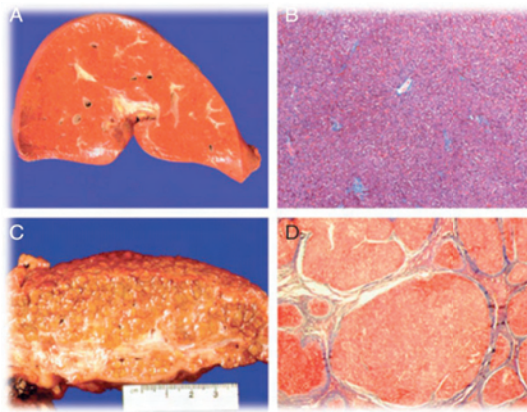
Cirrhosis can be classified histologically

- **Cirrhosis can be classified histologically into two types:**

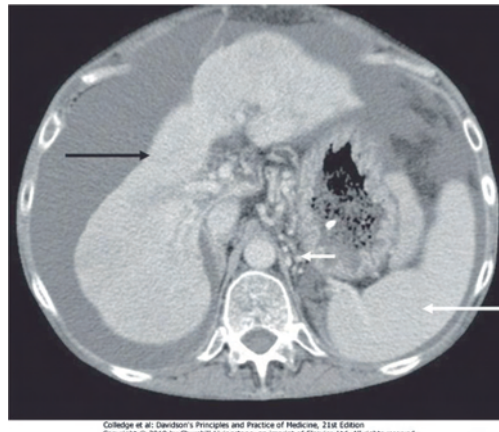
- ***Micronodular cirrhosis*** **characterized by small nodules about 1 mm in diameter and seen in alcoholic cirrhosis**

- ***Macronodular cirrhosis*** **characterized by larger nodules of various sizes. Areas of previous collapse of the liver architecture are evidenced by large fibrous scars**

Gross and microscopic images of a normal and cirrhotic liver

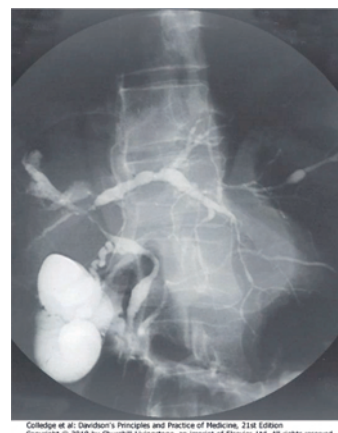


A, Gross image of a normal liver with a smooth surface and homogeneous texture. **B**, Microscopically, liver sinusoids are organized and vascular structures are normally distributed. **C**, Gross image of a cirrhotic liver. The liver has an orange-tawny color with an irregular surface and a nodular texture. **D**, Microscopically, the architecture is disorganized and there are regenerative nodules surrounded by fibrous tissues

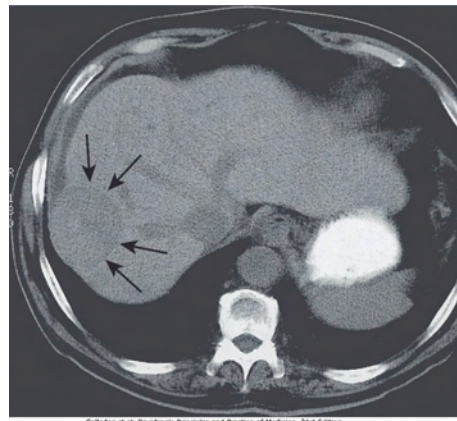


CT scan in a patient with cirrhosis.
The liver is small and has an irregular outline (black arrow), the spleen is enlarged (long white arrow), fluid (ascites) is seen around the liver, and collateral vessels are present around the proximal stomach (short white arrow)

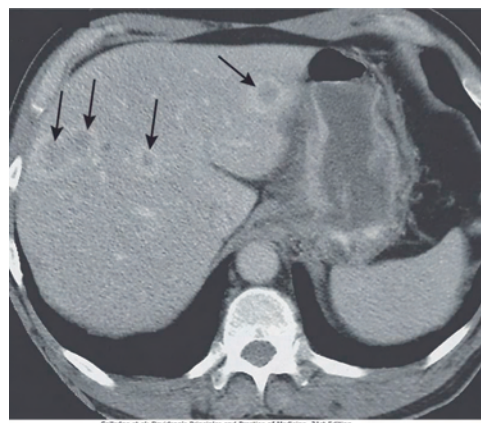
A percutaneous cholangiogram in sclerosing cholangitis showing characteristic irregularity of the biliary tree



CT showing a large hepatocellular carcinoma (arrows)



CT showing multiple liver metastases (arrows)



REFERENCES

Kovalyova O.N., Ashcheulova T.V. Propedeutics to Internal Medicine. Part 1. – Vinnytsya: NOVA KNYHA, 2017. – 424 p.

Kovalyova O.N., Asheulova T.V. General inspection: manual for students. – Kharkov: "Turbo". – 2004. – 60 p.

Khomazjuk V.A., Ostashevska T.G., Krasyuk I.V. Propaedeutics of Internal Medicine and Patient Care: Study guide for the practical classes. Part I. – Kyiv: NMU, 2005. – 44 p.

Kovalyova O.N., Asheulova T.V. Examination of the patients with cardiovascular disease: manual for students. – Kharkov: "Turbo". – 2003. – 92 p.

KovalyovaO.N., AsheulovaT.V., ShapovalovaS.A. Instrumental methods examination of cardiovascular system: manual for students. – Kharkov: KSMU. – 2004. – 147 p.

Bickley, Lynn S.; Szilagyi, Peter G. Bates' Guide to Physical Examination and History Taking, 10th Edition. – 934 p. Copyright ©2009 Lippincott Williams & Wilkins

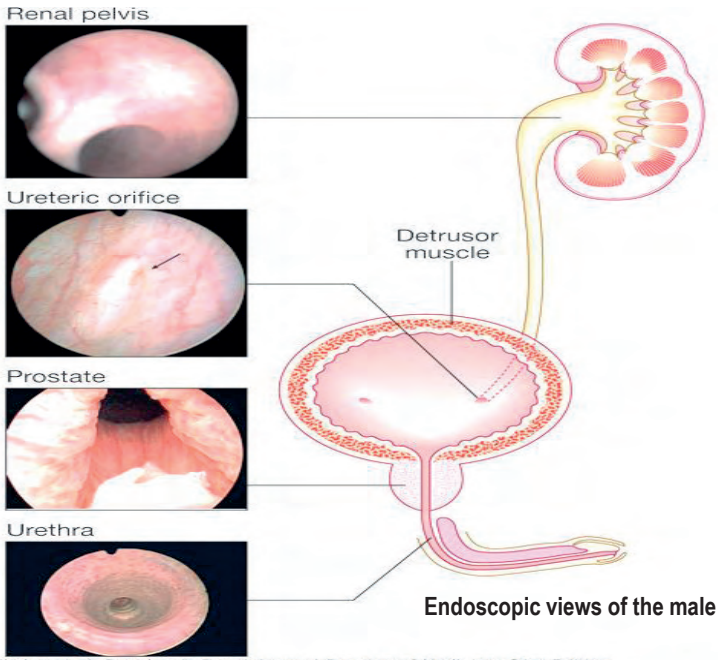
The Point online resources, http://thepoint.lww.com

LECTURE # 15

THE MAIN SYNDROMES OF RENAL DISEASES

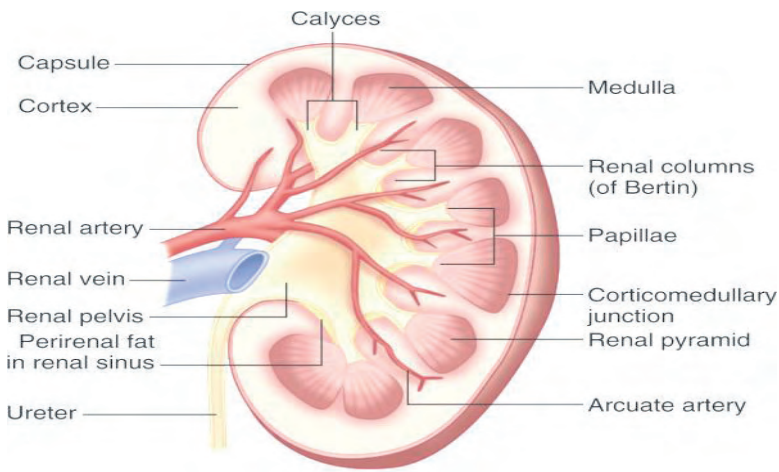
THE PLAN

- Anatomy & main kidney functions
- Classification and manifestations of renal and urinary tract disease
- MAIN SYNDROMES
- PAIN S.
- URINARY S.
- EDEMA S.
- NEPHRITIC S.
- NEPHROTIC S.
- HYPERTENSION S.
- ANEMIA S.
- UREMIA. Renal Failure S.
- ASTHENIC S.
- INFLAMENITORY S.
- Urinary tract obstruction s.
- Cardinal features of kidney and urinary tract disease
- Technique for palpating the kidneys
- Urinalysis. Laboratory Findings
- How is a urinary tract infection diagnosed?
- References

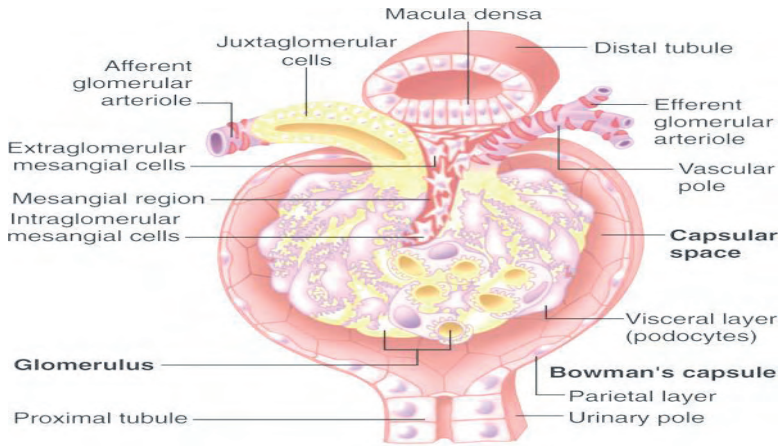


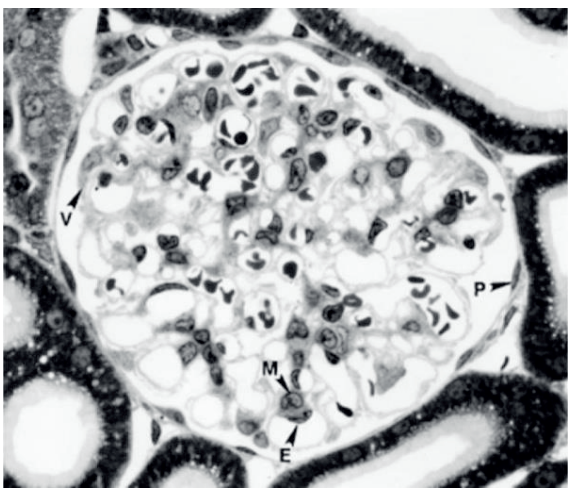
Endoscopic views of the male urinary tract

Sagittal section of the human kidney illustrating its gross anatomic features

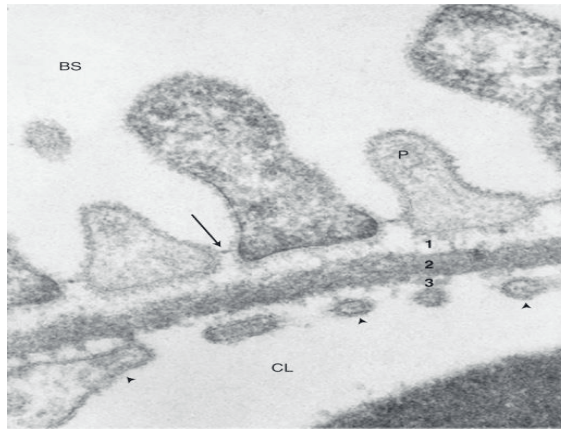


Schematic three-dimensional depiction of the glomerulus





Cross-sectional view of the glomerulus depicting endothelial cells (E), mesangial cells (M), visceral epithelial cells (V), and parietal epithelial cells (P) (×480)



Cross section of the glomerular capillary wall illustrating the pedicels (P) of the visceral epithelial cells, the fenestrated endothelium (arrowheads), and the three layers of the glomerular basement membrane, including the lamina rara externa (1), the lamina densa (2), and the lamina rara interna (3). BS = Bowman's space; CL = capillary lumen; arrow = filtration slit diaphragm (×120,000)

Particularly important kidney hormonal functions

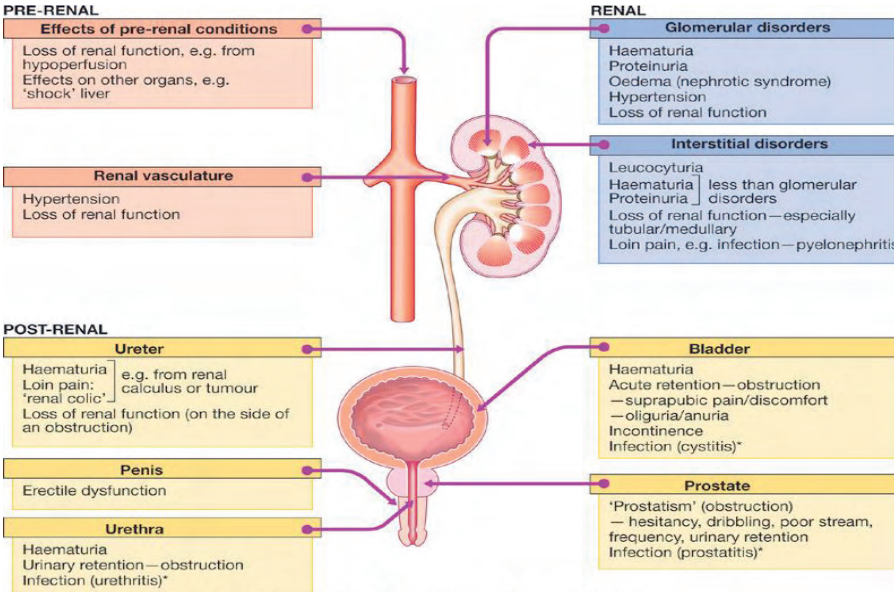
The kidney has a number of hormonal functions

Three of these are particularly important:

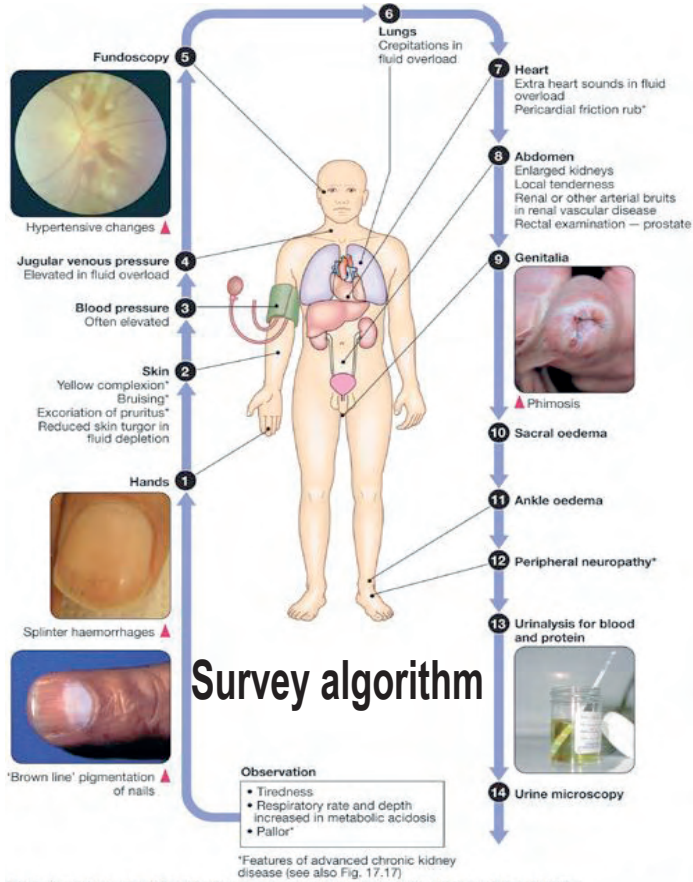
- ***Erythropoietin*** is produced by interstitial peritubular cells in response to hypoxia. Replacement of erythropoietin reverses the anemia of chronic kidney disease
- In ***vitamin D metabolism***, the kidneys hydroxylate 25-hydroxycholecalciferol to the active form, 1,25-dihydroxycholecalciferol. Failure of this process contributes to the hypocalcaemia and bone disease of chronic kidney disease
- ***Renin*** is secreted from the juxtaglomerular apparatus in response to reduced afferent arteriolar pressure, stimulation of sympathetic nerves, and changes in sodium content of fluid in the distal convoluted tubule at the macula densa. Renin generates angiotensin II, which causes aldosterone release from the adrenal cortex, constricts the efferent arteriole of the glomerulus and thereby increases glomerular filtration pressure . Angiotensin II also induces systemic vasoconstriction

- By these mechanisms, the kidneys 'defend' circulating blood volume, blood pressure and glomerular filtration during circulatory shock. However, the same mechanisms lead to systemic hypertension in renal ischemia

Classification and manifestations of renal and urinary tract disease



APPROACH TO THE PATIENT WITH RENAL DISEASE



MAIN SYNDROMES

- PAIN S.
- URINARY S.
- EDEMA S.
- NEPHRITIC S.
- NEPHROTIC S.
- HYPERTENSION S.
- ANEMIA S.
- Renal Failure S.
- UREMIA
- Asthenic syndrome S.
- INFLAMENITORY S.
- Urinary tract obstruction s.

Cardinal features of kidney and urinary tract disease (1)

Upper urinary tract symptoms

- ***Loin pain/tenderness:***

renal infection, renal infarction or rarely obstruction and glomerulonephritis

- ***Severe loin pain (renal or ureteric colic) ± radiation to iliac fossa, groin and genitalia:***

acute obstruction of the renal pelvis and ureter by calculus or blood clot

Cardinal features of kidney and urinary tract disease (2)

Lower urinary tract symptoms

- ***Dysuria, frequency, urgency:***

lower urinary tract infection

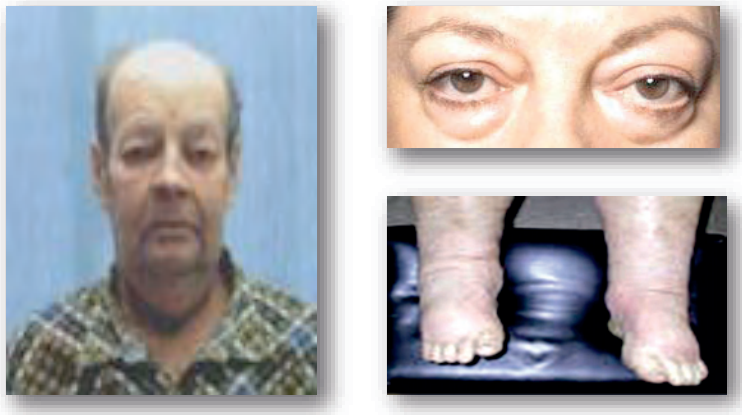
- ***Impaired urinary flow, hesitancy, dribbling of urine, incomplete emptying of bladder:***

bladder outflow obstruction

- ***Urinary retention, incontinence/enuresis:***

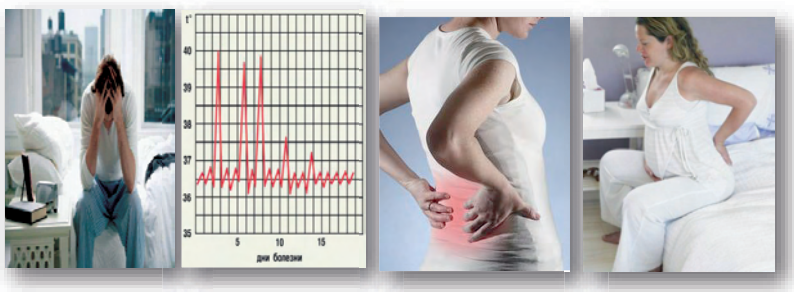
sphincter or bladder wall dysfunction

General observation



Typical edema

COMPLAINS



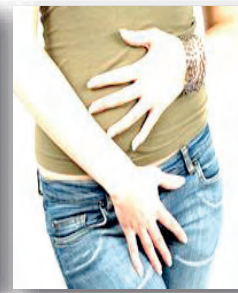
Dysuria
Frequency
Nocturia

Fever with chills

Acute loin pain
(two side)

Dull ache

PAIN



'Renal colic'

Acute loin pain (one side)radiating anteriorly and often to the groin

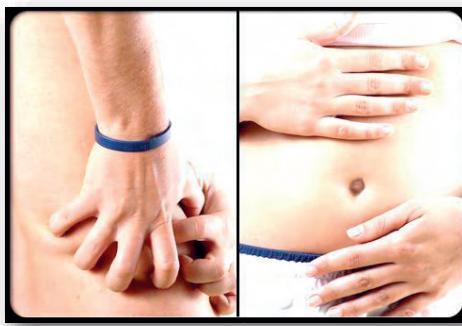
Paranephritis
Forced position

Dull ache in the loin is rarely due to renal disease but the differential diagnosis includes renal stone, renal tumor, acute pyelonephritis or urinary tract obstruction. Upper urinary tract obstruction is most commonly caused by a congenital abnormality of the pelvi-ureteric junction when typically loin pain is precipitated by a large fluid intake. Lower urinary tract obstruction usually presents with oliguria/anuria

Renal colic

Acute loin pain radiating anteriorly and often to the groin ('renal colic'), together with haematuria, is typical of ureteric obstruction most commonly due to calculi, although a sloughed renal papilla, tumor or blood clot may be responsible

What are symptoms of kidney stones?



