# Introduction to Pathophysiology as an integrating medical discipline

Etiology and pathogenesis of disease

Definition of health vs. disease

Problem of normality in medicine



# Pathophysiology (PP) as a medical discipline

- medical science dealing with the study of disease
  - physiology = how the healthy body works
  - pathophysiology = how the ill body works (or does not)
    - PP is "physiology of altered health"
    - **PP explains functional consequences of a disease process**
- PP studies namely two processes
  - disease etiology – i.e. what causes disease to develop
  - disease pathogenesis – how the disease develops
  - disease pathology – what anatomic changes disease produces
- PP bridges basic medical sciences with clinical medicine
  - experimental approach
    - molecular biology, genetics, immunology, …
    - models (in vitro, animals, simulations)
    - human samples (DNA, proteins, fluids, tissues)
  - clinical trials
    - observational studies
    - interventional studies

# WHO definition of health

- Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.
  - Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948.
    - The Definition has not been amended since 1948.

# Distinction between health and disease

- stating disease can have a profound mental, social, economic and philosophical consequences for the individual
- however, distinction is not always easy
  - see further interindividual variability and normality
- disease is perceived both subjectively
  - "I am not feeling well", anxiety, fear, failure, …
- objectively by medical specialists
  - to some extent independently from the subject

# Two approaches to definition of disease

- neutral
  - each organ and organ system in our body has its function and the function is impaired than there is a disease
    - does not take into account the subjective feelings of a subjects
    - more close to the current medicine paradigm
- normative
  - if the person is not limited by his/her condition and can achieve the desired goals than he/she is healthy
    - blindness or autism is not a disease if the person suffering from it does not feel limited in any way

# Disease etiology

- endogenous = internal factors
  - congenital
    - genetic (monogenic as well as polygenic)
    - malformations due to prenatal exposure to viruses of toxins
    - fetal programing
  - acquired
    - metabolic
    - immune
    - circulatory
    - neoplastic
- exogenous = external factors
  - physical
    - mechanical, thermal, irradiation, electricity, …
  - chemical
    - xenobiotics incl. drugs
    - toxins and poisons
    - environmental contaminant
    - smoke
    - excess or deficit of nutrients
  - biological
    - infections (bacterial, viral, fungal, parasites, …)
    - toxins
    - prions
  - psychological and social
    - mental trauma
    - stress

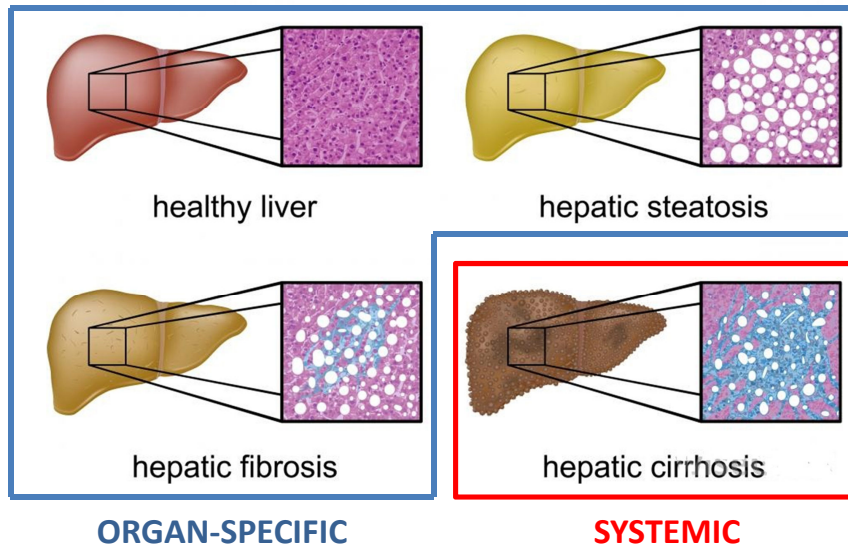**majority of diseases are multifactorial in origin**

# Diseases from one single cause vs. multifactorial

- Monofactorial
  - one single cause potent enough to cause disease
  - environment and lifestyle play generally minor role
  - examples
    - trauma
    - highly virulent infection
    - monogenic disease
- Multifactorial (= complex)
  - products of concomitant exposure to internal and external factors with typically equal role of both, so called "diseases of civilization"
  - examples
    - obesity
    - diabetes
    - atherosclerosis
    - allergy
    - cancers

# Disease pathogenesis

- Response of the body to the action of etiological factor(s)
  - adaptation = no disease
  - dysadaptation = disease
- Pathogenesis of disease
  - sequence of molecular, cellular, tissue and organ events taking the place from the initial contact/exposure to etiological factor(s) until the expression of disease
  - organ-centered
    - limited to a single organ (system)
    - however, usually only at the beginning of the disease
    - later, majority of diseases becomes systemic, i.e. having systemic signs
      - for example tumors, liver steatosis and fibrosis, …
  - systemic
    - some disease are widespread

