Introduction to Pathophysiology

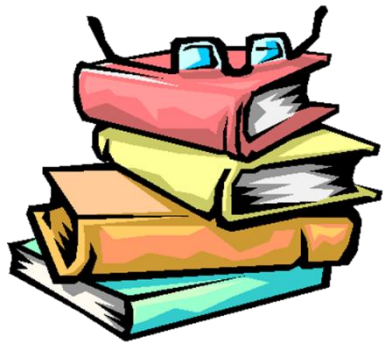
as an integrating medical discipline

Pathophysiology – what is it about?

Definition of health vs. disease/illness

Etiology and pathogenesis of disease

Problem how to define normality in medicine



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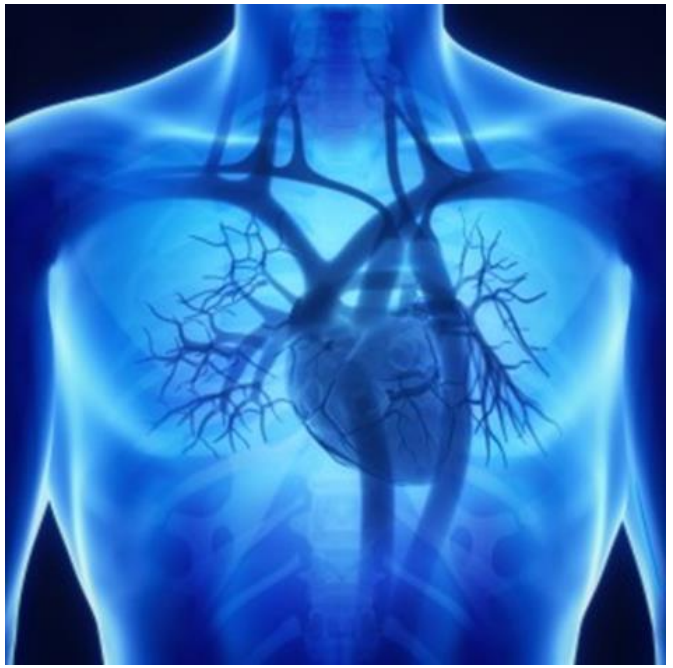
Pathophysiology (PP) as a medical discipline

- medical science dealing with the study of disease, in particular how the disease develops and progresses (i.e. aetiology and pathogenesis) and also how the cells, tissues, organ systems and whole body react in time (i.e. adaptation and compensation)
  - physiology = how the prototypical/textbook healthy body works
  - pathophysiology = how the real ill body works (or it does not)
    - PP is "physiology of altered health"
    - **PP explains functional consequences of a disease process**
    - PP has to consider interindividual variability in disease susceptibility, onset, rate of progression, response to therapy, …
- PP studies namely two processes
  - disease (a)etiology – i.e. what causes the disease to develop
  - disease pathogenesis – how the disease develops
  - has to considetr also disease pathology – describes what anatomic changes disease produces
- PP bridges basic medical sciences with clinical medicine
- PP knowledge on etiopathogenesis of disease is based on:
  - basic research and experimental approach
    - molecular biology, genetics, immunology, …
    - models (in vitro, animals, humans)
    - human samples (DNA, proteins, fluids, tissues)
  - clinical observation, evidence and trials
    - observational studies – no intervention, just observation of natural history
    - interventional studies – intervention in controlled settings (drugs, surgery, behavioral therapy, …)



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How does pathophysiology differs from previous disciplines?

- Physiology and other previous subjects mainly focuses/assumes
  - a prototypical human being (e.g. 70kg healthy man of unknown age)
  - and isolated processes (healthy or pathological)
- PP on the contrary tries to bring the knowledge close to clinics and general population by accounting for:
  - **variability** (intra- and inter-individual)
    - e.g. chronobiology
  - **temporal dynamics** of disease (time, aging, exposures etc.)
  - **spatial dynamics** of disease (e.g. from initially local process to systemic)
    - e.g. coronary AS to congestive heart failure
  - **complexity** (single disease is a rare situation, very often comorbidities)
  - gender (and possibly ethnic or other) **differences**
- PP has a unique position in a medical curriculum enabling to
  - synthetize all preclinical knowledge
    - morphology, biochemistry, physiology, immunology etc.
  - document its clinical relevance
  - extent particular information to general (generalisation) and vice versa
    - many diseases share the same etiopatogenetic mechanisms – **analogy**
      - we do not need to repeat them again and again
  - thereby we can use the time effectively

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Pathophysiology (PP) as a medical discipline

- What we are going to study?
  - **General PP**
    - deals with general pathologic processes and mechanisms that are involved in pathogenesis of more than one disease
    - in fact, majority of diseases are a mixture of just a few pathologic processes
      - hypoxia/ischemia, abnormal cell proliferation (too much or too little), inflammation, various metabolic abnormalities inducing toxic or hypo-nutritive environment, effect of external factors (such as temperature, mechanical forces, radiation, …) etc.
    - there are also powerful defensive mechanisms in body operating together with disease mechanisms
      - innate and adaptive immunity, atrophy/hypertrophy, cellular and tissue remodelling, hypo-/hyperfunction, altered homeostasis etc.
  - **Special (organ, systems) PP**
    - explanation of pathomechanisms involved in functional disturbances of the organs and systems of the organism
  - **Pathophysiology help us to understand the logic of life during development of pathological processes**

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HEALTH vs. DISEASE

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Distinction between health and disease