'Renal colic'

- Kidney stones often cause no pain while they are in the kidneys, but they can cause suddenly, severe pain as they travel from the kidneys to the bladder
- Symptoms and signs include excruciating, cramping pain in the lower back and/or side, groin, or abdomen as well as blood in the urine
- If infection is present in the urinary tract along with the stones, there may be fever and chills

- **Pain and pressure**

- Pain or pressure in the rectum for men or in the area of the pubic bone for women is another possible symptom of urinary tract infection

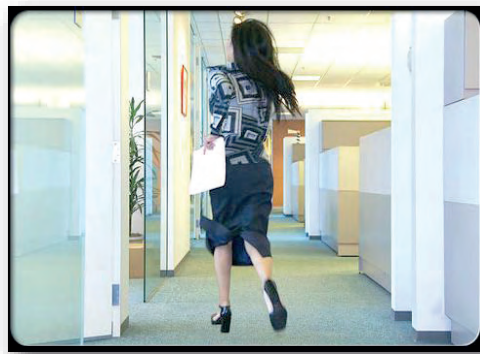
• Painful urination

- Painful or difficult urination, including a burning feeling upon urination, is most commonly due to bacterial infection of the urinary tract causing inflammation of the bladder (cystitis) or urethra (the tube through which urine exits the body)

• Frequent urination

- A feeling of urgency, or feeling the need to urinate frequently, (or waking up at night to urinate), and not being able to hold it is a common symptom of a urinary tract infection

The sudden, overwhelming need to urinate is thought to be caused by spasms of the bladder muscles. These spasms may stem from nerve or muscle damage. In some cases, the damage is associated with a serious illness, such as a stroke or irritation of the bladder caused by an infection or inflammation



Overactive bladder is another name for urge incontinence. There is the same sudden, frequent need to urinate. But not everyone with overactive bladder has incontinence; many women are able to “hold it” until they reach the toilet. Rather than leaking urine, the main challenge for these patients is constantly having to interrupt their activities for trips to the bathroom. Some people have symptoms only during the daytime, while others have frequency only at night

Nocturia

- Waking up at night to void urine may be a consequence of polyuria but may also result from fluid intake or diuretic use in the late evening
- Nocturia also occurs in CKD, and in prostatic enlargement when it is associated with poor stream, hesitancy, incomplete bladder emptying, terminal dribbling and urinary frequency due to partial urethral obstruction
- Nocturia may also occur in sleep disturbance without functional abnormalities of the urinary tract

Urge Incontinence: Symptoms

If often struck by a desperate need to urinate but you can't reach the toilet in time, it may be urge incontinence. The sudden urge may be triggered by the sound of running water, by sipping a drink, or by nothing at all. With this type of incontinence, you may leak large amounts of urine. Also may be find running to the bathroom even when bladder is mostly empty

Incontinence in old age

- **Prevalence:**

Urinary incontinence affects 15% of women and 10% of men aged over 65 years

- **Cause:**

incontinence may be transient due to an acute confusional state, urinary infection, medication (such as diuretics), faecal impaction or restricted mobility, and these should be treated before embarking on further specific investigation

- **Detrusor over-activity:**

established incontinence in old age is most commonly due to detrusor over-activity which may be caused by damage to central inhibitory centres or local detrusor muscle abnormalities

- **Catheterisation:**

poor manual dexterity or cognitive impairment may necessitate the help of a carer to assist with intermittent catheterisation

Cardinal features of kidney and urinary tract disease (3)

- **Abnormal urine volume**

- ***Anuria or oliguria:***

  acute renal failure or obstruction to urine flow

- ***Polyuria or nocturia:***

  failure to concentrate urine (e.g. diabetes insipidus, chronic kidney disease)

Abnormal micturition

Oliguria/anuria

- On an average diet, between 300 and 500 mL/day of urine is required to excrete the solute load at maximum concentration
- **Volumes below this are termed oliguria**
- **Anuria is the (almost) total absence of urine (< 50 mL/day)**
- A low measured urine volume is an important finding, as it suggests reduced production of urine or obstruction to urine flow

Causes of polyuria

- **Excess fluid intake**
- **Osmotic, e.g. hyperglycaemia, hypercalcaemia**
- **Cranial diabetes insipidus** (reduced antidiuretic hormone (ADH) secretion)
  - Idiopathic (50%), mass lesion, trauma, infection
- **Nephrogenic diabetes insipidus** (tubular dysfunction)
  - Genetic tubular defects
  - Drugs/toxins, e.g. lithium, diuretics
  - Interstitial renal disease
  - Hypokalaemia, hypercalcaemia

Urinary tract obstruction

- The most common causes of lower urinary tract obstruction causing reduced volume of micturition are urinary calculi, prostatic enlargement (benign or malignant), or pelvic and retroperitoneal tumors in an older age group
- About 50% of cases of acute urinary retention are seen after general anesthesia, particularly in those with pre-existing prostatic enlargement. In young men, bladder neck dyssynergia may also cause obstruction
- Urethral strictures (more likely if there is a history of instrumentation), trauma or urethral infection, urethral valves, phimosis and meatal stenosis are other common causes. Poor flow and post-micturition residual bladder volume are also seen in atonic bladders (e.g. in neurological disorders such as multiple sclerosis and spina bifida), when there is reduced/absent detrusor muscle activity and a failure of the distal sphincter to relax

Cardinal features of kidney and urinary tract disease (4)

Abnormal urinary constituents

- *Proteinuria:*
  suggests glomerular disease; massive proteinuria causes edema

- *Haematuria:*
  disease anywhere in the urinary tract

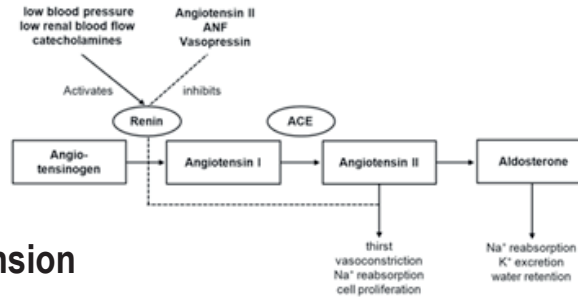
Nephritic syndrome

- **Haematuria (red or brown urine)**
- **Edema and generalized fluid retention**
- **Hypertension**
- **Oliguria**

Nephrotic syndrome

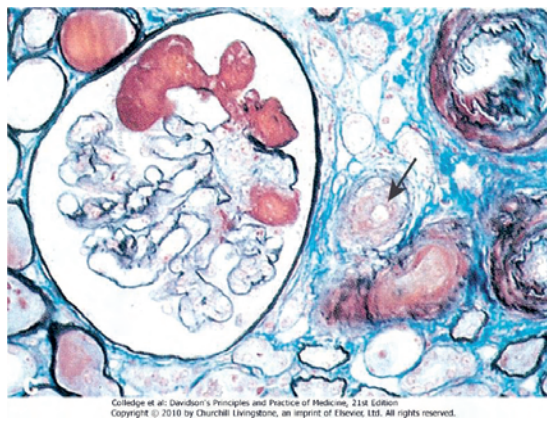
- **Overt proteinuria:** usually > 3.5 g/24 hrs (urine may be frothy)
- **Hypoalbuminaemia (**< 30 g/L, disproteinemia)
- **Hyperlipidemia** (& dislipidemia)
- **Oedema** and generalised fluid retention
  (intravascular volume depletion with hypotension, or expansion with hypertension, may occur)

Cardinal features of kidney and urinary tract disease (5)

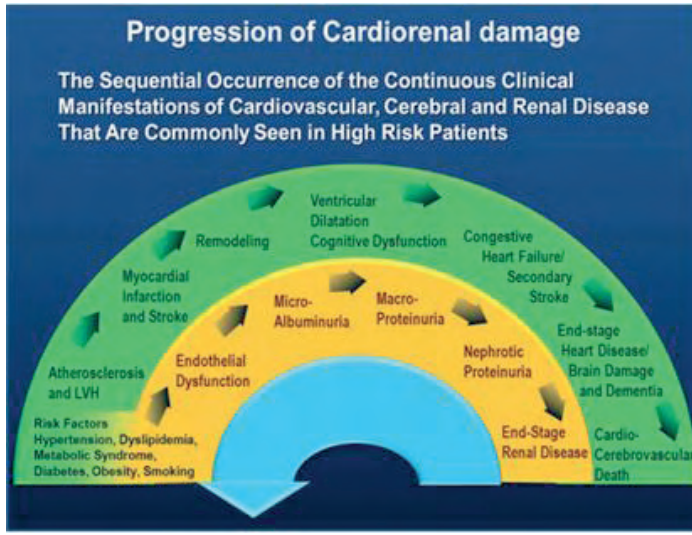


Hypertension

Acute or chronic parenchymal disease or renovascular disease



Glomerular capillary thrombosis in malignant hypertension.
Similar changes occur in thrombotic microangiopathy. The adjacent arteriole (arrow) shows gross intimal thickening



Cardinal features of kidney and urinary tract disease (6)

Uraemia

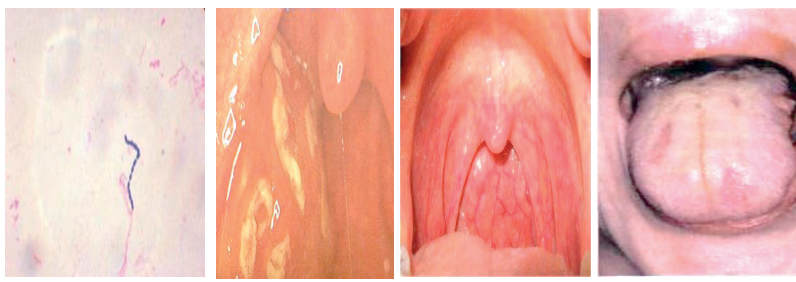
A group of symptoms and signs of advanced kidney disease

History

The history reviews potential factors that contribute to the development of renal disease and identifies the systemic features of diseases that may affect the kidney. These factors include

Family history of renal disease
The time of onset of symptoms of renal dysfunction
Changes in bladder function, including nocturia, polyuria, and hesitancy
Fatigue and weakness
Dyspnea on exertion, a manifestation of fluid overload or acidosis

Inciting causes of glomerulonephritis

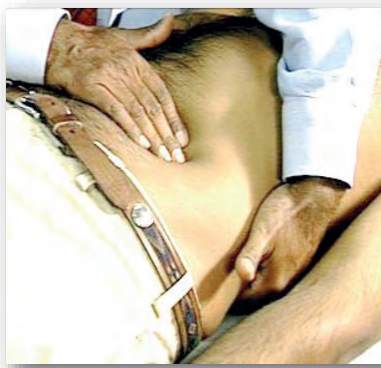


Infectious agents such as streptococci

Abdomen

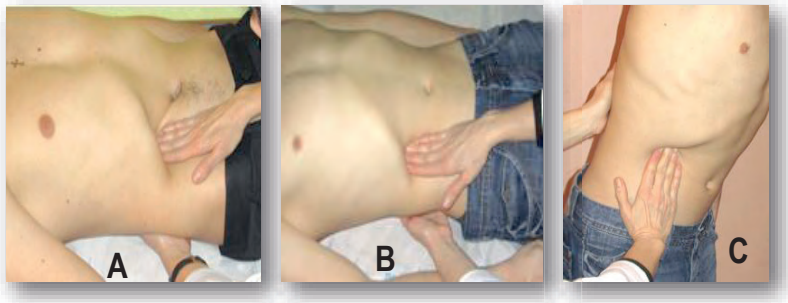
•Technique for palpating the kidneys

- Lie the patient flat with abdominal muscles relaxed
- Place one hand posteriorly just below the lower ribs and the other anteriorly over the upper quadrant
- Push the hands towards each other as the patient breathes out; feel for the lower pole of the kidney moving down between the hands as the patient breathes in
- To confirm a palpable kidney, push the kidney backwards and forwards between the hands ('ballotting')
- Assess the size, surface and consistency of a palpable kidney; e.g. polycystic kidneys are often massively enlarged with an irregular, nodular surface



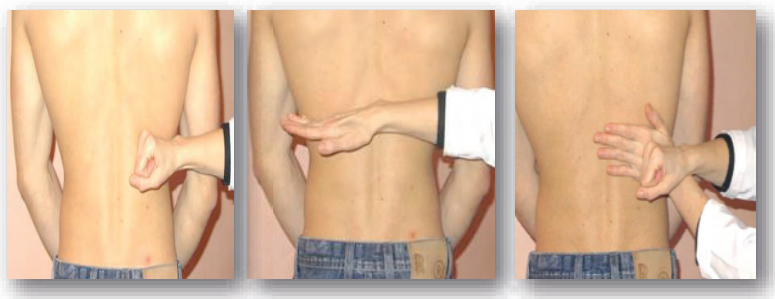
In an adult, the kidneys are not usually palpable, except occasionally for the inferior pole of the right kidney. The left kidney is rarely palpable. An easily palpable or tender kidney is abnormal. However, the right kidney is frequently palpable in very thin patients and children

- **A** Place one hand posteriorly just below the lower ribs and the other anteriorly over the upper quadrant
- Push the hands towards each other as the patient breathes out; feel for the lower pole of the kidney moving down between the hands as the patient breathes in

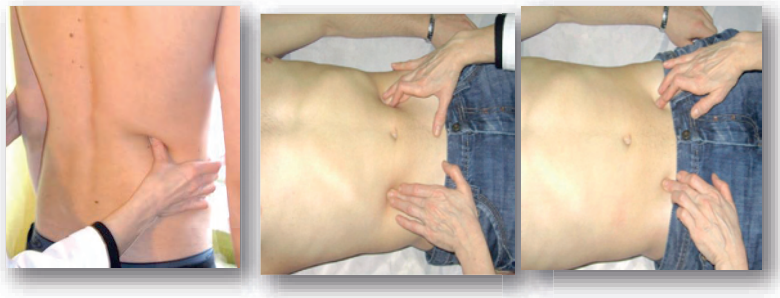


B To confirm a palpable kidney, push the kidney backwards and forwards between the hands ('ballotting')

C Upright position



"Knocking" symptom in lumbar area



Ureter's points

Possible findings

- **Normal findings:**

the right kidney and lower pole of the left kidney may be palpable in normal slim adults

- **Enlarged kidneys:**

polycystic kidney disease, hydronephrosis/pyonephrosis, solitary cyst, compensatory hypertrophy in a single kidney, renal tumors and renal amyloid

- **Tender kidneys:**

may reflect infection or inflammation

- **Transplanted kidney:**

palpable in the iliac fossa, with an overlying scar

- **Distended bladder:**

smooth midline mass arising from the pelvis, dull to percussion

- **Arterial bruits:**

on either side of the epigastrium, may indicate renal artery stenosis

- **Testicular mass**
- **Prostate enlargement on rectal examination:**

benign enlargement is characteristically smooth and regular; an enlarged, hard, irregular prostate suggests prostatic cancer

Urinalysis

The analysis of the urine sample involves simple observation and separate measurements using specific tools or commercially available dipsticks

Appearance and Color

The normal color of the urine is derived from urochromes, which are pigments excreted in the urine. Abnormal color or appearance of the urine may be explained by many conditions

• Urine color and clarity

• People with a urinary tract infection may notice an altered appearance of the urine. The urine may be as bloody (red), cloudy (containing pus), or bad-smelling

Appearance	Cause
Milky	Acid urine: urate crystals
	Alkaline urine: insoluble phosphates
	Infection: pus
	Spermatozoa
	Chyluria
Smoky pink	Hematuria (>0.54 mL blood/L urine)
Foamy	Proteinuria
Blue or green	*Pseudomonas* urinary tract infection
	Bilirubin
	Methylene blue
Pink or red	Aniline dyes in sweets
	Porphyrins (on standing)
	Blood, hemoglobin, myoglobin
	Drugs: phenindione, phenolphthalein
	Anthocyaninuria (beetroot-"beeturia")
Orange	Drugs: anthraquinones (laxatives), rifampicin
	Urobilinogenuria
Yellow	Mepacrine
	Conjugated bilirubin
	Phenacetin
	Riboflavin
Brown or black	Melanin (on standing)
	Myoglobin (on standing)
	Alkaptonuria
Green or black	Phenol
	Lysol
Brown	Drugs: phenazopyridine, furazolidone,
	L-dopa, niridazole
	Hemoglobin and myoglobin (on standing)
	Bilirubin

MACROSCOPIC APPEARANCE OF URINE

Specific Gravity

- The specific gravity of the urine can be raised by the presence of an increased number of solutes or by molecules with a high molecular weight, such as glucose or contrast dye
- There is a linear relationship between specific gravity and osmolality, unless there is glycosuria or excretion of contrast media, in which case the specific gravity is higher
- A fixed specific gravity of 1.010 is characteristic of chronic kidney disease

pH

- Urine pH is often 5 as a result of daily net acid excretion
- An alkaline pH often is noted after meals, when an "alkaline tide" associated with gastric acid excretion causes a high urine pH. A high urine pH also is seen in patients who are on a vegetarian diet or who have an infection with a urea-splitting organism, such as *Proteus*
- An inappropriately high urine pH in the setting of systemic non–anion gap metabolic acidosis may be seen in certain forms of renal tubular acidosis (RTA)
- In a proximal RTA, the urine pH is high until the tubular threshold for bicarbonate, which is reset, is reached. At this point, the urine pH decreases to 5
- In distal RTA, there is usually an inability to create a sufficient gradient for hydrogen ion (H^+) excretion, and the urine pH is always higher than 5.5
- The urine net charge gives complementary and confirmatory information
- In type 4 RTA, the urine pH is often 5, and the urine net charge is often positive, confirming the absence of significant amounts of ammonium in the urine, a defect that is exacerbated by the accompanying hyperkalemia

Glucose

- Glucose in the urine is detected by an assay using dipsticks impregnated with the enzyme glucose oxidase
- Glycosuria is seen in diabetes mellitus, when pregnancy causes the tubular threshold for glucose reabsorption to change, and in tubular diseases that affect the proximal convoluted tubule and cause tubular glycosuria
- Evidence for pan-proximal tubular dysfunction (e.g., glycosuria, aminoaciduria, phosphaturia) indicates that Fanconi's syndrome is present

Protein

- The dipstick for protein is a sensitive assay based on color change induced by the presence of proteins at a given pH. It is most sensitive to the presence of albumin and is much less sensitive to other proteins, such as the light chains of Bence Jones protein

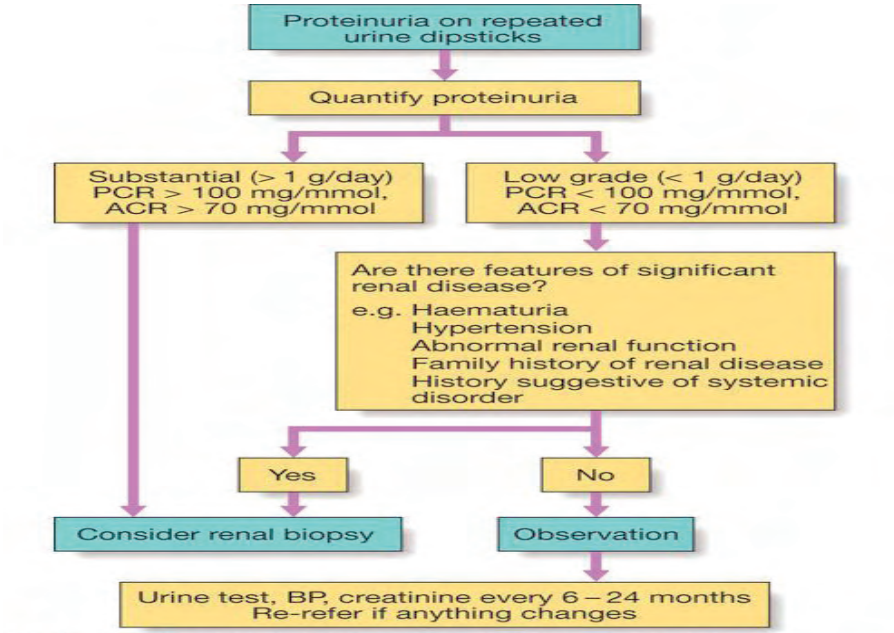
- The presence of 1+ protein correlates with about 30 mg/dL of albuminuria, and 3+ protein correlates with greater than 500 mg/dL of proteinuria. Because the dipstick is not a quantitative measurement, small amounts of proteinuria in an oliguric patient may give the false appearance of high-grade proteinuria

Urine for Microalbumin

- The excretion of abnormal quantities of albumin below the level detectable by the urine dipstick is called *microalbuminuria*.
- Normal albumin excretion is less than 30 mg/day. This is detected by radioimmunoassay or enzyme immunoassay
- Microalbuminuria is the earliest clinically detectable stage of diabetic nephropathy

Proteinuria

Moderate amounts of low molecular weight protein pass through the healthy GBM. These proteins are normally reabsorbed by receptors on tubular cells. Less than 150 mg/day of protein normally appears in urine, and a proportion of that is Tamm-Horsfall protein secreted by the tubules



Colledge et al: Davidson's Principles and Practice of Medicine, 21st Edition

Microalbuminuria

- **Microalbuminuria** describes the urinary excretion of small amounts of albumin
- The presence of albumin in the urine is a clear sign of glomerular abnormality and can identify the very early stages of progressive glomerular disease, e.g. in diabetic nephropathy. Because significant renal damage will have occurred before dipstick tests become positive, patients with diabetes mellitus should be screened regularly for **microalbuminuria**
- **Persistent microalbuminuria** has also been associated with an increased risk of atherosclerosis and cardiovascular mortality; neither the mechanism of proteinuria nor an explanation of these associations has yet been established

Laboratory Findings

Urinalysis is central to the renal evaluation of the patient. The following aspects of the assessment of the urine are important in the approach to the patient with renal disease

Twenty-four Hour Urine Collection for Protein Excretion

- **Proteinuria (as albuminuria) of greater than 3.5 g in 24 hours indicates glomerular disease.** Lesser quantities do not preclude glomerular disease, and electrophoresis gives valuable insight into the composition of the proteinuria
- Occasionally, overflow proteinuria of a small-molecular-weight protein, such as light chains in **Bence Jones proteinuria**, can be greater than 3.5 g/day without any of the manifestations or implications of the **nephrotic syndrome**
- A urine protein electrophoresis study is important in making the distinction. Collection must be done by discarding the first morning void and collecting the voids for the next 24 hours, including the first morning void the next day

Urine Sediment

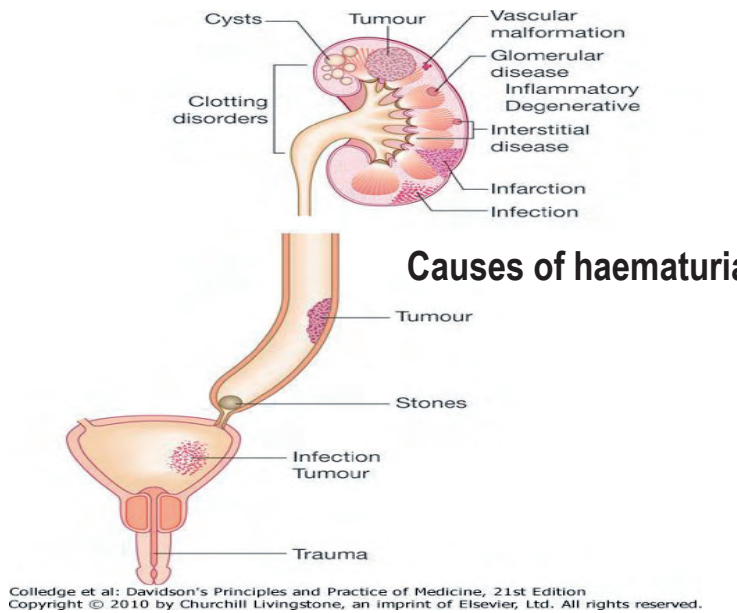
Cells

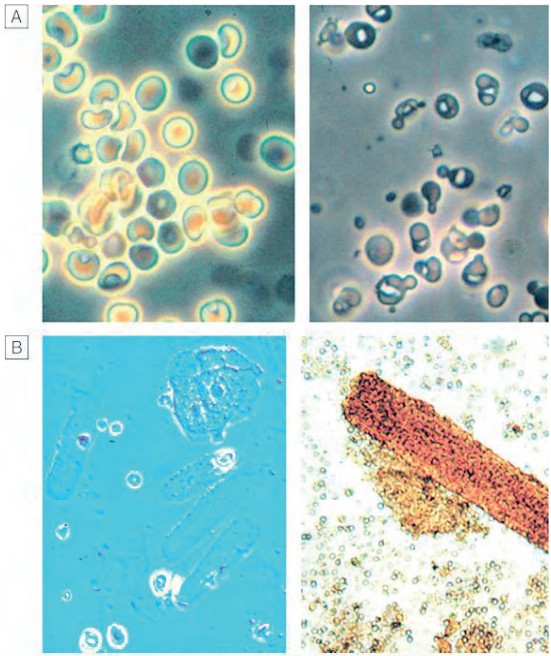
The urine sediment is the most crucial step in the evaluation of renal disease. The sediment gives an insight through the cellular elements resulting from activity within the kidney. The cells that may be seen include RBCs, white blood cells (WBCs), tubular cells, transitional cells, and squamous epithelial cells. Casts are formed in tubules and may contain cells or be acellular

Urine Sediment

Cells

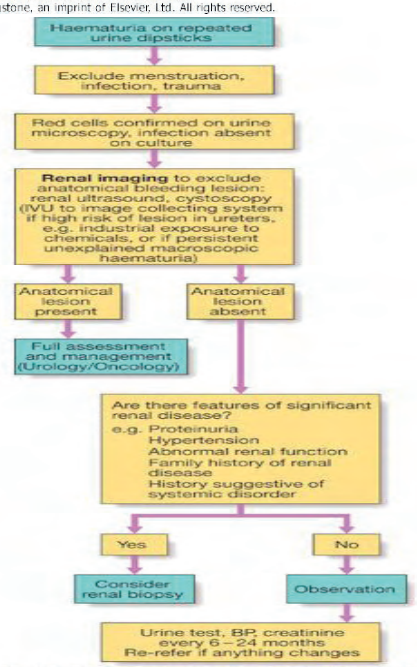
- RBCs may originate from intrarenal vessels, glomeruli, tubules, or anywhere in the urogenital tract
- Dysmorphic RBCs are cells that have been deformed by transit through glomeruli, as opposed to RBCs from the remainder of the genitourinary tract
- The cells are often lysed and less refractile than nonglomerular RBCs. They often fragment with poikilocytosis and with blebs, forming so-called Mickey Mouse RBCs. Phase contrast microscopy aids in the identification of dysmorphic RBCs
- The presence of a majority of dysmorphic RBCs in a urine sediment points to a glomerular origin for the hematuria
- The presence of RBC casts is often conclusive evidence for the presence of glomerulonephritis