# Liver Disease



| healthy liver | hepatic steatosis |
| hepatic fibrosis | hepatic cirrhosis |

**ORGAN-SPECIFIC**          **SYSTEMIC**

# Common misconceptions

- Atherosclerosis might be cited as a etiology of coronary artery disease
- However, progression of the process from initial clinically unapparent lesion (fatty streak) to manifest occlusive vessel disease is a continuum of pathogenesis
- the very cause(s) of atherosclerosis are generally unknown and subjects of research with many identified etiologic contributors
  – external – diet, exercise, smoking,
  – internal – genetic susceptibility, metabolic, inflammation, …
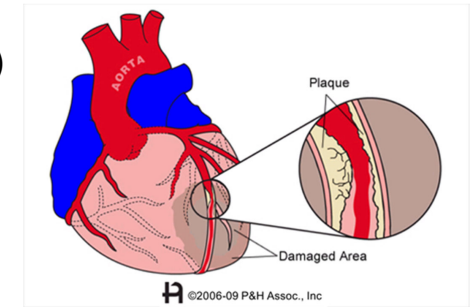


# Clinical manifestation of diseases

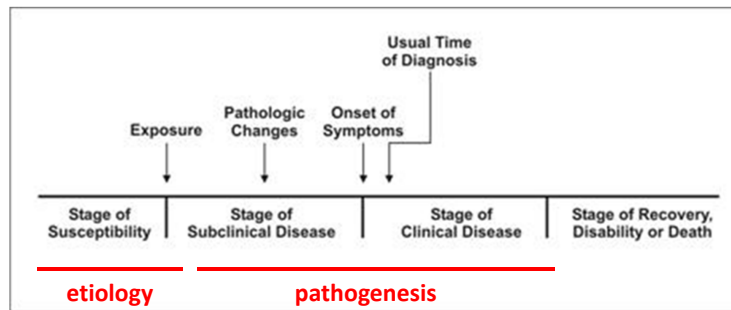- diagnosis of diseases is based on the recognition and proper interpretation of diseases manifestation
  – symptom = feature recognized subjectively by the patient
  – sign = objectively noticeable
    • physical examination
    • diagnostic method (laboratory, X-ray, ultrasound, …)
- typical cluster of signs and symptoms present usually together creates a syndrome
  – however, many conditions can present by the same syndrome, therefore one must test multiple working hypotheses as to what led to this particular state = differential diagnosis

# Pathophysiology vs. clinical medicine



**pathophysiology is inductive**

**clinical medicine is deductive**
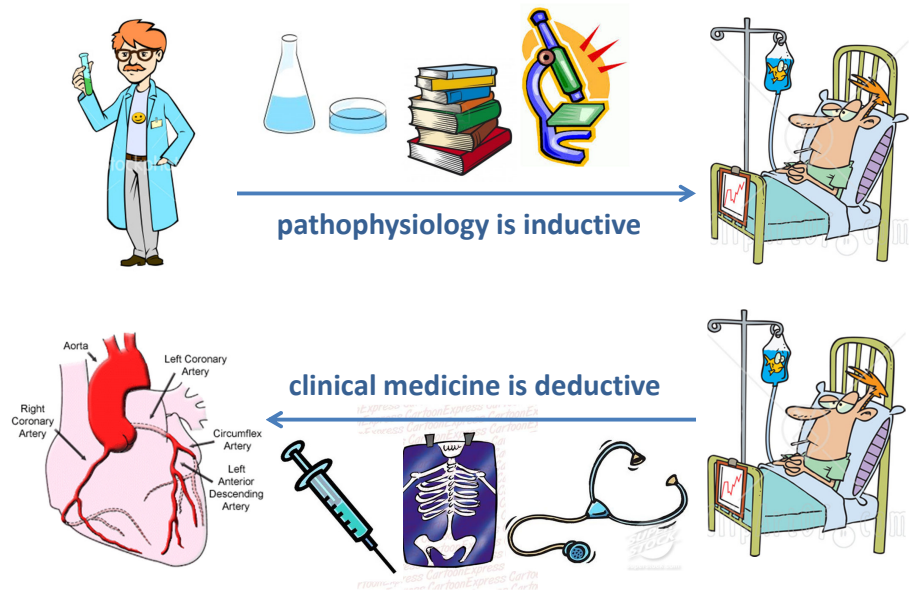
# Natural history of disease

- refers to the progression of a disease process in an individual over time in the absence of treatment
- this is how the PP is usually taught



| Exposure | Pathologic Changes | Onset of Symptoms | Usual Time of Diagnosis |

Stage of Susceptibility | Stage of Subclinical Disease | Stage of Clinical Disease | Stage of Recovery, Disability or Death