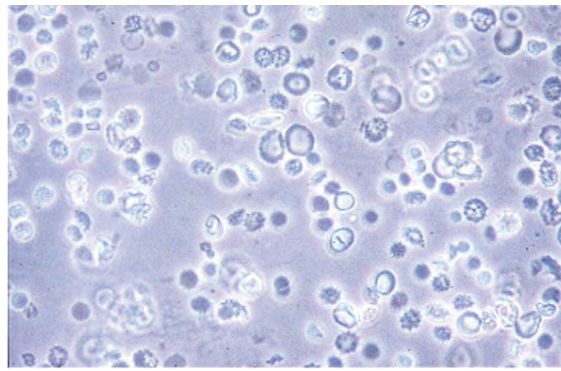




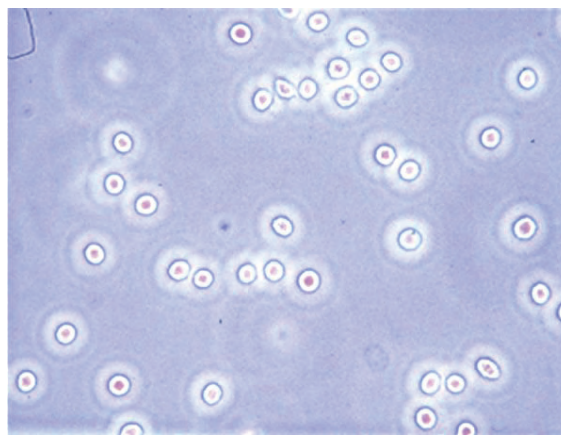
Urine microscopy

Phase contrast images of red blood cells (× 400) showing on the right glomerular bleeding with many dysmorphic forms including acanthocytes (teardrop forms), and on the left bleeding from lower in the urinary tract. On the left, phase contrast images show hyaline casts, a normal feature of urine (× 160). On the right, numerous red cells and a large red cell cast in acute glomerular inflammation (× 100, not phase contrast)





Dysmorphic erythrocytes.
These dysmorphic erythrocytes vary in size, shape, and hemoglobin content and reflect glomerular bleeding



Isomorphic erythrocytes.
These erythrocytes are similar in size, shape, and hemoglobin content. Isomorphic cells reflect nonglomerular bleeding from lesions such as calculi or papillomas or hemorrhage from cysts in polycystic renal disease

Haematuria and urothelial malignancy

Macroscopic haematuria has a positive predictive value of 83% for bladder cancer and 22% for all urothelial tumors, rising to 41% in patients over the age of 40'

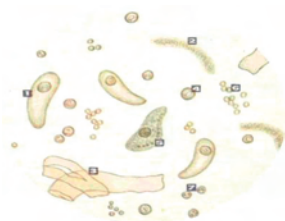
Urine Sediment

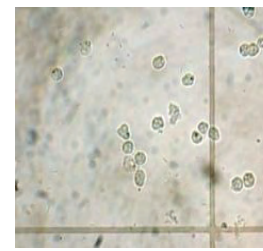
Cells

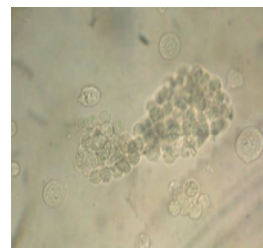
- WBCs are seen most commonly in urinary tract infections
- They also can be seen in acute interstitial nephritis, with *Legionella* and *Leptospira* infections, chronic infections such as tuberculosis, allergic interstitial nephritis, atheroembolic diseases, and granulomatous diseases such as sarcoidosis and tubulointerstitial nephritis syndrome
- Mononuclear cells often appear with transplant rejection. Tubular cells are seen in many conditions involving tubulointerstitial diseases
- They also are seen in ischemic and nephrotoxic injury, such as with myeloma kidney or cast nephropathy
- Eosinophils require special stains, with the Giemsa stain being much less sensitive than the Hansel stain. Urine eosinophils are seen in a variety of conditions. Classically associated with allergic interstitial nephritis, they also have been documented in atheroembolic disease, prostatitis, and vasculitis

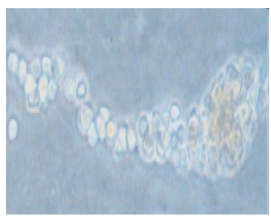
Leukocytes

The detection of leukocytes depends on the presence of leukocyte esterase in leukocytes. They usually are present in infections and in inflammatory conditions









Other Elements

- Other elements that may be seen in the urine sediment are bacteria
- A spun urine sediment may show rods or cocci in chains, but these are identified best by Gram staining of the urine sediment
- In the sediment, one may see budding yeast forms, which are highly refractile, and spermatozoa

Casts (1)

Casts are formed in tubules and are characterized by the arrangement of the cells in a clearly formed matrix composed of Tamm-Horsfall protein

Because casts are formed in the renal parenchyma, they may give a clue to the origin of accompanying cellular elements

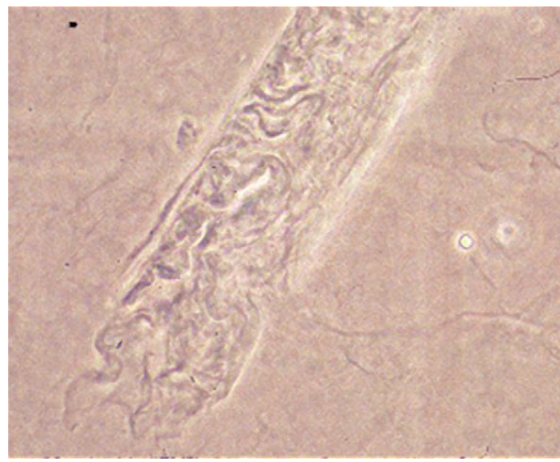
- ***Hyaline casts*** are casts of Tamm-Horsfall proteins that are formed normally and are seen in increased numbers after exercise
- ***Granular casts*** are degenerated tubular cell casts that are seen in the setting of tubular injury
- ***Pigmented granular casts*** are seen in rhabdomyolysis with myoglobinuria

Casts (2)

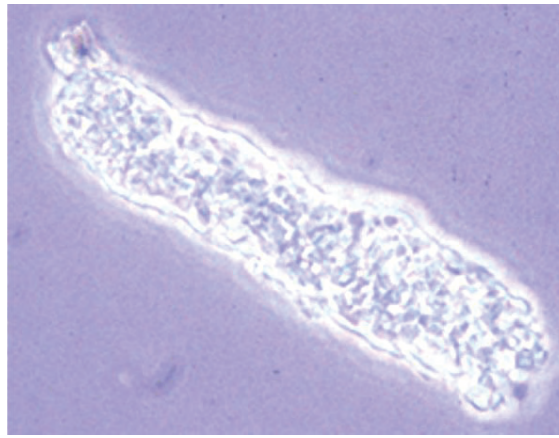
• ***RBC casts*** are diagnostic of glomerulonephritis . Although they have been reported in allergic interstitial nephritis and diabetic nephropathy, they almost always are seen in acute glomerulonephritis. The presence of RBC casts in a patient with microscopic hematuria can narrow the focus of the work-up to a glomerular lesion

• ***WBC casts*** are seen commonly in pyelonephritis and in acute and chronic nonbacterial infections. They also are seen in other conditions in which WBCs are associated with parenchymal renal processes, such as allergic interstitial nephritis, atheroembolic diseases, and granulomatous diseases such as sarcoidosis. Rarely, they can be a dominant feature of many diseases that traditionally are thought of as glomerular diseases, such as SLE and Wegener's granulomatosis

• ***Tubular cell casts*** are seen with any acute tubular injury and are the dominant cellular casts in ischemic acute tubular necrosis. They also can be seen with nephrotoxic injury, such as with aminoglycosides and cisplatin. Casts may have leukocytes and tubular cells or be difficult to distinguish.



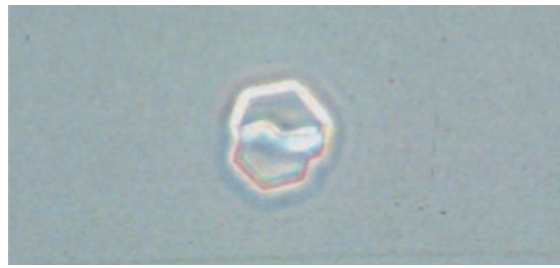
Hyaline cast of the type seen in small numbers in normal urine



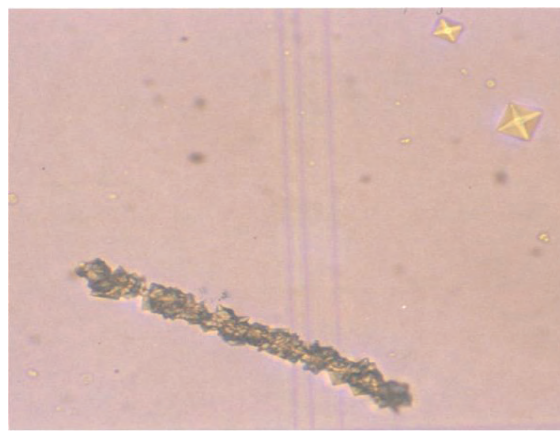
Number and type of granules and their density in the cast vary in different casts. The presence of erythrocytes in this cast may mean that the granules are derived partly from disrupted erythrocytes

Crystals

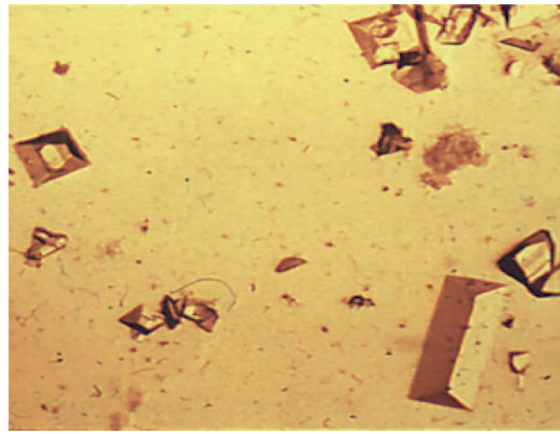
- Crystals often can be a normal finding in the urine or serve as clues to pathophysiologic processes. Certain crystals, such as the hexagonal crystals seen with cystinuria, are always abnormal
- Others, such as calcium oxalate crystals, may be a normal finding or may be evidence for ethylene glycol intoxication in a patient with anion gap metabolic acidosis, acute renal failure, or hypocalcemia and mental status change
- Triple phosphate crystals are composed of ammonium magnesium phosphate and are coffin shaped. These are seen in urinary tract infections with urea splitting organisms
- Uric acid crystals, sodium urate crystals , and calcium phosphate amorphous crystals all are common and do not denote any pathologic significance



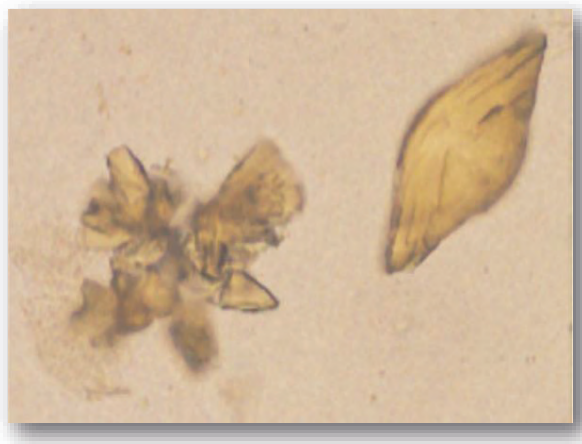
Typical hexagonal cystine crystal.
A single crystal provides a definitive diagnosis of cystinuria



Oxalate crystals.
A pseudocast of calcium oxalate crystals accompanied by crystals of calcium oxalate dehydrate



Coffin-lid crystals of magnesium ammonium phosphate (struvite)



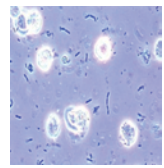
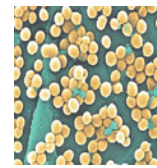
Urate crystals.
Complex crystals suggestive of acute urate nephropathy or urate nephrolithiasis

Serology and Urine Tests for the Evaluation of Renal Disease

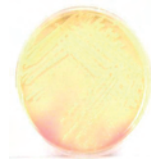
- The evaluation of renal dysfunction has to follow a stepwise progression from noninvasive serologic evaluation to a definitive or confirmatory diagnostic evaluation, such as a renal biopsy. Sometimes an expeditious diagnosis is needed, and a biopsy may be done relatively early in the evaluation
- The advent of improved serologic diagnostic markers for certain diseases such as Wegener's granulomatosis has made the role of biopsy less mandatory than in the past. The following serologic tests are used commonly in the evaluation of renal insufficiency

How is a urinary tract infection diagnosed?

- Urine testing (urinalysis) will establish the diagnosis of a urinary tract infection. The urine is examined for the presence of red blood cells that signify bleeding into the urine and for white blood cells that signify infection. A culture of the urine is also taken to identify the organism responsible for the infection and to determine the effectiveness of different antibiotics against the offending organism. If recurrent infections develop, further types of testing including imaging studies and/or visual examination of the bladder (cystoscopy) may be recommended

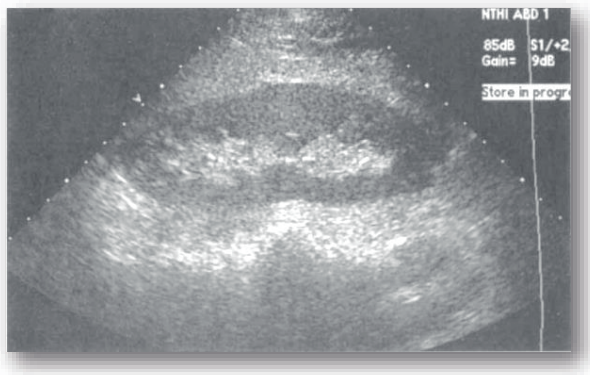





A culture of the urine

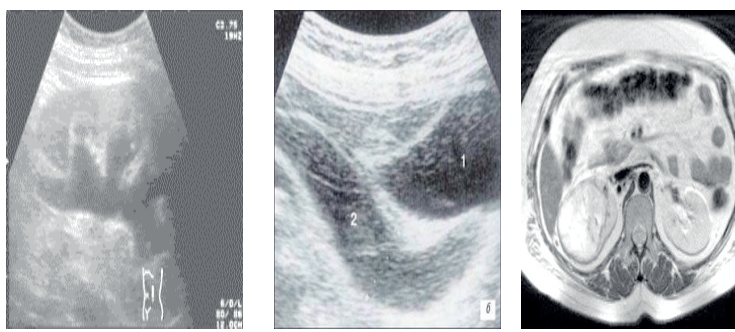



▪ Imaging

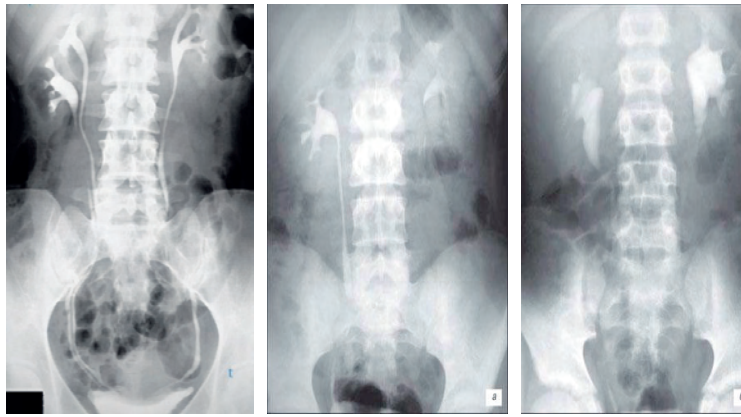
- A variety of renal imaging techniques have been developed to assist in the evaluation of diseases of the kidney
- Plain radiography of kidney, ureter, and bladder (KUB) was used in the past for estimation of renal size and in the evaluation of calcium stones. It has been largely replaced by other studies
- Intravenous pyelography has been largely replaced by computed tomography (CT) scanning for the evaluation of renal size and the detection of stones and masses



Normal sagittal renal ultrasound.
The cortex is hypoechoic compared with the echogenic fat containing the renal sinus

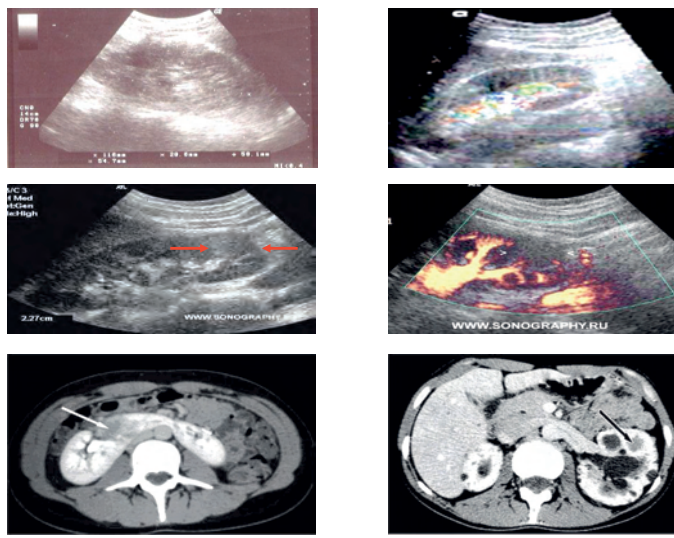


Imaging studies

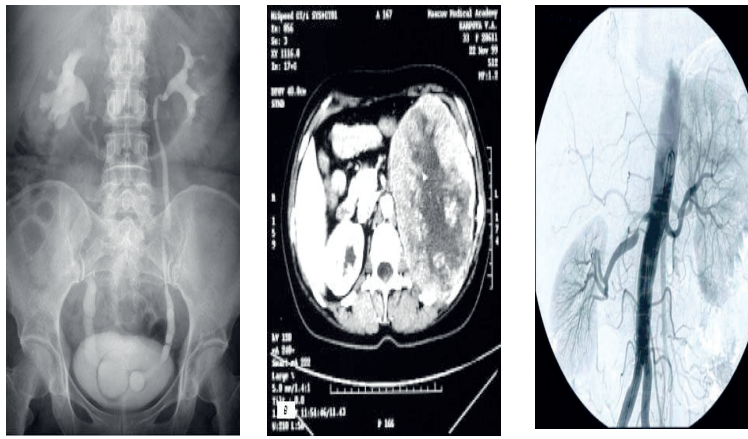


Imaging studies

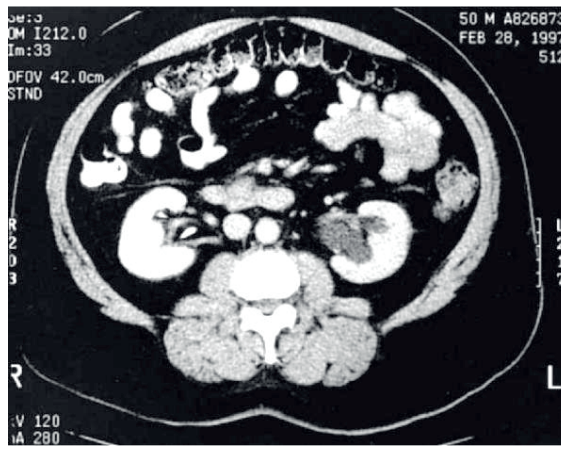
Imaging studies



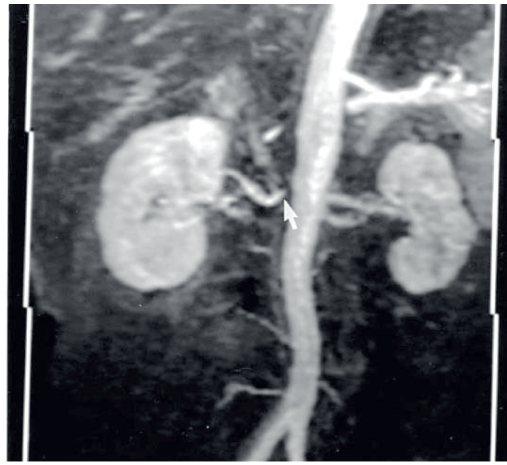
Horseshoe kidney



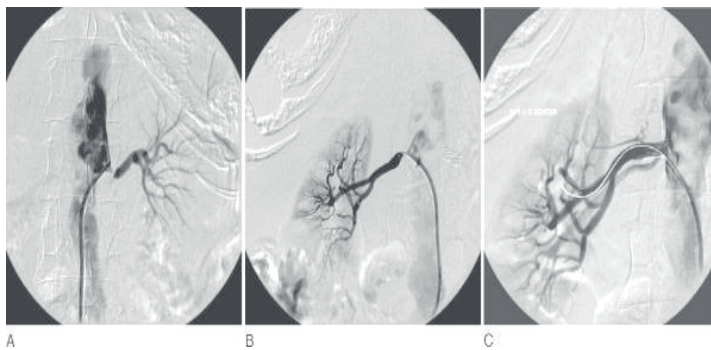
Imaging studies



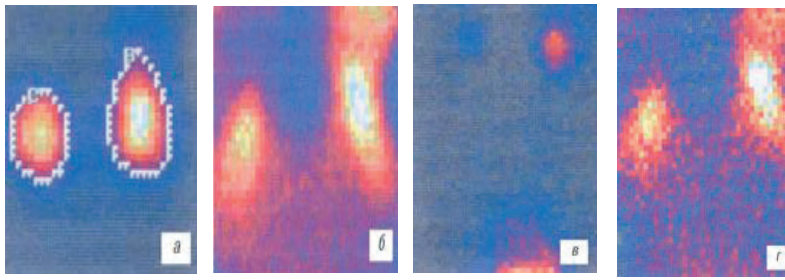
Delayed excretion in the left kidney secondary to a distal calculus. Contrast-enhanced computed tomography scan shows dilated left renal pelvis (arrow)



Magnetic resonance angiography.
Coronal three-dimensional image shows right renal artery stenosis (arrow)

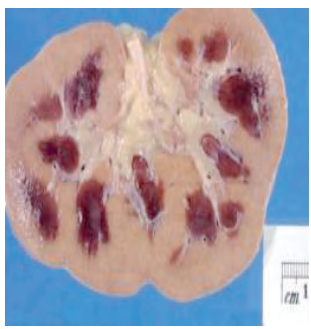


Renal angiograms from an elderly patient with heart failure. Cardiac catheterization revealed normal coronary arteries, but after initiation of therapy with an angiotensin-converting enzyme inhibitor and spironolactone, progressive kidney disease with hyperkalemia and poor blood pressure control ensued. Renal Doppler ultrasonography suggested bilateral renal artery stenosis, as confirmed by angiography (**A** and **B**). The patient underwent successful percutaneous revascularization in stages with return to normal left ventricular function and improved blood pressure control **(C)**

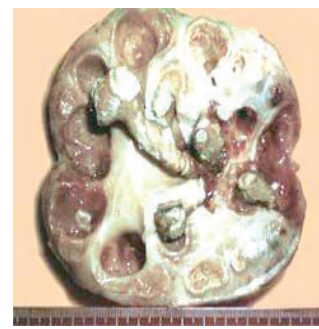


N

Imaging studies



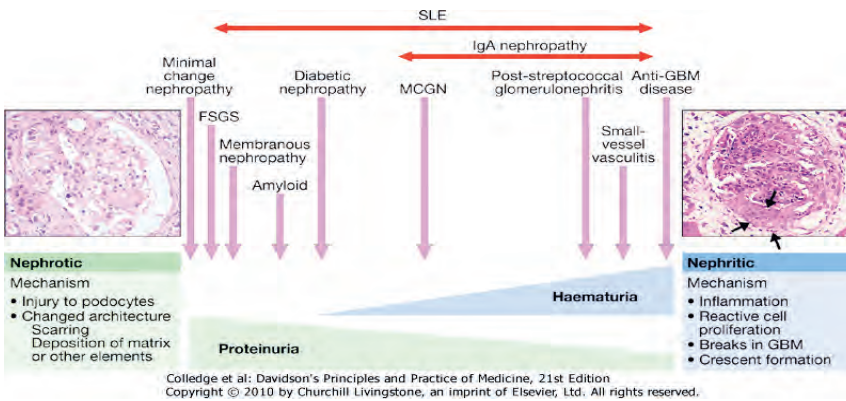
N



Polycystic kidney disease

Nephritic syndrome

- **Haematuria (red or brown urine)**
- **Edema and generalized fluid retention**
- **Hypertension**
- **Oliguria**



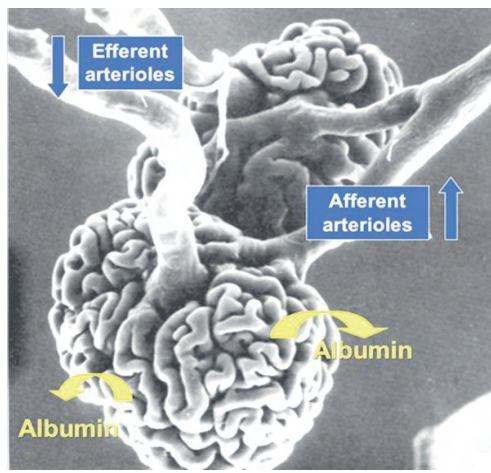
Spectrum of glomerular diseases

At one extreme, specific injury to podocytes, or structural alteration of the glomerulus affecting podocyte function causes proteinuria and nephrotic syndrome. The histology to the left shows diabetic nephropathy. At the other end of the spectrum, inflammation leads to cell damage and proliferation, breaks form in the GBM and blood leaks into urine. In its extreme form, with acute sodium retention and hypertension, such disease is labelled nephritic syndrome (FSGS = focal and segmental glomerulosclerosis; MCGN = mesangiocapillary glomerulonephritis). The histology to the right shows a glomerulus with many extra nuclei from proliferating intrinsic cells and influx of inflammatory cells shows crescent formation (arrows) in response to severe post-infectious glomerulonephritis

NEPHROTIC SYNDROME

Definition

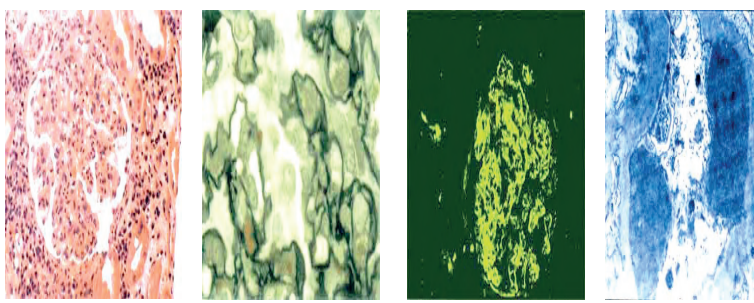
The nephrotic syndrome is defined by albuminuria in amounts of more than 3 to 3.5 g/day accompanied by hypoalbuminemia, edema, and hyperlipidemia. In practice, many clinicians refer to “nephrotic-range” proteinuria regardless of whether their patients have the other manifestations of the full syndrome because the latter are consequences of the proteinuria



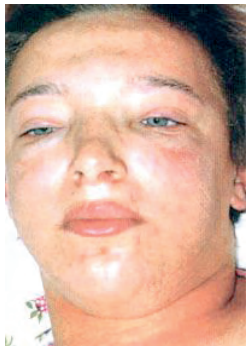
The nephrotic syndrome is defined by albuminuria

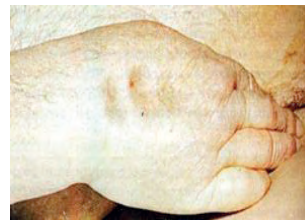
Pathobiology

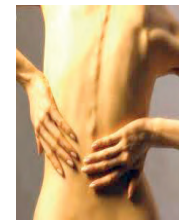
Hypoalbuminemia is in part a consequence of urinary protein loss. It is also due to the catabolism of filtered albumin by the proximal tubule, as well as redistribution of albumin within the body. This in part accounts for the inexact relationship between urinary protein loss, the serum albumin level, and other secondary consequences of heavy albuminuria



The histology shows a glomerulus specific injury to podocytes, or structural alteration of the glomerulus affecting podocyte function causes proteinuria and nephrotic syndrome

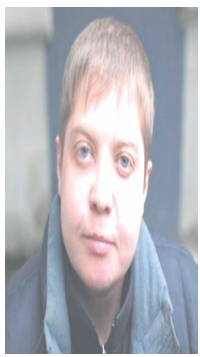




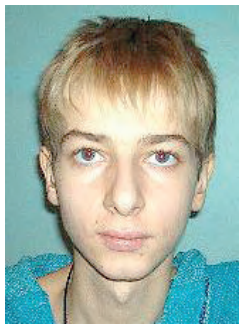
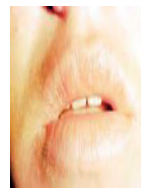
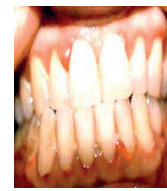


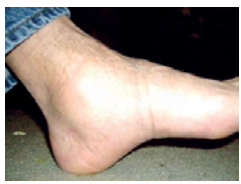
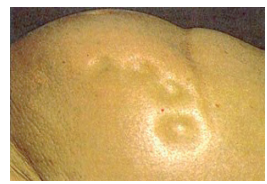
Typical oedema

Dull ache (two side)

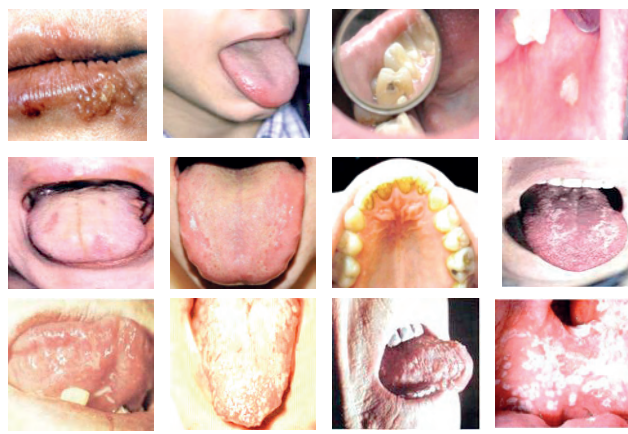


Typical “pale” or “yellowish” oedema


Typical “pale” or “yellowish” oedema, anemia, bleeding (gums, nose. ets.), HBP



Herpes labials, mucosal erosions, candidacies

WHEN TO CONSIDER A RENAL BIOPSY IN DIAGNOSING NEPHRITIS

The setting, history, or clinical findings do not support a diagnosis of acute tubular necrosis or volume depletion
The clinical setting warrants a tissue diagnosis to determine the type of lesion, the extent of involvement, or the degree of fibrosis
The patient is stable enough to undergo biopsy and receive immunosuppressive drugs
The physician believes that the choice of therapy or the length of treatment is partially determined by the type of tissue injury

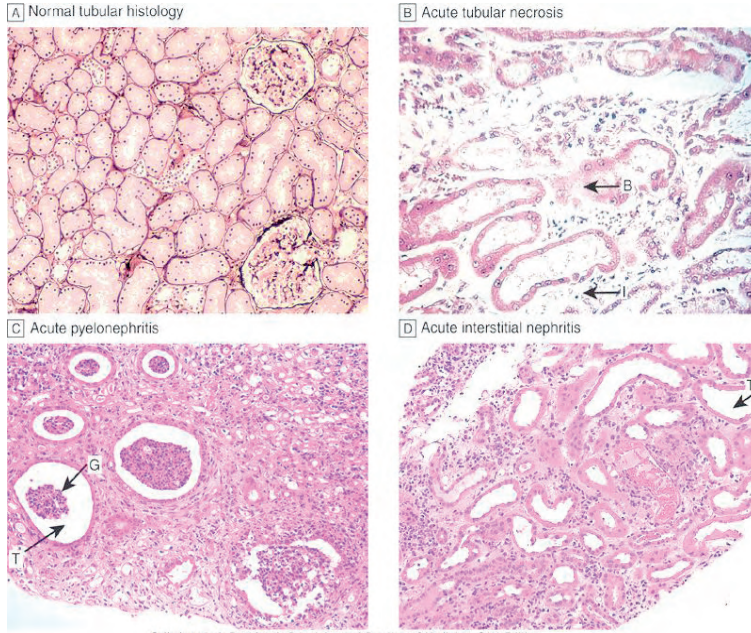
Renal biopsy

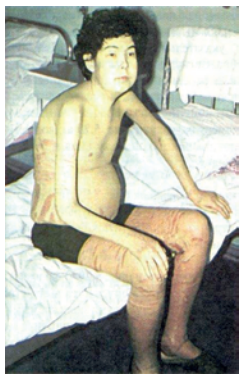
Indications

- Acute renal failure that is not adequately explained
- CKD with normal-sized kidneys
- Nephrotic syndrome or glomerular proteinuria in adults
- Nephrotic syndrome in children that has atypical features or is not responding to treatment
- Isolated haematuria or proteinuria with renal characteristics or associated abnormalities

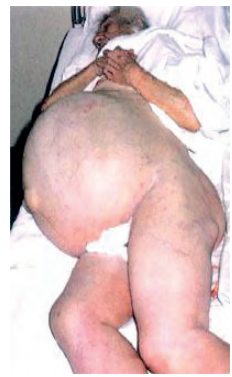
Contraindications

- Disordered coagulation or thrombocytopenia
- Aspirin and other antiplatelet agents increase bleeding risk
- Uncontrolled hypertension
- Kidneys < 60% predicted size
- Solitary kidney (except transplants) (relative contraindication)

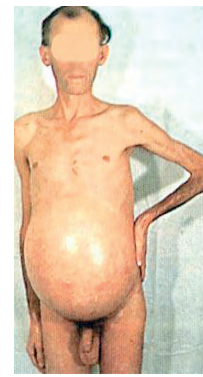




GLOMERULAR DISEASES



HEART DISEASES



LIVER DISEASES

General oedema, ascetics

Nephrolithiasis

Definition

- A kidney stone is a crystalline mass formed in the kidney that is of sufficient size to be clinically detectable, either by symptoms or imaging. Although stones may also form in other parts of the urinary tract, this chapter focuses on stones that originate in the kidney (but may subsequently move distally to other locations in the urinary tract)

- There are many different types of kidney stones, and the composition of the stone determines the clinical evaluation, treatment, and prognosis. The most common component is calcium oxalate; other types are calcium phosphate, uric acid, struvite, and cystine stones . Infrequently, stones may be composed of medications, including acyclovir, indinavir, and triamterene

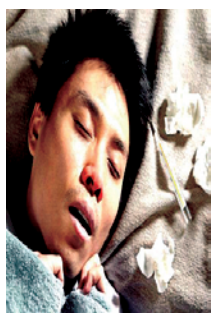
Common symptoms of a urinary tract infections.

In general, the most common symptoms of a urinary tract infection involve the process of urination:

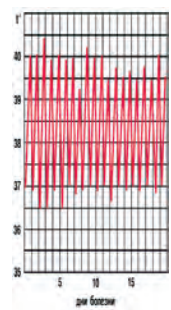
- Pain or a burning feeling during urination
- A feeling of urgency, or feeling the need to urinate frequently
- An altered appearance of the urine, either bloody (red) or cloudy (containing pus)
- Pain or pressure in the rectum (men) or in the area of the pubic bone (women)
- Passing only a tiny amount of urine even when the urge to urinate is strong

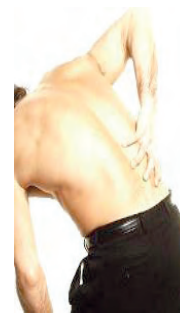
Common symptoms of a urinary tract infections.

- **Other, more generalized, symptoms can also accompany a urinary tract infection:**
- Tiredness
- Weakness
- Fever is not common if the infection is in the lower urinary tract (urethra or bladder), but may be present, especially if the infection has spread to the kidneys or blood



Fever with chills





Loin pain (one side)radiating often to the groin

Generalized urinary tract infection (UTI) symptoms

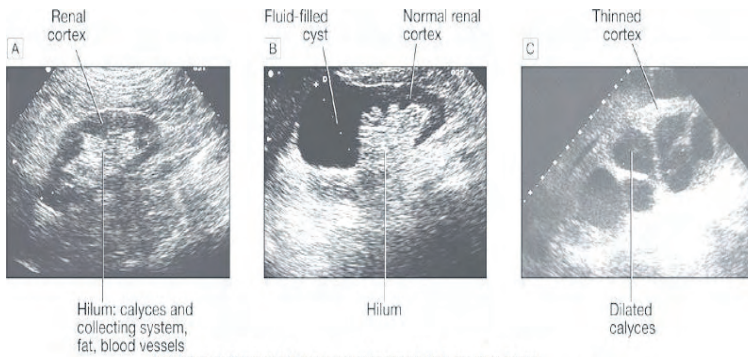
- Other, more generalized, symptoms can also accompany a urinary tract infection such as:
- Tiredness
- Weakness
- Fever is not common if the infection is in the lower urinary tract (urethra or bladder), but may be present, especially if the infection has spread to the kidneys or blood

Urinary tract infection (UTI) in the elderly

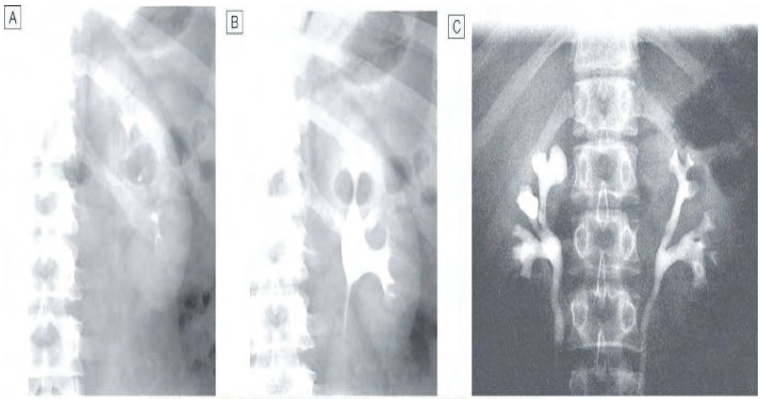
- The symptoms of a urinary tract infection can also appear nonspecific, and the diagnosis may be more difficult, in the elderly or those in health care settings who require long-term catheter use

• Hesitancy to urinate

- The sensation of not being able to urinate easily or completely (or feeling that you have to urinate strongly but only a few drops of urine come out) often accompanies a urinary tract infection

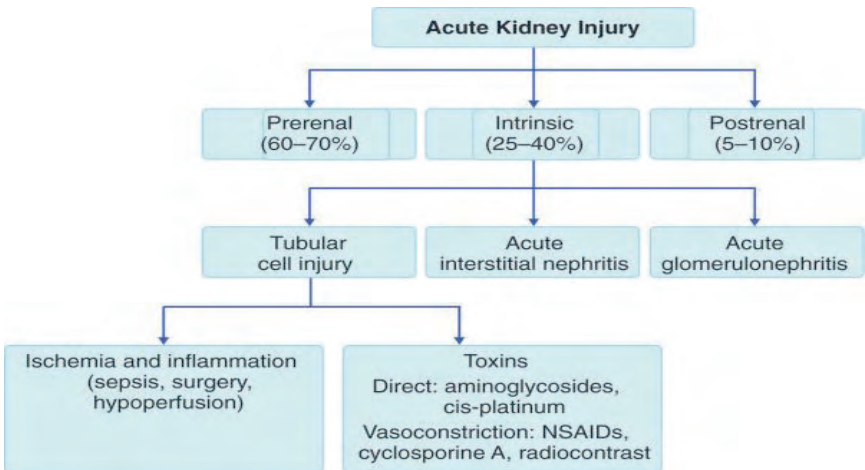


Renal ultrasound.
Normal kidney. The normal cortex is less echo-dense (blacker) than the adjacent liver. A simple cyst occupies the upper pole of an otherwise normal kidney. The renal pelvis and calyces are dilated by a chronic obstruction to urinary outflow. The thinness and increased density of the remaining renal cortex indicate chronic changes



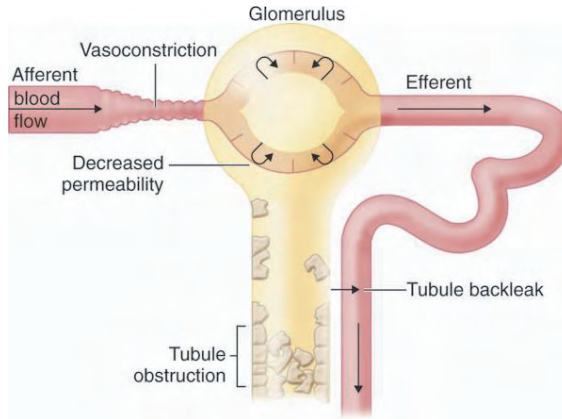
Intravenous urography (IVU).
Normal nephrogram phase at 1 minute. Normal collecting system at 5 minutes. Bilateral reflux nephropathy (and chronic pyelonephritis) showing clubbing of the calyces which is particularly marked in the upper right pole

Main categories of acute kidney injury

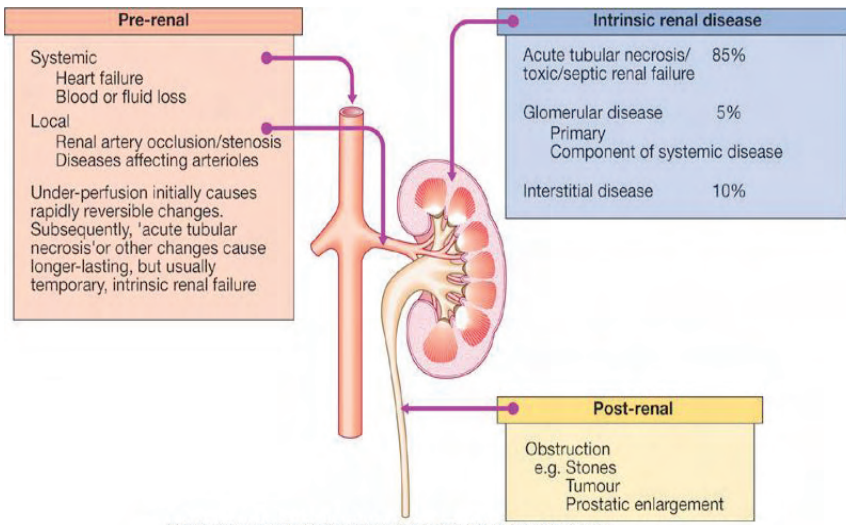


NSAIDs = nonsteroidal anti-inflammatory drugs

Mechanisms of prerenal and intrinsic acute renal injury



Causes of acute renal failure



Colledge et al: Davidson's Principles and Practice of Medicine, 21st Edition

Measurement of Renal Function

- In clinical practice, renal function is measured by serum creatinine. It is normally a relatively fixed value in a given patient. Creatine is released as a waste product from myocytes and converted to creatinine in the liver. **The normal range of serum creatinine is 0.6 to 1.5 mg/dL.** About 10% of the daily creatinine is excreted through tubular secretion. Mild elevations of the plasma creatinine concentration can occur during treatment with cimetidine or trimethoprim, both of which interfere with the tubular secretion of creatinine. They are unlikely to cause significant elevations of the plasma creatinine. Ketoacids cause an artifactual increase in the plasma creatinine by interfering with the creatinine assay
- The relationship between the glomerular filtration rate (GFR) and serum creatinine is such that there can be substantial loss of renal function while the serum creatinine concentration remains in the normal range
- The concentration of **blood urea nitrogen** (BUN), which is a product of protein catabolism, is about 10-fold higher than creatinine concentration, and the BUN-to-creatinine ratio commonly is used as a marker of volume status. There are circumstances, however, in which the BUN may be inappropriately high, such as with gastrointestinal bleeding or the use of steroids or tetracyclines. The BUN may be low if there is poor dietary intake of protein and in liver disease

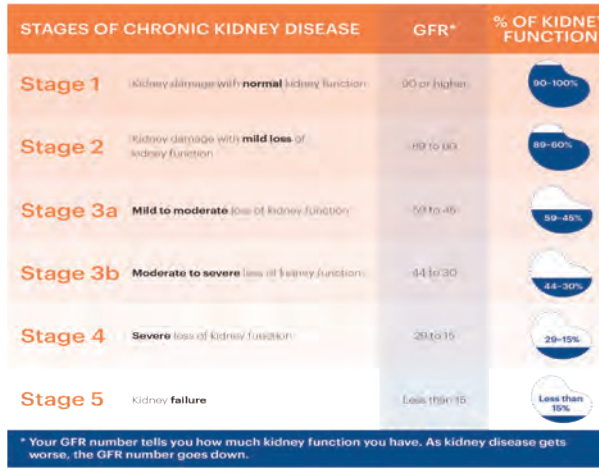
How to estimate glomerular filtration rate (GFR)

eGFR prediction equations based on plasma creatinine concentration

While recognising the inadequacies of plasma creatinine and a 24 h creatinine clearance, the National Kidney Foundation Disease Outcomes Quality Initiative (K-DOQI) recommended use of estimates of GFR calculated from prediction equations based on plasma or serum creatinine

The Modification of Diet in Renal Disease (MDRD) study equation
MDRD eGFR=186×[Plasma Creatinine (μmol/L)×0.0011312]−1.154 ×[age (years)]−0.203 ×[0.742 if female]×[1.212 if black]
CKD-Epidemiology Collaboration group (CKD-EPI)
CKD EPI eGFR; Female with Creatinine<62 μmol/L; use eGFR=144×(Cr/61.6)−0.329×(0.993)Age Female with Creatinine>62 μmol/L; use eGFR=144×(Cr/61.6)−1.209×(0.993)Age Male with Creatinine <80 μmol/L; use eGFR=141×(Cr/79.2)−0.411×(0.993)Age Male with Creatinine >80 μmol/L; use eGFR=141×(Cr/79.2)−1.209×(0.993)Age
where Cr is the plasma creatinine (μmol/L)

What are the Stages of Chronic Kidney Disease (CKD)?



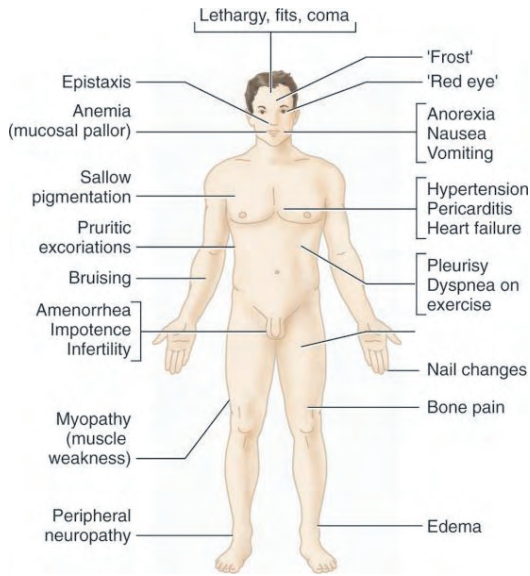
STAGES OF CHRONIC KIDNEY DISEASE		GFR*	% OF KIDNEY FUNCTION
Stage 1	Kidney damage with **normal** kidney function	90 or higher	90-100%
Stage 2	Kidney damage with **mild loss** of kidney function	60 to 89	89-60%
Stage 3a	**Mild to moderate** loss of kidney function	45 to 59	59-45%
Stage 3b	**Moderate to severe** loss of kidney function	30 to 44	44-30%
Stage 4	**Severe** loss of kidney function	15 to 29	29-15%
Stage 5	Kidney **failure**	Less than 15	Less than 15%

* Your GFR number tells you how much kidney function you have. As kidney disease gets worse, the GFR number goes down.