**etiology**     **pathogenesis**

# Clinical course of the disease

- "disease background"
  - individual constitution (incl. genetic susceptibility and lifelong fitness) matters, i.e. the same etiological factor will not have the same effect in various people
  - risk factors
    - variable exposure due to environment (incl. geographical location, altitude, climate etc.), individual lifestyle, history and social habits etc.
- pre- or subclinical stage
  - prodromal – usually unspecific signs of upcoming disease
    - e.g. fatigue, weakness, anorexia, pain, fever,
- acute illness (limited number of days, can be 1 day to 1 month)
  - severe but self-limiting
- chronic illness (longer that typical pro given disease)
  - long term, continuous process
  - follows the acute stage
    - disease was not eliminated completely due to various reasons (e.g. immune deficiency)
  - chronic from the very beginning
    - e.g. due to pathogen making itself inaccessible, or targeting the very means od body defense

# Chronic disease

- Exacerbations = aggravation of symptoms, signs and severity of disease
- Remissions = lessening of severity
- Remission = disappearance of disease induced by treatment however with the risk of reoccurrence
  - e.g. cancer – with current methods we cannot be sure we eliminated all cancer cells
- Residual disease = detectable with lab test but not by symptoms and clinical signs
  - e.g. leukemia – PCR detection of genetic changes typical of leukemic clone but otherwise patients appears healthy
- Carrier status = patient harbors the microorganism but may have few or no symptoms, clinical or laboratory signs
- Complication = possible adverse extensions of a disease in spite of the treatment



# Diagnosis of disease – problem with "normality"

- trait used as diagnostic parameters
- qualitative
  - alternatives yes/no
    - e.g. cleft palate, congenital valve disease etc.
- quantitative
  - measurable
  - continuous distribution in population
  - typically influenced by many factors
  - problem to distinguish what is normal and what is not
    - mean $\pm 2$ SD
- alternative vs. continuous model of disease
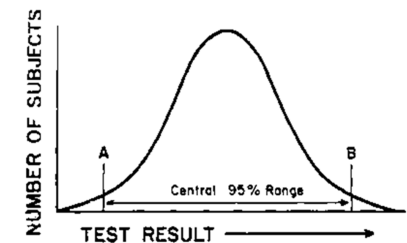
## Distribution vs. selection (mortality)
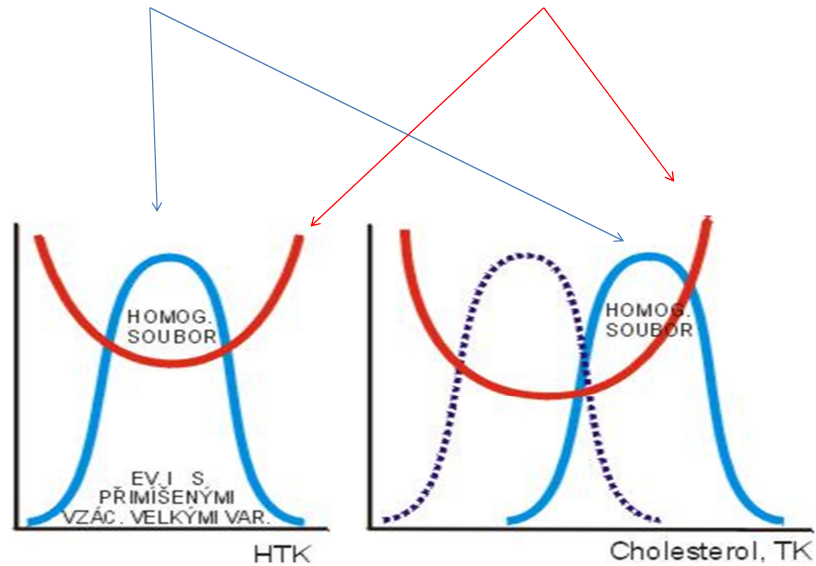


## Diagnostic tests

- diagnosis is performed using various ways
  - personal history
  - clinical examination
  - instrumental and laboratory test
- requirements on diagnostic tests
  - reproducibility = repeated measurements give equal results
  - validity = the extent to which measurement masures what is intended to measure
  - specificity = % of subjects free of disease correctly identified as negative (= true negativity)
    - 95% specificity = 95 out of 100 healthy people is diagnosed as healthy, 5% je false positivity
  - sensitivity = % of subjects with diseases correctly identified as ill (= true positivity)
- predictive value of diagnostic test
- biomarker
  - measured characteristic which may be used as an indicator of the probability of development of diseases or complication



## Practical notes

- http://www.med.muni.cz/patfyz
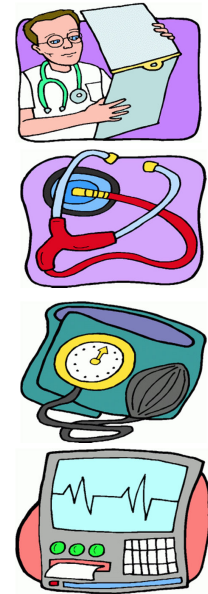
- literature:
  - Pathophysiology (Damjanov I), Elsevier 2009
  - Essentials of Pathophysiology (Porth CM), Lippincot W&W 2007