What are the Stages of Chronic Kidney Disease (CKD)?

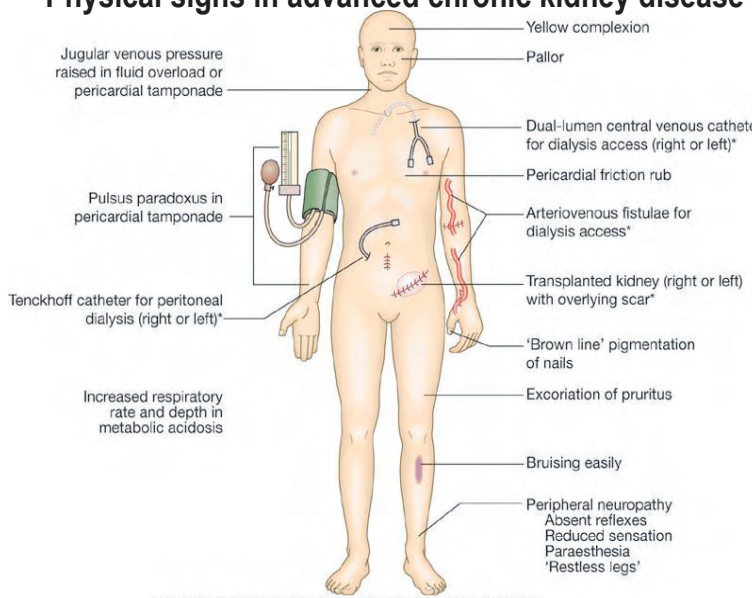
				Albuminuria categories		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR Stages	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

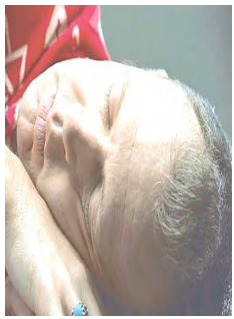
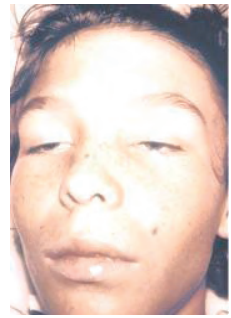
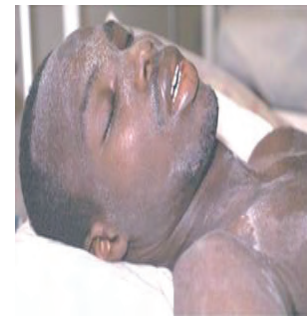
Key to Figure:
Colors: Represents the risk for progression, morbidity and mortality by color from best to worst.
Green: Low Risk (if no other markers of kidney disease, no CKD)
Yellow: Moderately Increased Risk
Orange: High Risk
Red: Very High Risk
Deep Red: Highest Risk



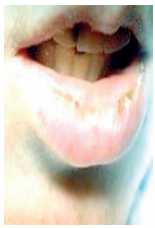
Common symptoms and signs of chronic renal failure s.

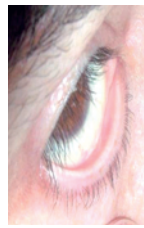
Physical signs in advanced chronic kidney disease

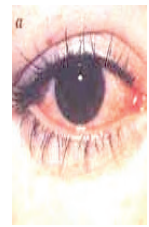


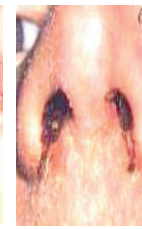




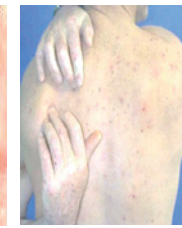
Ortopnoe, general **"yellowish"** oedema, ascetics


Keylit

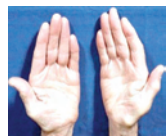

Anemia


Iridocyklit

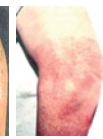

Bleeding

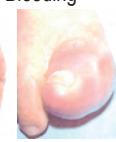

Itch

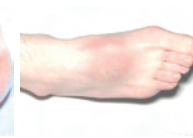

Yellowness of skin

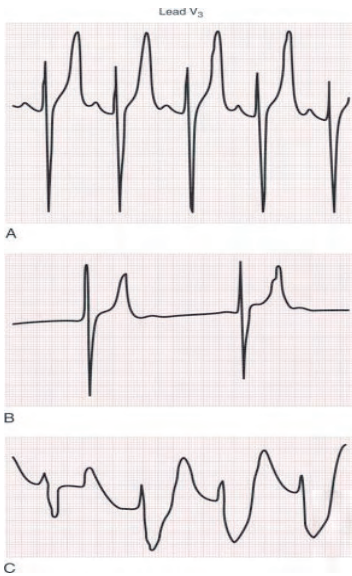

Neuropathy


Brown line nails


Toxic Capillary s.

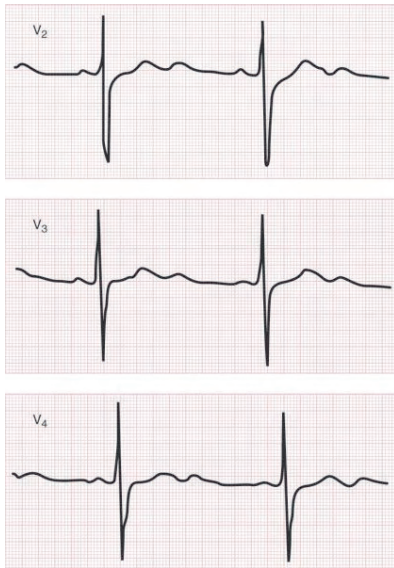

Gout


Reactive arthritis



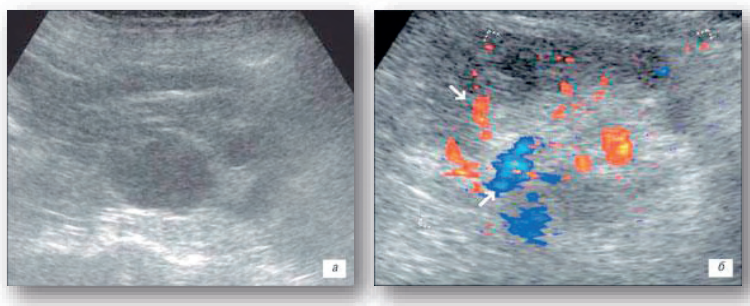
The effects of progressive hyperkalemia on the electrocardiogram

All of the illustrations are from lead V_3. **A,** Serum potassium concentration ($[K^+]$) = 6.8 mEq/L; note the peaked T waves together with normal sinus rhythm. **B,** Serum $[K^+]$ = 8.9 mEq/L; note the peaked T waves and absent P waves. **C,** Serum $[K^+]$ = >8.9 mEq/L; note the classic sine wave with absent P waves, marked prolongation of the QRS complex, and peaked T waves

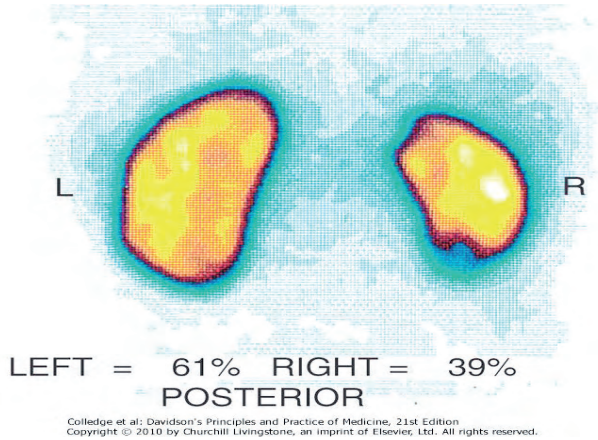


The electrocardiographic manifestations of hypokalemia

The serum potassium concentration was 2.2 mEq/L. The ST segment is prolonged, primarily because of a U wave following the T wave, and the T wave is flattened



Imaging studies



DMSA isotope renogram.
A posterior view is shown of a normal left kidney and a small right kidney (with evidence of cortical scarring at upper and lower poles) that contributes only 39% of total renal function

REFERENCES

Kovalyova O.N., Ashcheulova T.V. Propedeutics to Internal Medicine. Part 2. – Vinnytsya: NOVA KNYHA, 2017. – 264 p.

Kovalyova O.N., Asheulova T.V. General inspection: manual for students. – Kharkov: "Turbo". – 2004. – 60 p.

Khomazjuk V.A., Ostashevska T.G., Krasyuk I.V. Propaedeutics of Internal Medicine and Patient Care: Study guide for the practical classes. Part I. – Kyiv: NMU, 2005. – 44 p.

Bickley, Lynn S.; Szilagyi, Peter G. Bates' Guide to Physical Examination and History Taking, 10th Edition. – 934 p. Copyright ©2009 Lippincott Williams & Wilkins

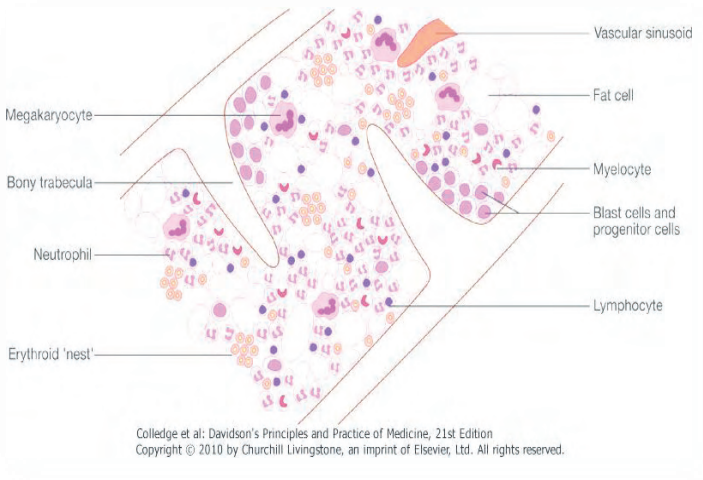
The Point online resources, http://thepoint.lww.com

LECTURE # 16

CLINICAL EXAMINATION IN BLOOD DISEASES. ANEMIA SYNDROME

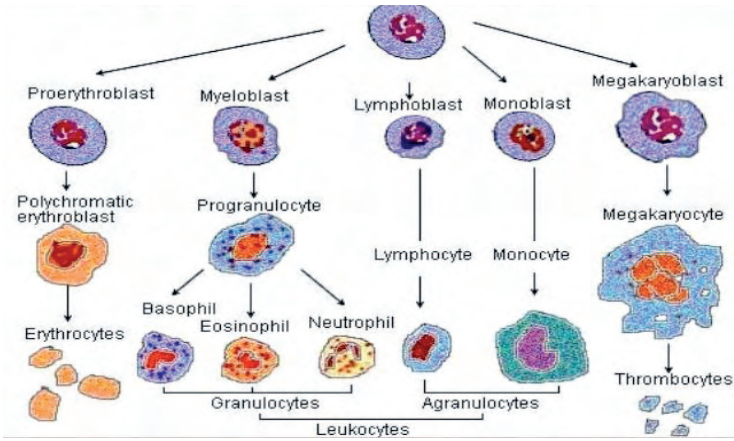
THE PLAN

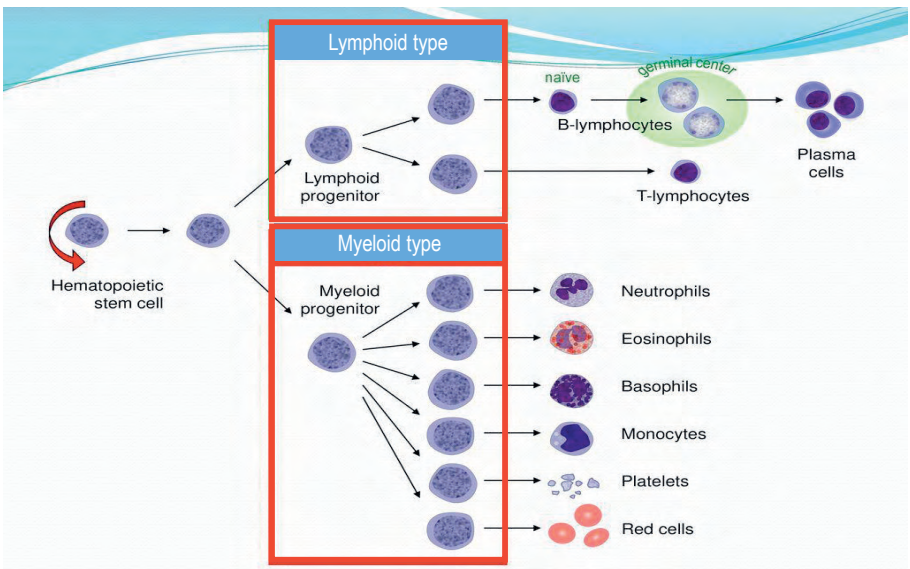
- The ORIGIN of blood diseases
- Hematopoietic scheme
- FBC
- WBC formula
- CLINICAL EXAMINATION FOR BLOOD DISEASES
- Inspection
- Lymphadenopathy
- Spleen Examination
- Hepatosplenomegaly
- Anemia s.
- Hemoglobin
- Microcytic hypochromic anemia types
- Macrocytic hypochromic anemia types
- Normocytic normochromic anemia types
- Anemia of Chronic Disease
- Aplastic anemia
- Hemolytic anemia
- References



Structural organisation of normal bone marrow

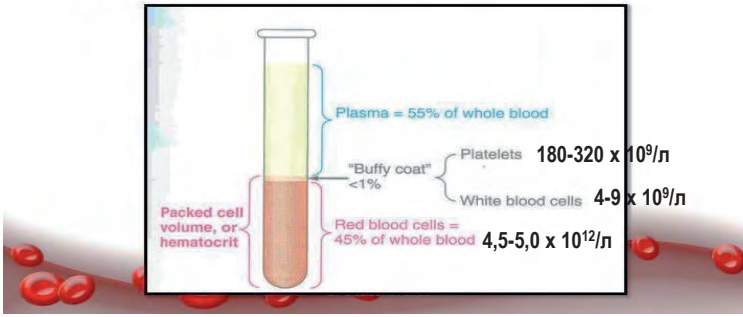
The ORIGIN


Proerythroblast
Myeloblast
Lymphoblast
Monoblast
Megakaryoblast
Polychromatic erythroblast
Progranulocyte
Megakaryocyte
Lymphocyte
Monocyte
Basophil
Eosinophil
Neutrophil
Erythrocytes
Thrombocytes
Granulocytes
Agranulocytes
Leukocytes


Lymphoid type
naïve
germinal center
B-lymphocytes
Plasma cells
Lymphoid progenitor
T-lymphocytes
Myeloid type
Hematopoietic stem cell
Myeloid progenitor
Neutrophils
Eosinophils
Basophils
Monocytes
Platelets
Red cells

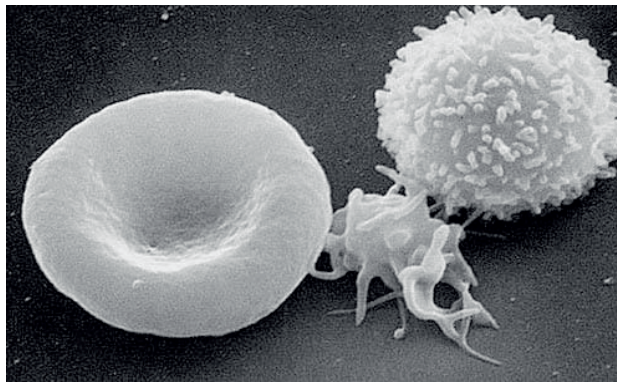
The packed cell volume (PCV) hematocrit

- The ratio of packed blood cells volume to plasma.



FBC

NORMAL VALUES FOR RED BLOOD CELL MEASUREMENTS	Unit	Normal Range (Approximate)[*]
Hemoglobin	g/dL	**Males: 13.5–17.5**
		Females: 12–16
Hematocrit	%	Males: 40–52
		Females: 36–48
Red blood cell (RBC) count	× 10^6/μL of blood	**Males: 4.5–6.0**
		Females: 4.0–5.4
Mean cell volume (**MCV**)	fL	**81–99**
Mean cell hemoglobin (MCH)	pg	30–34
Mean cell hemoglobin concentration (MCHC)	g/dL	30–36
Reticulocyte count (absolute number)	No./μL of blood	40,000–100,000
Reticulocyte percentage	% of RBCs	**0.5–1.5**



Erythrocyte. Platelet. Leukocyte.
The image of a scanning electron microscope, left to right: red blood cell, platelet and white blood cell (T-lymphocyte). The picture scanning electron microscope

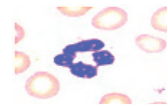
Clinical Application

- **Leucocytosis: High WBC count,** in **infection,** allergy, systemic illness, inflammation, tissue injury.
- Differential count provides clues about certain illnesses -->
  1. **Neutrophilia:** pyogenic illness.
  2. **Eosinophilia:** Allergy.
  3. **Lymphocytosis:** infectious mononucleosis.

Neutrophils A

Neutrophilia
- Infection: bacterial, fungal
- Trauma: surgery, burns
- Infarction: myocardial infarct, pulmonary embolus, sickle-cell crisis
- Inflammation: gout, rheumatoid arthritis, ulcerative colitis, Crohn's disease
- Malignancy: solid tumours, Hodgkin lymphoma
- Myeloproliferative disease: polycythaemia, chronic myeloid leukaemia
- Physiological: exercise, pregnancy

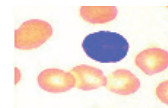
Neutropenia
- Infection: viral, bacterial (e.g. *Salmonella*), protozoal (e.g. malaria[1])
- Drugs:
- Autoimmune: connective tissue disease
- Alcohol
- Bone marrow infiltration: leukaemia, myelodysplasia
- Congenital: Kostmann's syndrome
- Constitutional: Afro-Caribbean and Middle Eastern descent



Lymphocytes E

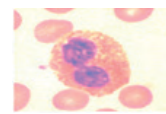
Lymphocytosis
- Infection: viral, bacterial (e.g. *Bordetella pertussis*)
- Lymphoproliferative disease: chronic lymphocytic leukaemia, lymphoma
- Post-splenectomy

Lymphopenia
- Inflammation: connective tissue disease
- Lymphoma
- Renal failure
- Sarcoidosis
- Drugs: corticosteroids, cytotoxics
- Congenital: severe combined immunodeficiency
- HIV infection



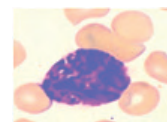
Eosinophils B

Eosinophilia
- Allergy: hay fever, asthma, eczema
- Infection: parasitic
- Drug hypersensitivity: e.g. gold, sulphonamides
- Vasculitis, e.g. Churg–Strauss syndrome, granulomatosis with polyangiitis (Wegener's granulomatosis)
- Connective tissue disease: polyarteritis nodosa
- Malignancy: solid tumours, lymphomas
- Primary bone marrow disorders: myeloproliferative disorders, hypereosinophilic syndrome (HES), acute myeloid leukaemia



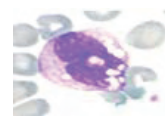
Basophils C

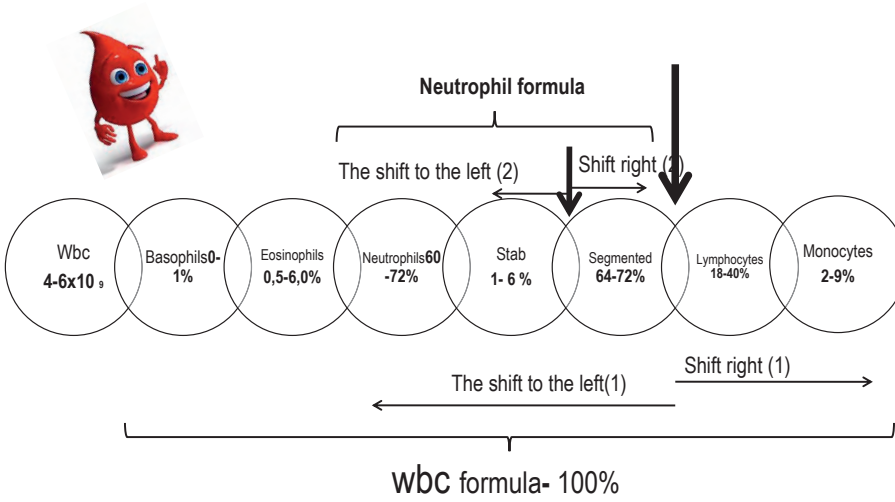
Basophilia
- Myeloproliferative disease: polycythaemia, chronic myeloid leukaemia
- Inflammation: acute hypersensitivity, ulcerative colitis, Crohn's disease
- Iron deficiency



Monocytes D

Monocytosis
- Infection: bacterial (e.g. tuberculosis)
- Inflammation: connective tissue disease, ulcerative colitis, Crohn's disease
- Malignancy: solid tumours, chronic myelomonocytic leukaemia

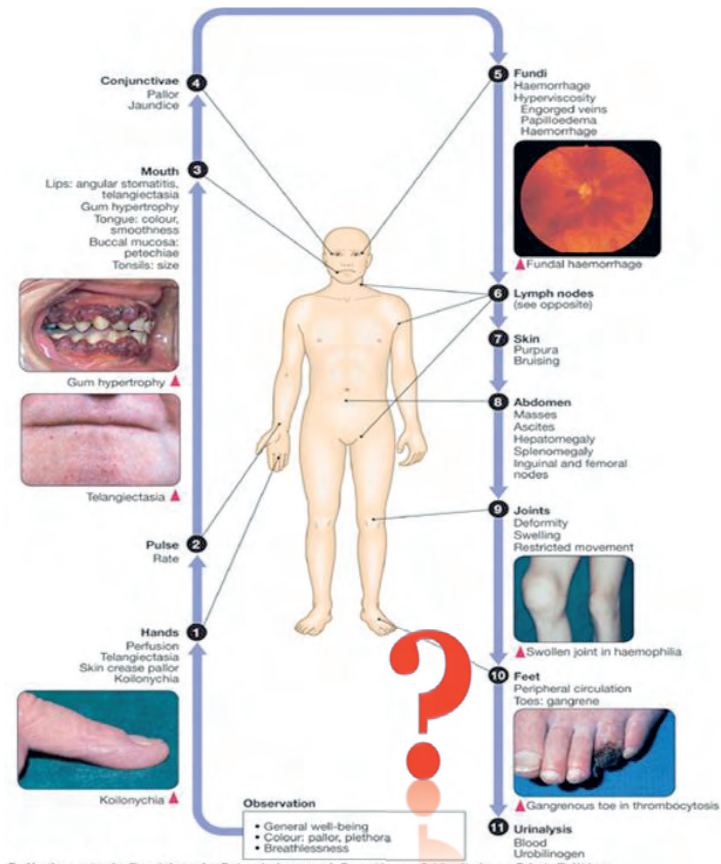




Erythrocyte Sedimentation Rate (ESR)

- Is the rate at which **red blood cells** sediment in a period of 1 hour.
- non-specific measure of **inflammation**.

Disorders of the blood cover a **wide spectrum of illnesses**, ranging from some of the most common disorders affecting mankind - **anemia**, to relatively rare conditions such as **leukemia** and **congenital coagulation disorders**



Colledge et al: Davidson's Principles and Practice of Medicine, 21st Edition

CLINICAL EXAMINATION FOR BLOOD DISEASES

Abnormalities detected in the blood are caused not only by primary diseases of the blood and lymphoreticular systems, but also by diseases affecting other systems of the body

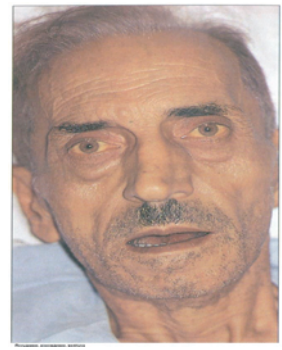
The clinical assessment of patients with haematological abnormalities must include

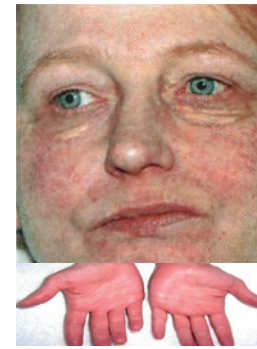
- a general history and examination, as well as
- a search for symptoms and signs of abnormalities of red cells,
- white cells,
- platelets, bleeding and clotting systems,
- lymph nodes and lymphoreticular tissues

Inspection

Inspection

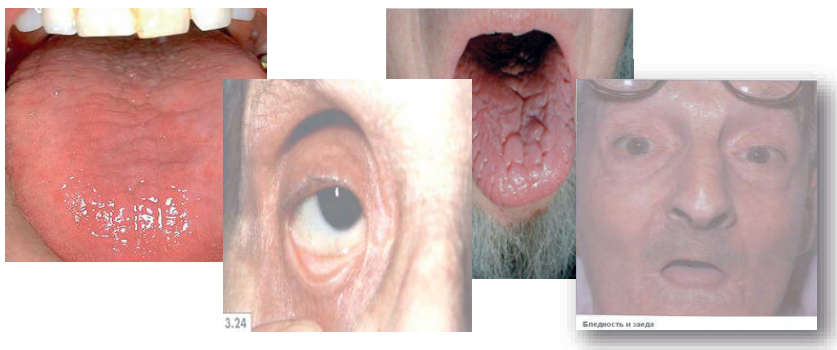
- Skin
  Color: pale, jaundiced, purplish red





Inspection

- Mucosal, oral inspection
  Condition of the gums, tongue, oral mucosa, tonsils



Lymphadenopathy

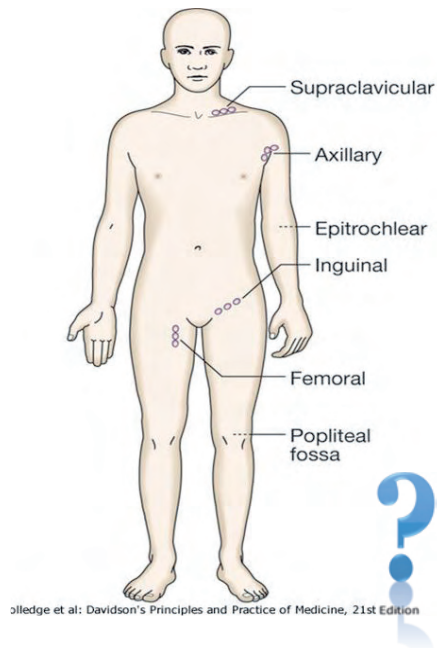
Lymphadenopathy can be caused by benign or malignant disease

History

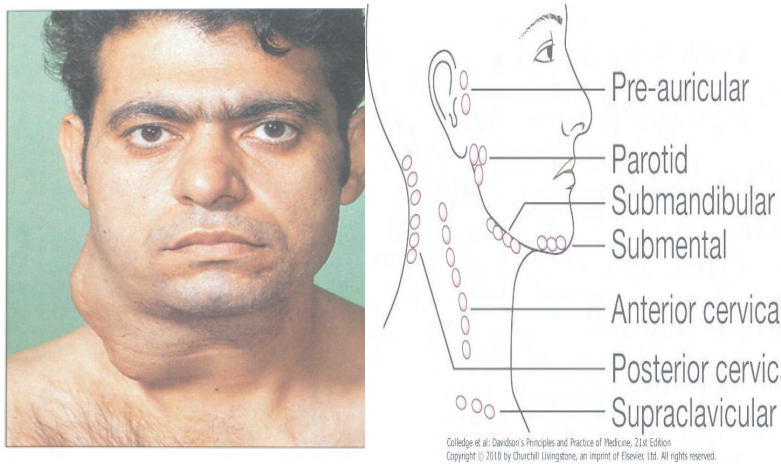
- ✓ Speed of onset, rate of enlargement
- ✓ Painful or painless
- ✓ Associated symptoms: weight loss, night sweats, itch

Examination

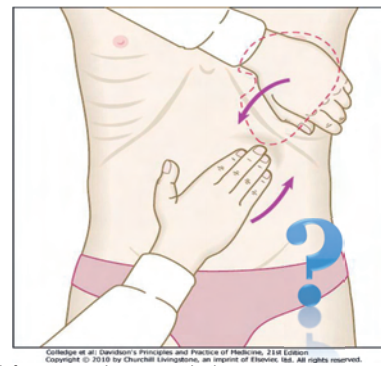
- ✓ Sites: localised, generalised
- ✓ Size (cm)
- ✓ Character: hard, soft, rubbery
- ✓ Fixed, mobile
- ✓ Search area that node drains for abnormalities (e.g. tooth abscess)
- ✓ Other general examination (e.g. joints, rashes, finger clubbing)



olledge et al: Davidson's Principles and Practice of Medicine, 21st Edition



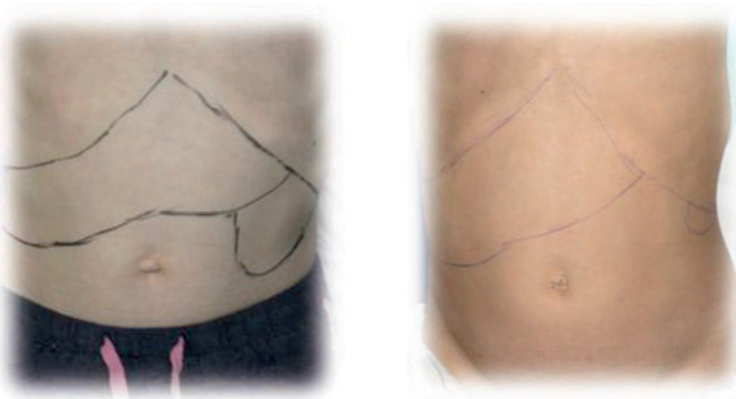
Spleen Examination



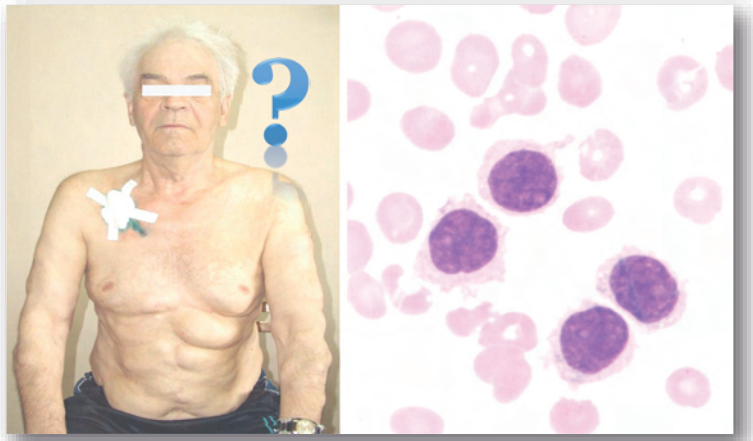
1. Move hand up from right iliac fossa, towards left upper quadrant on expiration
2. Keep hand still and ask patient to take a deep breath through the mouth to feel spleen edge being displaced downwards
3. Place your left hand around patient's lower ribs and approach costal margin to pull spleen forward
4. To help palpate small spleens, roll patient on to the right side and examine as before

Spleen Characteristics

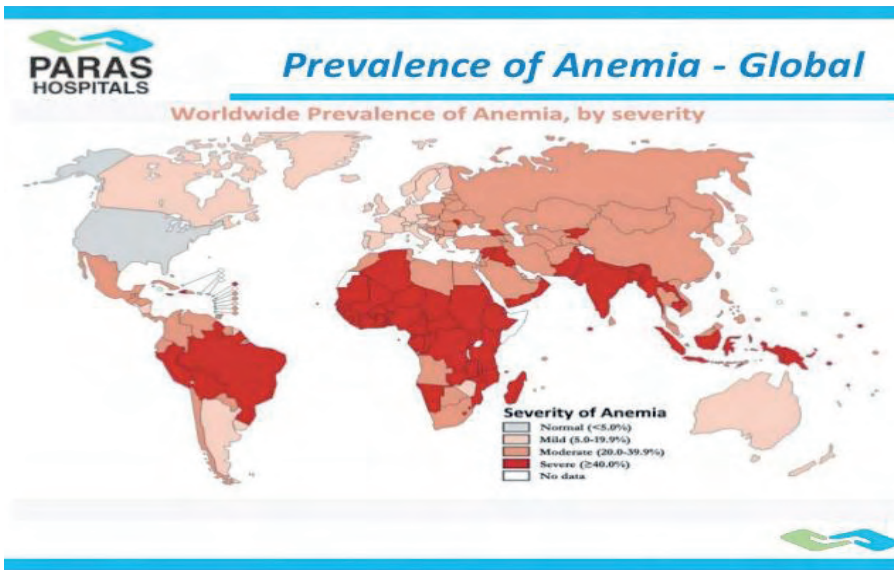
- ✓ Notch
- ✓ Superficial
- ✓ Dull to percussion
- ✓ Cannot get between ribs and spleen
- ✓ Moves well with respiration



Hepatosplenomegaly



Splenomegaly & cytopenia



The main problems with blood diseases

Anemia

❑ Anemia refers to a state in which the level of hemoglobin in the blood is below the normal range appropriate for age and sex

❑ The clinical features of anemia reflect diminished oxygen supply to the tissues. A rapid onset of anemia (e.g. due to blood loss) causes more profound symptoms than a gradually developing anemia

❑ Individuals with cardio respiratory disease are more susceptible to symptoms of anemia

Causes of anaemia

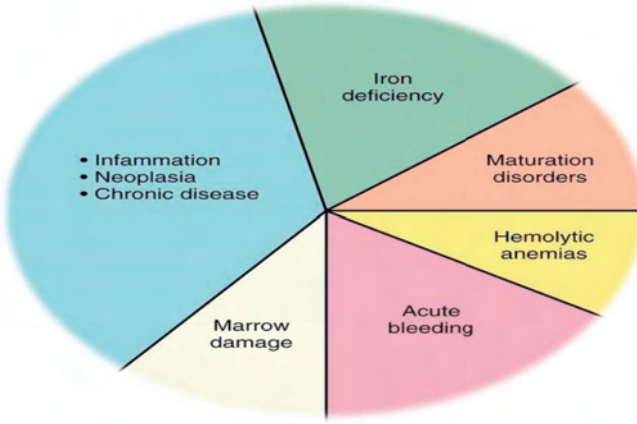
Decreased or ineffective marrow production

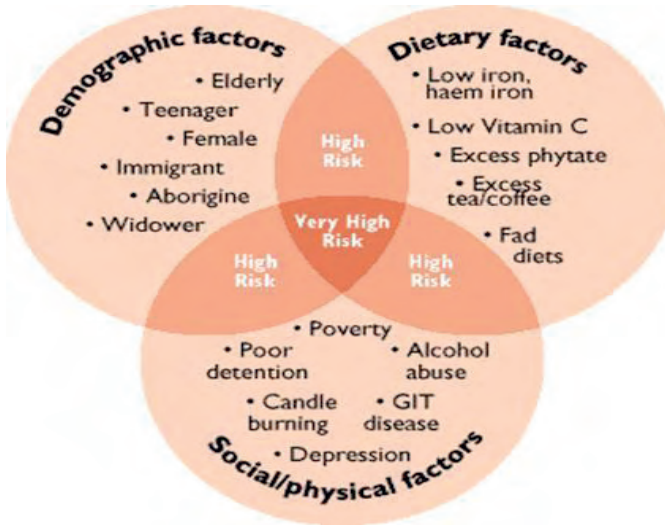
- Lack of iron, vitamin B_{12} or folate
- Hypoplasia/myelodysplasia
- Invasion by malignant cells
- Renal failure
- Anaemia of chronic disease

Normal marrow production but increased removal of cells

- Blood loss
- Haemolysis
- Hypersplenism

Anemia


Iron deficiency
Maturation disorders
Hemolytic anemias
Acute bleeding
Marrow damage
• Infammation
• Neoplasia
• Chronic disease


Demographic factors
• Elderly
• Teenager
• Female
• Immigrant
• Aborigine
• Widower
Dietary factors
• Low iron, haem iron
• Low Vitamin C
• Excess phytate
• Excess tea/coffee
• Fad diets
High Risk
Very High Risk
High Risk
High Risk
• Poverty
• Poor detention
• Alcohol abuse
• Candle burning
• GIT disease
• Depression
Social/physical factors

Decreased or ineffective marrow production

- ✓ Lack of iron, vitamin B_{12} or folate
- ✓ Hypoplasia
- ✓ Invasion by malignant cells
- ✓ Renal failure
- ✓ Anemia of chronic disease

Peripheral causes

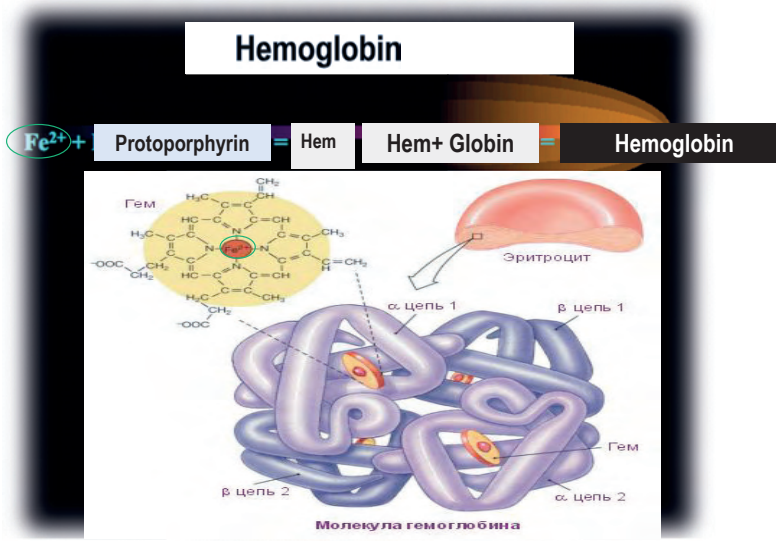
- ✓ Blood loss
- ✓ Hemolysis
- ✓ Hypersplenism

Clinical assessment

On examination, as well as the general physical findings of anemia, there may be specific findings related to the etiology of the anemia; for example:

- ❑ a patient may be found to have a right iliac fossa mass due to an underlying caecal carcinoma
- ❑ Hemolytic anemias can cause jaundice
- ❑ Vitamin B_{12} deficiency may be associated with neurological signs including peripheral neuropathy, dementia and signs of subacute combined degeneration of the cord
- ❑ Sickle-cell anemia may result in leg ulcers, stroke or features of pulmonary hypertension

Anemia may be multifactorial and the lack of specific symptoms and signs does not rule out silent pathology

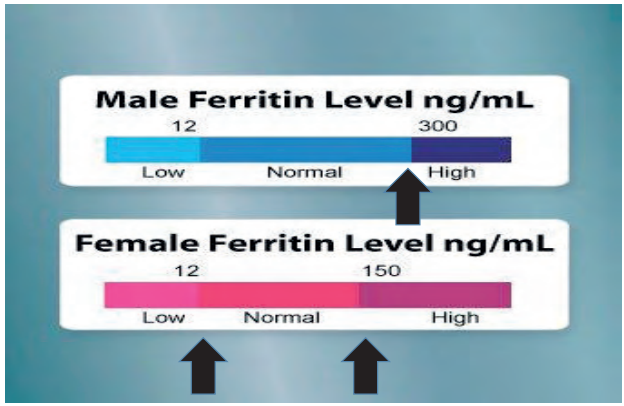


Depending on the age and sex norm hemoglobin index may differ in liter of blood

Age & SEX	Hb(Г/Л)	Hb(Г/%)
Children (3 months to 5 years old)	110	11,0
Children (5—12 y.o)	115	11,5
Children (12—15 y.o)	120	12,0
The male (> 15 years)	130—160	13,0—16,0
Nonpregnant female (> 15 years)	120—140	12,0—14,0
Pregnant female	110	11,0

Fe serum /Iron serum:
f — 9 - 30 mmol/l,
m — 12 - 31 mmol/l

Depending on the age and sex norm hemoglobin index may differ in liter of blood



Clinical assessment

•*Iron deficiency anemia* is the most common type of anemia world-wide

✓A thorough gastrointestinal history is important, looking in particular for symptoms of blood loss. Menorrhagia is a common cause of anemia in pre-menopausal females, so women should always be asked about their periods

✓*A dietary history* should assess the intake of iron and folate which may become deficient in comparison to needs (e.g. in pregnancy or during periods of rapid growth

✓*Past medical history* may reveal a disease which is known to be associated with anaemia, such as rheumatoid arthritis (the anaemia of chronic disease), or previous surgery (e.g. resection of the stomach or small bowel which may lead to malabsorption of iron and/or vitamin B_{12})

✓*Family history and ethnic background* may raise suspicion of haemolytic anemias such as the hemoglobinopathies and hereditary spherocytosis. Pernicious anemia may also be familial

✓*A drug history* may reveal the ingestion of drugs which cause blood loss (e.g. aspirin and anti-inflammatory drugs), hemolysis or aplasia

Consequences of anemia

- Depression
- Angina
- LVH
- Cardiac failure
- Myopathy
- Renal disease progression
- Morbidity
- Mortality
- Exercise capacity
- Coagulation
- Immune response
- Cognitive function
- Sexual function

- Appetite/Nutrition
- Growth (in children)
- Quality of life

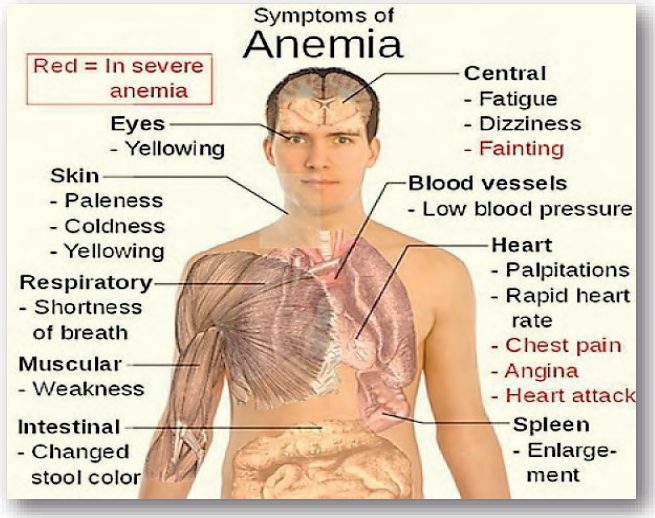
Anemia

Non-specific symptoms

- ✓ Tiredness
- ✓ Lightheadedness
- ✓ Breathlessness
- ✓ Ankle-swelling
- ✓ Development/worsening of ischemic symptoms e.g. angina or claudication

Non-specific signs

- ✓ Mucous membrane pallor
- ✓ Tachypnea
- ✓ Raised jugular venous pressure
- ✓ Flow murmurs
- ✓ Ankle edema
- ✓ Postural hypotension
- ✓ Tachycardia



Hemodynamic (Increased Cardiac Output)

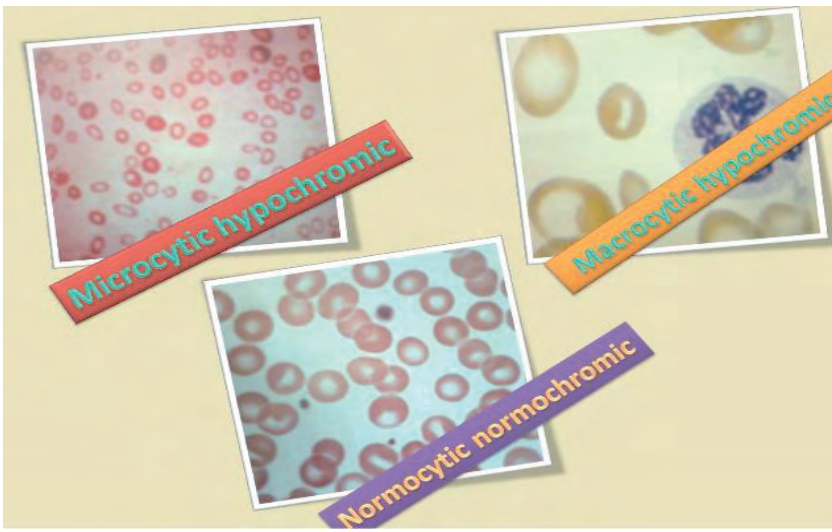
- Systemic arterial dilatation
- Decreased TPR
- Reduced afterload
- Increased stroke volume
- Decreased blood viscosity
- Increased venous return
- Increased preload
- Sympathetic activation
- Increased heart rate

- **Non-hemodynamic**

- (Increased O2 extraction)
- Increased EPO production (?)
- Increased 2,3-DPG

Evaluation of anemia

- Hb concentration, white blood cell count and platelet count
- Red blood cell indices
- mean corpuscular volume [MCV] mean corpuscular hemoglobin [MCH] mean corpuscular hemoglobin concentration [MCHC])
- Absolute reticulocyte count
- Serum ferritin
- Serum TSAT or Content of Hb in reticulocytes (CHr)



Microcytic hypochromic anemia's

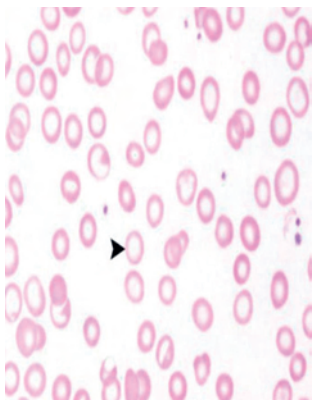
types

MCV <80

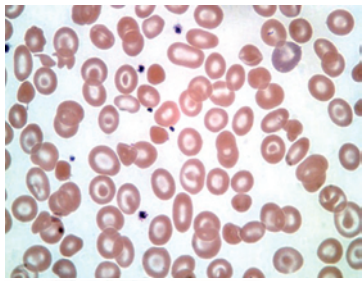
Mean cell volume (**MCV**)

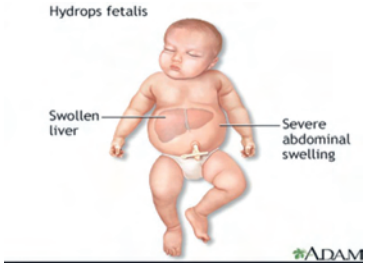
- Iron deficiency,
- α-thalassemia,
- β-thalassemia,
- Lead poisoning,
- sideroblastic anemia

Iron deficiency anemia



Type of anemia: Microcytic hypochromic
Etiology:
↓Iron due to chronic bleeding (i.e. GI loss, menorrhagia), malnutrition, absorptive disorders,
or ↑demand (i.e. pregnancy) → ↓final step in heme synthesis
Labs:
↓Iron,
↓ferritin,
↑TIBC/transferrin (liver wants to maximize use of the little iron left)
Histology: Microcytosis and hypochromasia (central pallor)
Presentation: Fatigue, conjunctival pallor, pica, koilonychia
Plummer-Vinson Syndrome
Triad of iron deficiency anemia,
esophageal webs, dysphagia



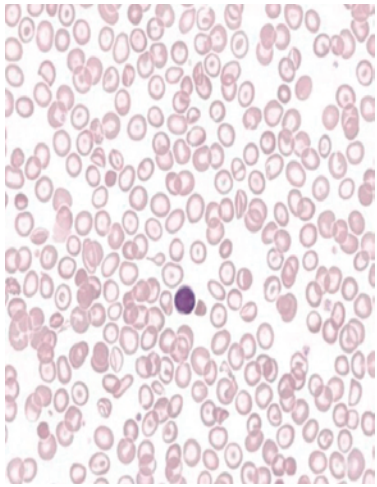


α-thalassemia

Type of anemia: Microcytic hypochromic
Etiology: α-globin gene deletions → ↓α-globin synthesis
cis deletion: Both deletions on same chromosome, seen in Asian populations
trans deletion: Deletions occur son separate chromosomes. Prevalent in African populations

4 allele deletion: No α-globin. Excess γ-globin forms γ4 (Hb Barts). Incompatible with life (causes hydrops fetalis)
3 allele deletion: Inheritance of chromo-some with cis deletion + a chromosome with 1 allele affected --> HbH disease. Very little α-globin, so that excess β-globin forms β4 (HbH)
2 allele deletion: Less clinically severe anemia
1 allele deletion: No anemia (clinically silent)

The geographical distribution of the haemoglobinopathies. From Hoffbrand and Pettit 1992 – see p. 1056.



β-thalassemia

Type of anemia: Microcytic hypochromic

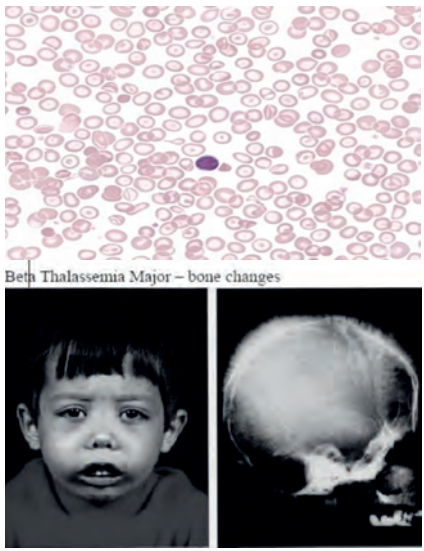
Etiology: Point mutations in splice sites and promoter sequences → ↓β-globin synthesis

Prevalent in Mediterranean populations

β-thalassemia minor:

Heterozygote. β-chain is underproduced. Usually asymptomatic.

β-thalassemia minor labs: ↑HbA2 (>3.5%) on electrophoresis



β-thalassemia

β-thalassemia major resentation:

Marrow expansion → skeletal deformities ("crew cut" on X-ray and chipmunk facies). Extra medullary hematopoiesis --> hepatosplenomegaly. Only becomes symptomatic 6 months after birth, when fetal hemoglobin declines

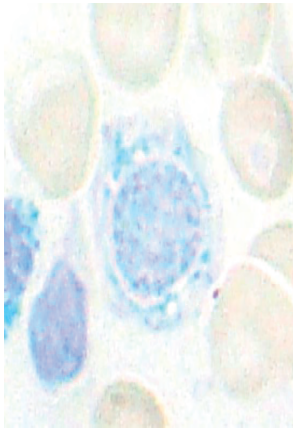
β-thalassemia major: increases risk of Parvovirus B19 infection-induced aplastic crisis

β-thalassemia major labs: ↑HbF (α2γ2)

HbS/β-Thalassemia: Heterozygote

Causes mild to moderate sickle cell disease depending on amount of β-globin production

Sideroblastic Anemia



type of anemia: Microcytic hypochromic
Genetic Etiology: Defect in heme synthesis due to X-linked defect in δ-ALA synthase gene (RLS in protoporphorin synthesis)
Causes: Genetic, acquired (myelodysplastic syndromes) and reversible (alcohol most common, lead, vit. B6 deficiency copper deficiency, isoniazid)
Lab Findings:
↑iron,
normal/↓TIBC,
↑ferritin

Histology: Ringed sideroblasts (iron-laden, Prussian blue-stained mitochondria) in bone marrow. Basophilic stippling of RBCs in peripheral blood smear.
Treatment: Pyridoxine (vitamin B6, cofactor for δ-ALA synthase)

IRON-deficiency anemia

Syndromes:

1. Circulatory-hypoxic
2. Gastroenterological
3. Hematological

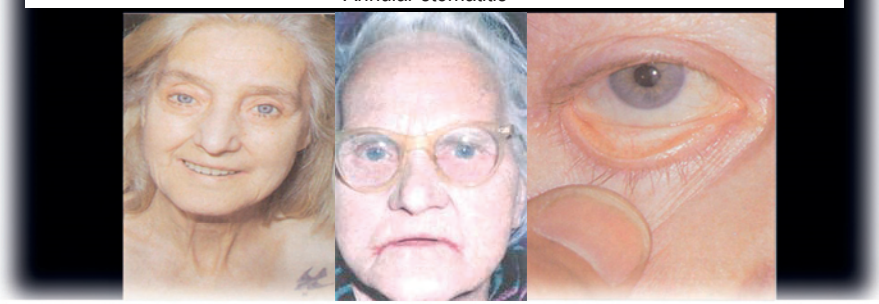
Investigations to differentiate anaemia of chronic disease from iron deficiency anaemia

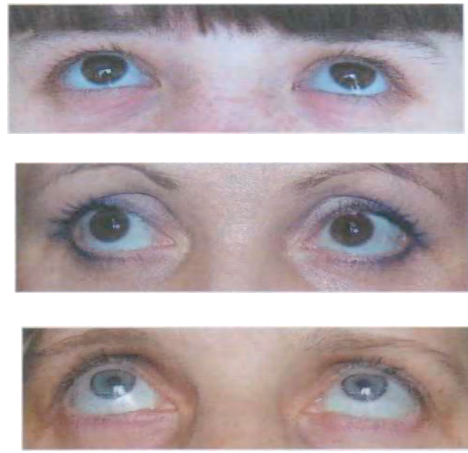
	Ferritin	Iron	TIBC	Transferrin saturation	Soluble transferrin receptor
Iron deficiency anaemia	↓	↓	↑	↓	↑
Anaemia of chronic disease	↑/Normal	↓	↓	↓	↓/Normal

(TIBC = total iron binding capacity)

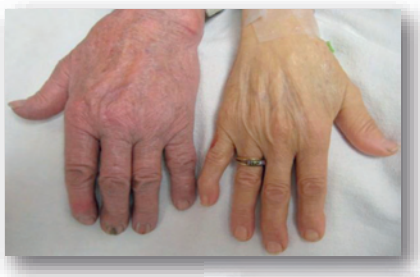
IRON-deficiency anemia

Annular stomatitis

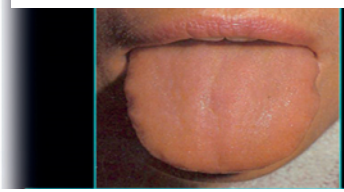




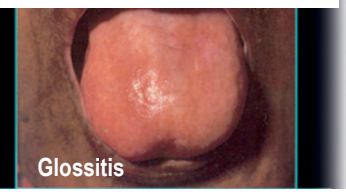
Blue sclera sing



Pica chlorotica: The desire to eat chalk, tooth powder, clay, coal, raw meat, benzene, acetone, lacquer, and others.
Pain when swallowing (s. Plummer-Vinson)



N tongue papilla



atrophy of tongue papilla

Anemia

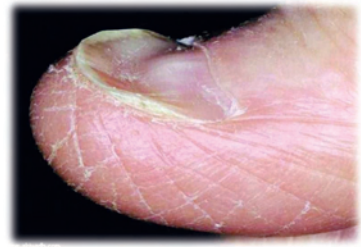
Non-specific signs (2)

- brittle nails
- spoon-shaped nails (koilonychia)
- atrophy of the papillae of the tongue
- angular stomatitis
- brittle hair
- a syndrome of dysphagia and glossitis

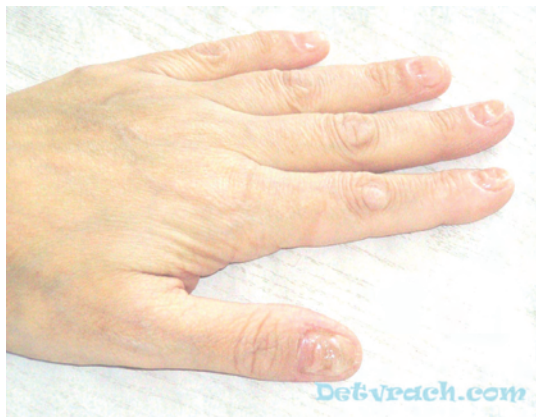
(Plummer–Vinson

or Paterson–Brown–Kelly syndrome)

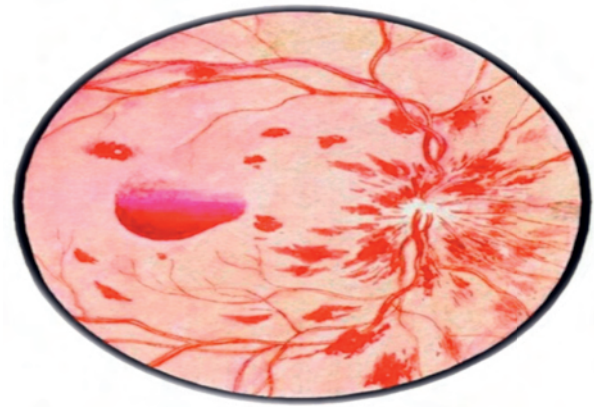
Hair dry, dull, loss



The skin is dry, cracked



Koilonychia - "spoon-shaped" nails

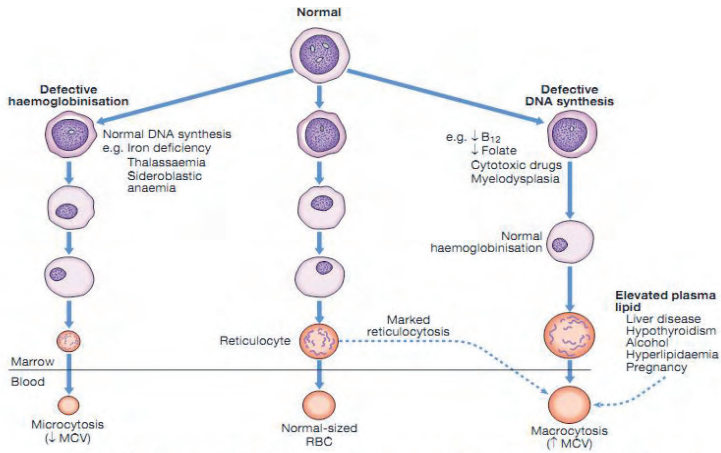


Retinopathy with anemia: the pale against the background of the fundus visible focal hemorrhages in the retina, in the macular area of extensive hemorrhage preretinal

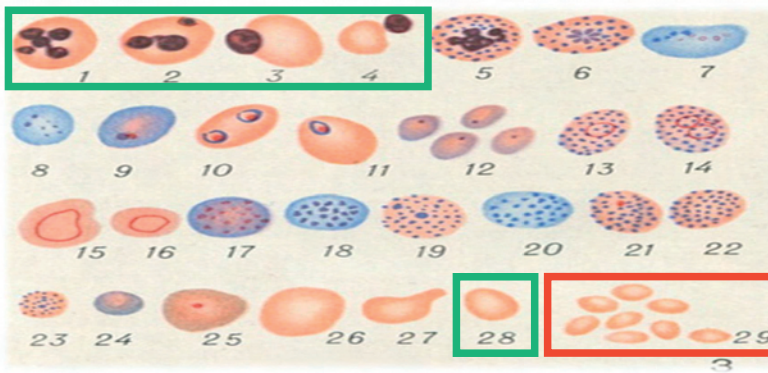
Investigations

Schemes for the investigation of anemias are often based on the size of the red cells, which is most accurately indicated by the MCV in the FBC. Commonly, in the presence of anemia:

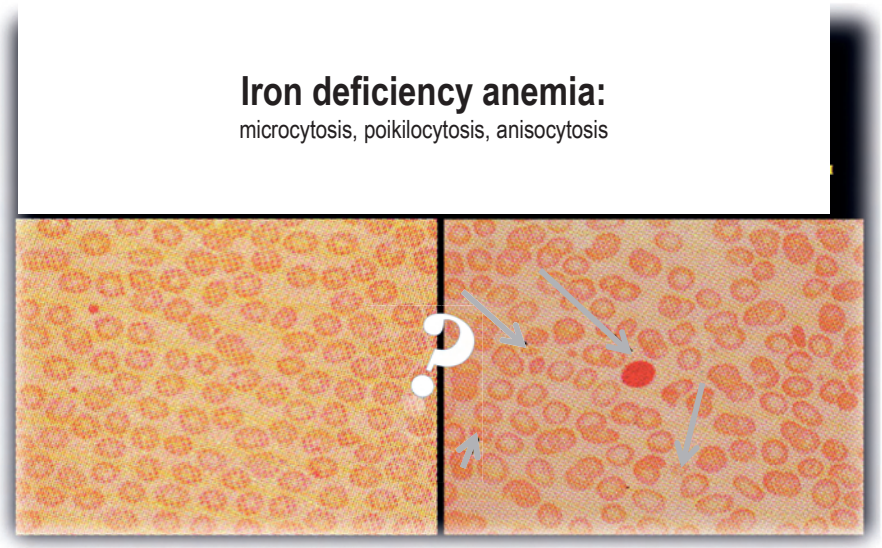
- ✓ A normal MCV (normocytic anemia) suggests either acute blood loss or the anaemia of chronic disease (ACD)
- ✓ A low MCV (microcytic anemia) suggests iron deficiency or thalassaemia
- ✓ A high MCV (macrocytic anemia) suggests vitamin B_{12} or folate deficiency or myelodysplasia

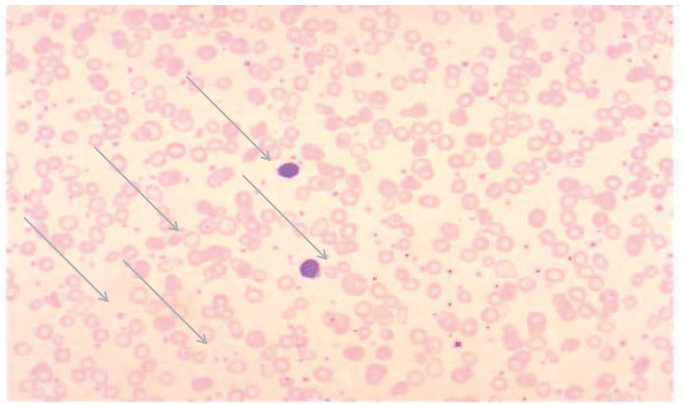


Factors which influence the size of red cells in anaemia. In microcytosis, the MCV is < 76 fL. In macrocytosis, the MCV is > 100 fL. (MCV = mean cell volume; RBC = red blood cell)



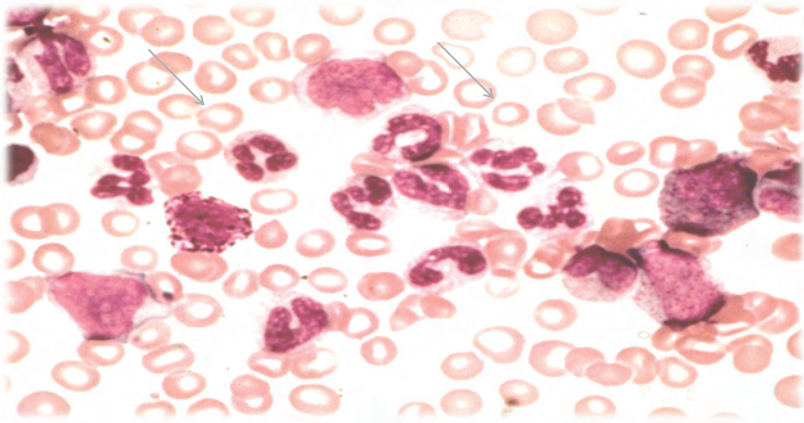
The blood with anemia: 1.4 - the last stage of red blood cells of normal hematopoiesis (the conversion of erythroblasts in the red blood cell); 5 -9 - the disintegration of the core to form a Jolly bodies in basophilic pointed (5, 6) and polychromatic (7 - 9), red blood cells; 10 and 11- calf Jolly ortohromnyh in erythrocytes; 12 - chromatin motes in red blood cells; 13 - 16 - in a ring Kebota basophilic punctured (13, 14) and ortohromnyh (15, 16), erythrocytes (pernicious anemia); 17 - 23 - basophilic punctate erythrocytes with a lead of anemia; 24 and 25 - polychromatic erythrocytes (mikrotsit and megalocyte); megalotsit (26) and poykilotsit (27) for pernicious anemia; 28 - normotsit; 29 - microcytes





Source: McPhee SJ, Papadakis MA: *Current Medical Diagnosis and Treatment 2010*, 49th Edition: http://www.accessmedicine.com

Iron deficiency anemia. (Peripheral blood, 50 ×.) Hypochromic and microcytic cells due to iron deficiency. The diameter of the normal red blood cell should be approximately the same as that of the nucleus of a small lymphocyte. This smear shows that most of the red cells are much smaller than the lymphocytes. This patient also has an increased platelet count—a common finding in patients with iron deficiency. (Courtesy of L Damon.)



Hypochromic Anemia during pregnancy

Macrocytic anemia types

MCV > 100

Mean cell volume (**MCV**)

- Nonmegaloblastic anemia
- **Megaloblastic anemia**
  - **(folate deficiency,**
  - **vitamin b12 deficiency,**
  - orotic aciduria,
  - Diamond-Blackfan anemia)

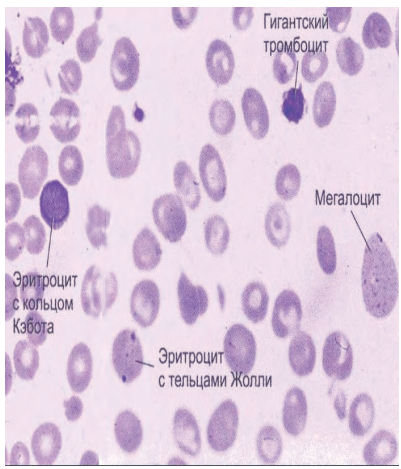
Megaloblastic anemia

Common Presentation RBC: macrocytosis, hypersegmented neutrophils (not seen in non-megaloblastic), glossitis

Causes: Folate deficiency, B12 deficiency, Orotic aciduria, Diamond-Blackfan anemia

Pathophysiology: Impaired DNA synthesis --> maturation of nucleus of precursor cells in bone marrow is delayed relative to maturation of cytoplasm

Vitamin B12 (cobalamin) Deficiency



Causes: Insufficient intake (i.e. vegans), malabsorption, pernicious anemia, Diphylloborthium latum (fish tapework), gastrectomy

Lab Findings: ↑homocysteine, ↑methylmalonic acid

Neurological presentation: B/c of involvement of B12 in myelin/FA synthesis → subacute combined degeneration of Spinocerebellar tract, lateral corticospinal tract, dorsal column dysfunction

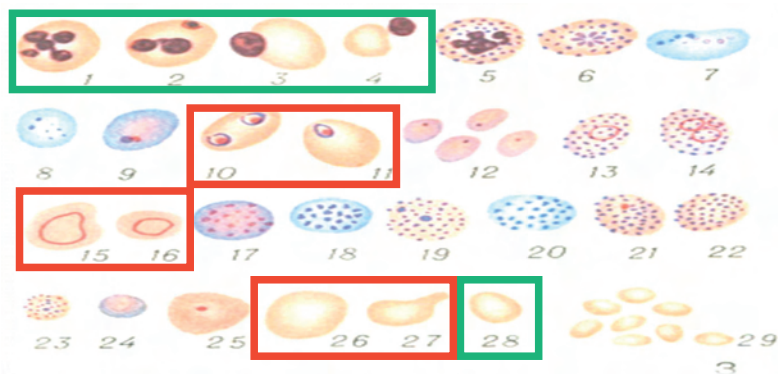
Historically diagnosed with Schilling test--a 4 stage test that determines if cause is dietary insufficiency or malabsorption

type of anemia Megaloblastic

B-12 deficiency anemia

Syndromes:

1. Circulatory-hypoxic
2. Gastroenterological
3. Psycho-neurological
4. Hematological



The blood with anemia: 1.4 - the last stage of red blood cells of normal hematopoiesis (the conversion of erythroblasts in the red blood cell); 5 -9 - the disintegration of the core to form a Jolly bodies in basophilic pointed (5, 6) and polychromatic (7 - 9), red blood cells; 10 and 11- calf Jolly ortohromnyh in erythrocytes; 12 - chromatin motes in red blood cells; 13 - 16 - in a ring Kebota basophilic punctured (13, 14) and ortohromnyh (15, 16), erythrocytes (pernicious anemia); 17 - 23 - basophilic punctate erythrocytes with a lead of anemia; 24 and 25 - polychromatic erythrocytes (mikrotsit and megalocyte); megalotsit (26) and poykilotsit (27) for pernicious anemia; 28 - normotsit; 29 - microcytes

Clinical features of megaloblastic anaemia

Symptoms

- Malaise (90%)
- Breathlessness (50%)
- Paraesthesiae (80%)
- Sore mouth (20%)
- Weight loss
- Altered skin pigmentation
- Impotence
- Poor memory
- Depression
- Personality change
- Hallucinations
- Visual disturbance

Signs

- Smooth tongue
- Angular cheilosis
- Vitiligo
- Skin pigmentation
- Heart failure
- Pyrexia

Neurological findings in B_{12} deficiency

Peripheral nerves

- Glove and stocking paraesthesiae
- Loss of ankle reflexes

Spinal cord

- Subacute combined degeneration of the cord
  - Posterior columns – diminished vibration sensation and proprioception
  - Corticospinal tracts – upper motor neuron signs

Cerebrum

- Dementia
- Optic atrophy

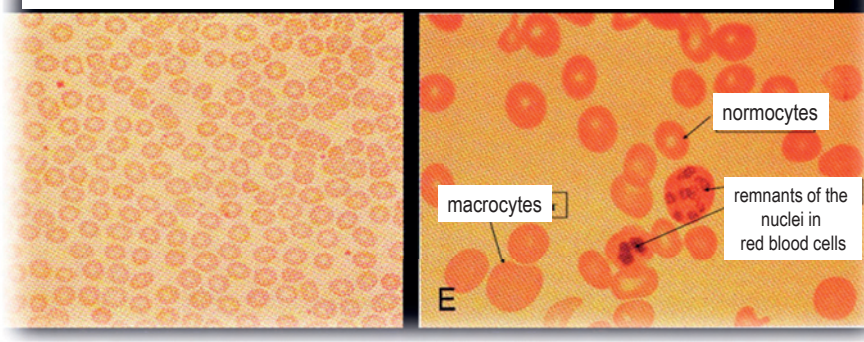
Autonomic neuropathy

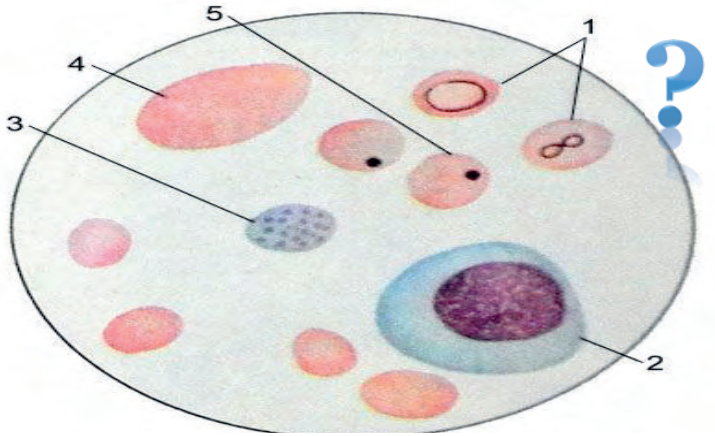
Investigations in megaloblastic anaemia

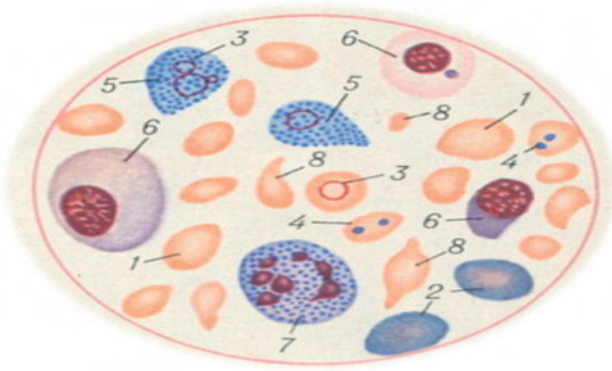
Investigation	Result
Haemoglobin	Often reduced, may be very low
MCV	Usually raised, commonly > 120 fL
Erythrocyte count	Low for degree of anaemia
Blood film	Oval macrocytosis, poikilocytosis, red cell fragmentation, neutrophil hypersegmentation
Reticulocyte count	Low for degree of anaemia
Leucocyte count	Low or normal
Platelet count	Low or normal
Bone marrow	Increased cellularity, megaloblastic changes in erythroid series, giant metamyelocytes, dysplastic megakaryocytes, increased iron in stores, pathological non-ring sideroblasts
Serum ferritin	Elevated
Plasma lactate dehydrogenase (LDH)	Elevated, often markedly

B-12 deficiency anemia:

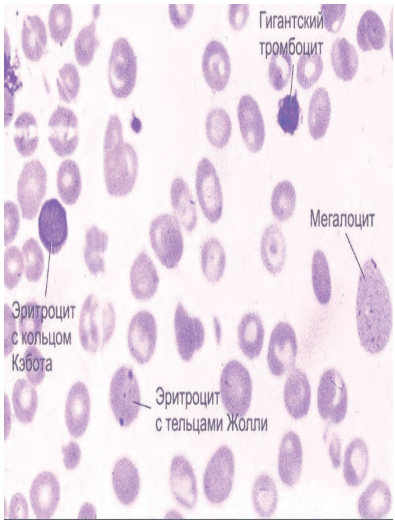
macrocytes, remnants of the nuclei in red blood cells, normocytes







Blood with pernicious anemia (severe relapse): megalocytes ortohromnye (1) and polychromatic (2), red blood cells with Kebota rings (3), calves Jolly (4) with basophilic punktatsiey (5), megaloblasts (6), polisegmentoyaderny neutrophil (7) , anisocytosis poikilocytosis and (8)



Folate Deficiency

Causes: Malnutrition (i.e. alcohol!!!), malabsorption, drugs (i.e. methotrexate, TMP, phenytoin), increased folate requirement (i.e. pregnancy, hemolytic anemia)

Lab Findings: ↑ homocysteine, normal methylmalonic acid

How to differentiate from b12 deficiency!!

Will not have neurological symptoms!

Also will not have increased methylmalonic acid

Type of anemia: Megaloblastic

Folic acid deficiency anemia

- Folic acid deficiency anemia is caused by reduction in serum folate concentration of less than 4 ng / ml
- Often it occurs in alcoholics

Causes of folate deficiency
Diet
• Poor intake of vegetables
Malabsorption
• e.g. Coeliac disease
Increased demand
• Cell proliferation, e.g. haemolysis • Pregnancy
Drugs*
• Certain anticonvulsants (e.g. phenytoin) • Contraceptive pill • Certain cytotoxic drugs (e.g. methotrexate)
*Usually only a problem in patients deficient in folate from another cause

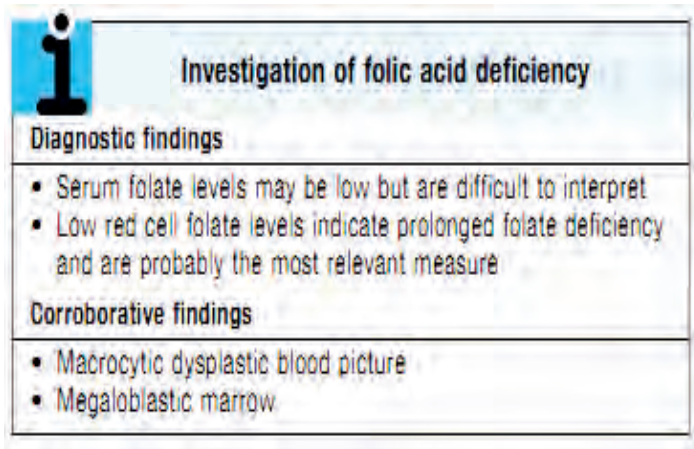
Etiology

- ❑ Insufficient folic acid intake (daily requirement - 50 micrograms, children and pregnant women - in 2-3 times higher)
- ❑ Violation of folic acid absorption in the intestine
- ❑ Increased folic acid requirements (for example, during pregnancy, malignancy)
- ❑ Long reception of drugs (trimethoprim, methotrexate, sulfasalazine, oral contraceptives, anticonvulsants)
- ❑ Chronic alcoholism

Folic acid deficiency anemia

Syndromes:

1. circulatory-hypoxic,
2. gastroenterological,
3. hematological



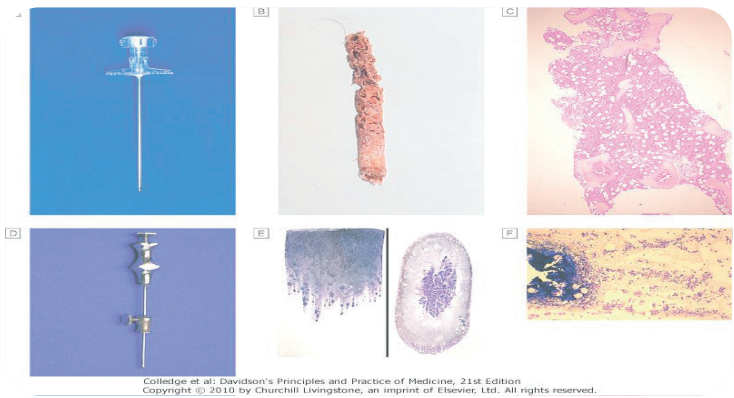
Investigation of folic acid deficiency

Diagnostic findings

- Serum folate levels may be low but are difficult to interpret
- Low red cell folate levels indicate prolonged folate deficiency and are probably the most relevant measure

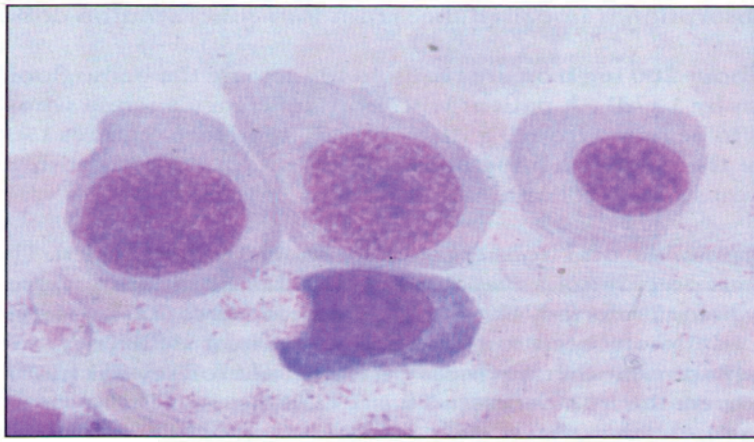
Corroborative findings

- Macrocytic dysplastic blood picture
- Megaloblastic marrow

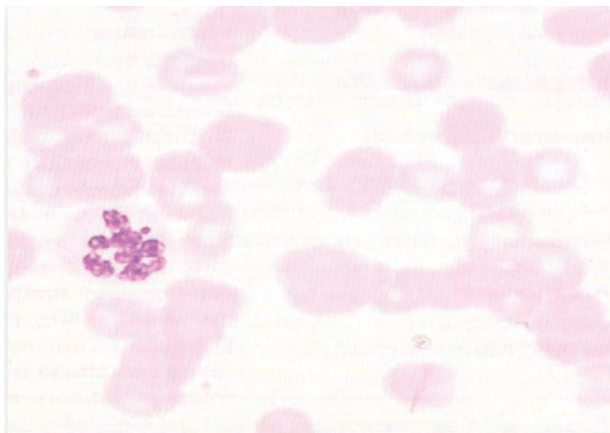


Bone marrow aspirate and trephine

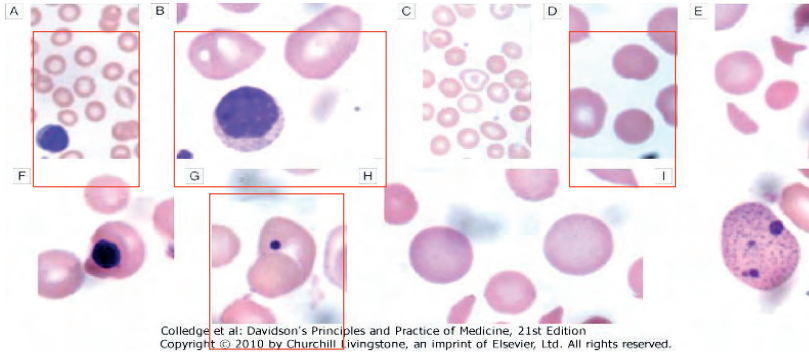
A. Trephine biopsy needle.
B. Macroscopic appearance of a trephine biopsy.
C. Microscopic appearance of stained section of trephine.
D. Bone marrow aspirate needle.
E. Stained macroscopic appearance of marrow aspirate: smear (left) and squash (right).
F. Microscopic appearance of stained marrow particles and trails of haematopoietic cells.



Typical megaloblasts in the bone marrow.



Hypersegmented granulocyte in vitamin B_{12} deficiency.



A. Microcytosis.
B. Macrocytosis.
C. Target cells.
D. Spherocytes.
E. Red cell fragments.
F. Nucleated red blood cells.
G. Howell-Jolly bodies.
H. Polychromasia.
I. Basophilic stippling

Diamond-Blackfan Anemia

Is Rapid-onset anemia within 1st year of life due to intrinsic defect in erythroid progenitor cells

Physical Presentation: Short stature, craniofacial abnormalities, and upper extremity malformations (triphalangeal thumbs, i.e.) in up to 50% cases

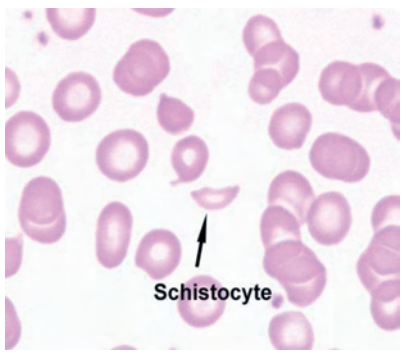
Type of anemia: Megaloblastic

Nonmegaloblastic anemia

Causes: Alcoholism, liver disease

Histology: RBC macrocytosis without hyperhsegmented neutrophils

Is: Macrocytic anemia in which DNA synthesis is not impaired



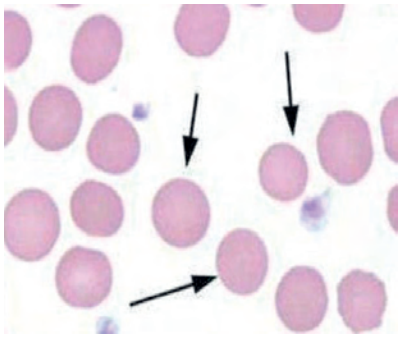
Normocytic, normochromic anemia

Intravascular hemolysis causes Include mechanical hemolysis, PNH, microangiopathic hemolytic anemias

Intravascular hemolysis lab findings
↓Haptoglobin,
↑LDH,
hemoglobinuria,
hemosiderinuria,
urobilinogen in urine.
May see ↑ unconjugated bilirubin

Intravascular hemolysis histology Schistocytes and reticulocytes on blood smear

Normocytic, normochromic anemia



Extravascular hemolysis Histology: Spherocytes on peripheral blood smear

Extravascular hemolysis lab findings

↑LDH,

↑unconjugated bilirubin.

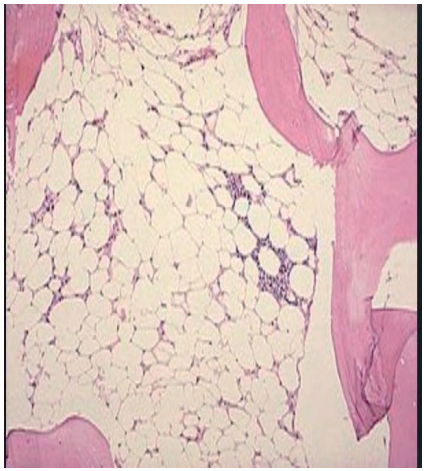
NO hemoglobinuria/hemosiderinuria.

Can have urobilinogen in urine.

Classification: Hemolytic or non-hemolytic

Anemia of Chronic Disease

Associated with:
RA, SLE,
neoplasms,
CKD, etc.
Lab Findings:
↓Iron, ↓TIBC, ↑ferritin (increased iron stores!)
Type of anemia: Nonhemolytic normocytic, or microcytic if progressed enough
treatment EPO (only for CKD). Treat underlying cause.
Pathophysiology: **Inflammation** --> Hepcidin (from liver) binds ferroportin on intestinal mucosal cells and macrophages, inhibiting iron transport --> ↓release of Fe from macrophages, decreased gut absorption



Aplastic Anemia

Pathogenesis: Failure/destruction of myeloid stem cells (i.e. XRT, drugs, viral agents, Fanconi anemia, idiopathic)

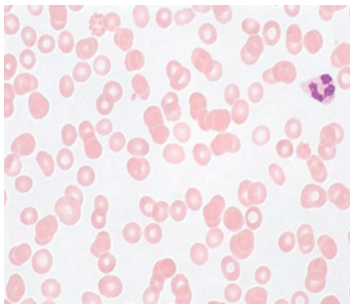
Drug causes:

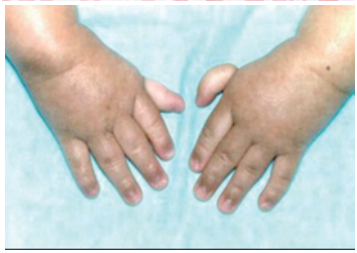
Benzene, chloramphenicol, alkylating agents, antimetabolites

VIRAL causes: Parvovirus B19, EBV, HIV, hepatitis

Causes of secondary aplastic anaemia

- Drugs
  - Cytotoxic drugs
  - Antibiotics – chloramphenicol, sulphonamides
  - Antirheumatic agents – penicillamine, gold, phenylbutazone, indometacin
  - Antithyroid drugs
  - Anticonvulsants
  - Immunosuppressants – azathioprine
- Chemicals
  - Benzene toluene solvent misuse – glue-sniffing
  - Insecticides – chlorinated hydrocarbons (DDT), organophosphates and carbamates
- Radiation
- Viral hepatitis
- Pregnancy
- Paroxysmal nocturnal haemoglobinuria

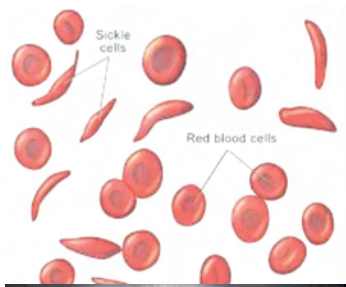




Aplastic Anemia

Type of anemia: Nonhemolytic normocytic

Fanconi anemia: DNA repair defect causing bone marrow failure, in addition to short stature, cafe-au-lait spots, ↑incidence tumors/leukemia, thumb/radial defects
Lab Findings: ↓Reticulocyte count, ↑EPO. Pancytopenia with severe anemia.
Histology: Hypocellular bone marrow with fatty infiltrate. Normal cell morphology.
Presentation: Fatigue, malaise, pallor, purpura, mucosal bleeding, petechiae, INFECTION
Treatment: Withdraw offending agent. Immunosuppressants, bone marrow allograft, RBC/platelet transfusion, bone marrow stimulation (i.e. GM-CSF)

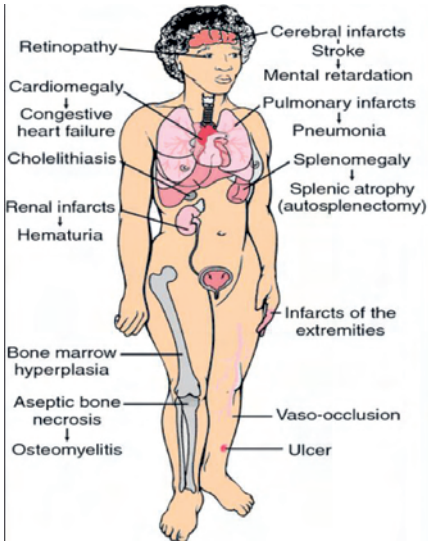


Sickle Cell Anemia

biochemical etiology: Substitution of GLU → VAL in β-globin → intravascular and extravascular hemolysis
Precipitating factors: Low O2, high altitude, acidosis cause HbS to polymerize (b/c HbS changes conformation in these conditions)
Presentation: Anemia and vasoocclusive disease, PAIN
Newborn presentation: Initially asymptomatic b/c protected by HbF, which doesn't have any beta globin
Sickle cell: trait Heterozygote. Have resistance to malaria.
Prevalence: 8% of African Americans have an allele

Histology: Crescent-shaped RBCs

Radiology: "Crew cut" on skull X-ray due to marrow expansion from ↑ erythropoiesis (like thalassemias!)



Sickle Cell Anemia

Complications Aplastic crisis (parvovirus B19), autosplenectomy (will see Howell-Jolly bodies) → risk of infection by encapsulated organisms, Splenic infarct, Salmonella osteomyelitis, Painful crises (dactylics, priapism, acute chest syndrome, avascular necrosis, stroke), Renal papillary necrosis (↓PO2 in papilla) and microhematuria (medullary infarcts)

Diagnosis: Hgb electrophoresis

treatment Hydroxyurea → ↑HbF. Hydration

Genetics: HbS point mutation causes single AA replacement in β-chain

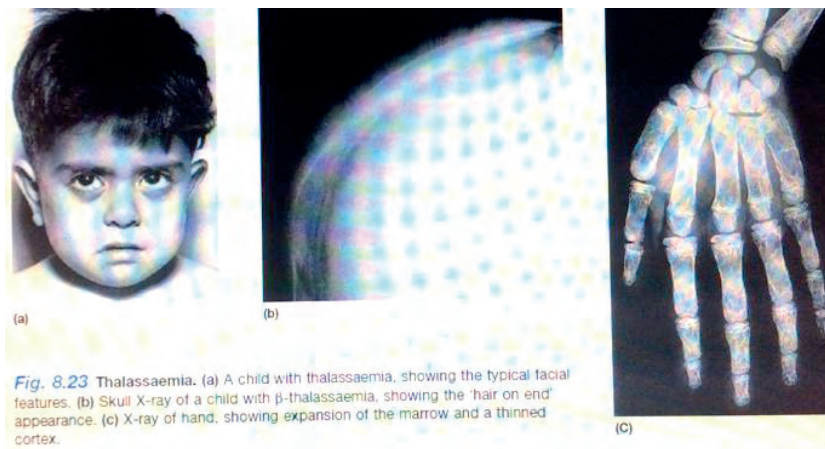
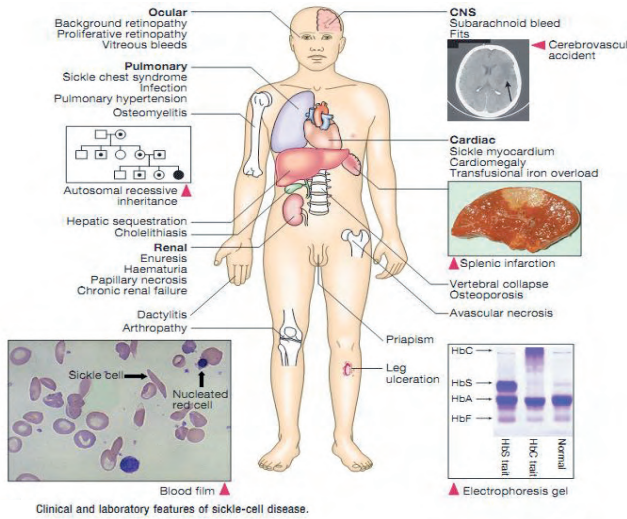


Fig. 8.23 Thalassaemia. (a) A child with thalassaemia, showing the typical facial features. (b) Skull X-ray of a child with β-thalassaemia, showing the 'hair on end' appearance. (c) X-ray of hand, showing expansion of the marrow and a thinned cortex.



Clinical and laboratory features of sickle-cell disease.

Intrinsic Hemolytic Anemia
types

- Hereditary spherocytosis,
- G6PD deficiency,
- PK deficiency,
- HbC disease,
- PNH,
- Sickle cell anemia

Hemolytic anemia

Investigation results indicating active haemolysis

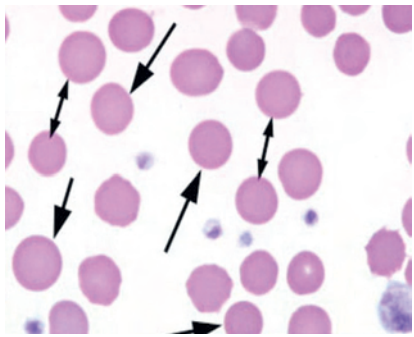
Hallmarks of haemolysis

- ↓Haemoglobin
- ↑Unconjugated bilirubin
- ↑Lactate dehydrogenase
- ↑Reticulocytes
- ↑Urinary urobilinogen

Additional features of intravascular haemolysis

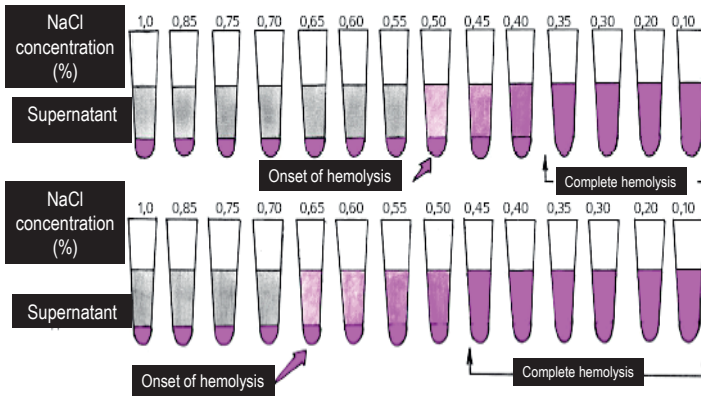
- ↓Haptoglobin
- ↑Methaemalbumin
- Positive urinary haemosiderin
- Haemoglobinuria

Hereditary Spherocytosis



Histology: Small, round RBCs with less surface area and no central pallor (↑MCHC)
Presentation: Splenomegaly, aplastic crisis (from overlying parvovirus B19 infection)
susceptible to Parvovirus B19 infection --> aplastic crisis
Lab Findings: Osmotic fragility test +, normal or decreased MCV with abundance of cells
Treatment: Splenectomy
Pathophysiology: Defect in RBC membrane proteins (ankyrin, band 3, protein 4.2, spectrin) --> extravascular hemolysis

The Coombs test
(positive for immune hemolytic forms)



REFERENCES

Kovalyova O.N., Ashcheulova T.V. Propedeutics to Internal Medicine. Part 2. – Vinnytsya: NOVA KNYHA, 2017. – 264 p.

Kovalyova O.N., Asheulova T.V. General inspection: manual for students. – Kharkov: "Turbo". – 2004. – 60 p.

Khomazjuk V.A., Ostashevska T.G., Krasyuk I.V. Propaedeutics of Internal Medicine and Patient Care: Study guide for the practical classes. Part I. – Kyiv: NMU, 2005. – 44 p.

Bickley, Lynn S.; Szilagyi, Peter G. Bates' Guide to Physical Examination and History Taking, 10th Edition. – 934p. Copyright ©2009 Lippincott Williams & Wilkins

The Point online resources, http://thepoint.lww.com

Учбове видання

ХОМАЗЮК Тетяна Анастасіївна

ПРОПЕДЕВТИКА ВНУТРІШНЬОЇ МЕДИЦИНИ

Учбово-наочний посібник

В двух частях. Частина 2
(англійською мовою)

Відповідальна за випуск О.В. Вінниченко

Макет та верстка Misheal_D

Формат 60x90/16. Папір офсетний. Гарнітура Myriad Pro.
Ум. друк. арк. 22,0. Замовлення № 19/19.

Видавець і виготовлювач видавництво «ГЕРДА»,
49000, м. Дніпро, пр. Д. Яворницького, 60
Свідоцтво суб'єкта видавничої справи ДК № 397 від 03.04.2001
www. book-shop.in.ua

ISBN 978-617-7639-17-5
ISBN 978-617-7639-19-9 (ч. 2, pdf)