- In order to study diseases we have to be able to distinguish between health and disease
  - the pragmatic reason – who should be given a health care
    - on the other hand many physiological conditions are a subject of health care system
      - childhood paediatric care, pregnancy, preventive measures, aesthetic reasons (dentistry, surgery, dermatology), …
  - the philosophical/ethical reason
    - to say that somebody has a disease/is ill can have a profound mental, social, economic and **consequences** for the individual, however, distinction is not always easy
- **Disease is perceived** both **subjectively**
  - "I am not feeling well", anxiety, fear, failure, …
- **and objectively** by medical specialists
  - to some extent independently from the subject
- **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 July 22, 1946 by the representatives of 61 member states (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948
    - this definition has not been amended since 1948

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Disease vs. Illness

- It is not “just” a discussion of semantics – it’s about clarity
  - these two words are often used interchangeably, but this is incorrect
- **Disease** is an objectively detectable state, very often a subject of a screening or prevention
  - an abnormal condition/process affecting cell, tissue, organ or organism (quite often in this order)
    - could be due to infection, degeneration of tissue, injury/trauma, toxic exposure, development of cancer, etc.
  - disease does not need to be accompanied by subjective symptoms (asymptomatic, latent)
- **Illness** best refers to the feelings that might come with having a disease, it borders the patient, creates reason for treatment
  - pain, fatigue, weakness, discomfort, distress
  - illness is profoundly affected by many factors such as education, cultural and socio-economical circumstances, experience, mentality, age etc.
- Disease and illness are mutually interconnected – possible scenarios:
  - disease leads to illness = following asymptomatic phase (of variable length) symptoms appear
  - disease without illness = e.g. mild hypertension, hypercholesterolemia or compensated illness
  - illness without disease = e.g. surgery, trauma, „psychosomatic“ diseases
- **“Disease is something an organ has; illness is something a man has”** (Eric J. Cassell, 1978)
- **Illness is the reason to seek the doctor, disease is what stays afterwards**

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Example of approaches to definition of disease

- **Neutral (objective) - closer to PF and clinical disease concept**
  - each organ and organ system in our body has its function (that is usually measurable – e.g. cardiac output, GFR, pO_2/CO_2, …) and when the function is impaired than there is a disease
    - health equals to the ability of organism (and its parts/organs and systems) to perform all the functions under the typical circumstances with at least typical efficiency (closely related terms are adaptation and homeostasis)
      - **it is necessary to define normality** (reference population/reference interval – statistical approach) *
    - disease is a state that is a subject of healthcare
    - does not take into account the subjective feelings of a subjects, although later nearly every disease can cause discomfort, disability, pain, suffering and be thus perceived subjectively
      - on the contrary there are plethora of situations when the same feelings are not considered pathological (such as dentition, menstruation, pregnancy etc.)
    - more close to the current medicine paradigm
- **Normative (subjective) – closer to illness concept**
  - if the person is not limited by his/her condition and can achieve the desired goals than he/she is healthy
    - blindness, dwarfism or autism is not a disease if the person suffering from it does not feel limited in any way

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Disease and health are however natural and cultural phenomena incl. their historical context

- Historical stigma – very often rare conditions
  - albinism, dwarfism, …
- Perfect body ideal
  - asthenic vs. obesity
  - mutilations/body decorations
- Age-related changes can become unacceptable
  - e.g. post-menopausal complaints
  - osteoporosis
  - skin, hair, dental age-related changes
- On the contrary, some conditions no longer diseases
  - e.g. homosexuality
- And new ones are emerging
  - ADHD, dyslexia, …

Alison Lapper (8 months) by Marc Quinn (2000). This sculpture caused controversy in UK when it was chosen as one of two pieces to occupy the vacant fourth plinth in Trafalgar Square, London.

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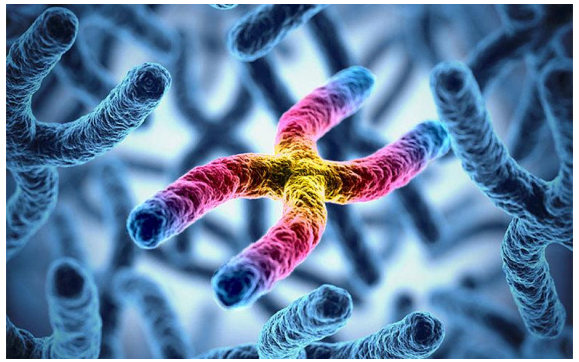

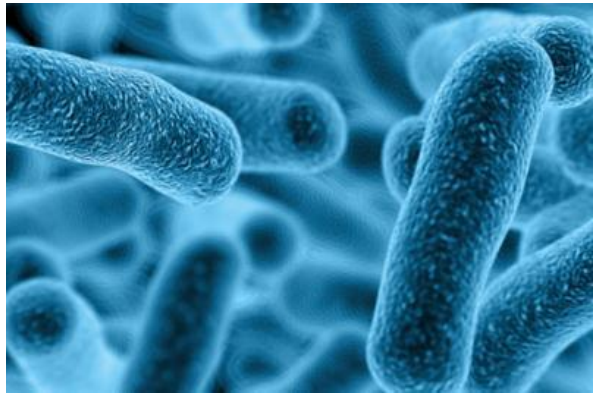

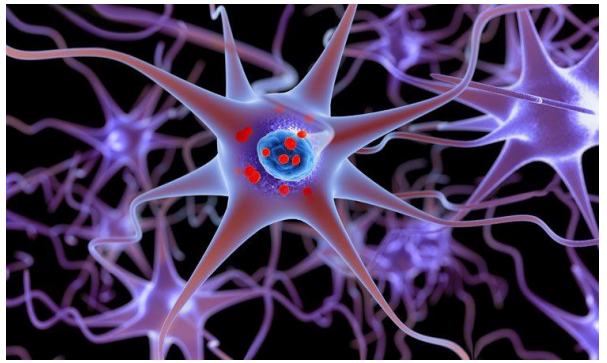

ETIOLOGY and PATHOGENESIS OF DISEASE

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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

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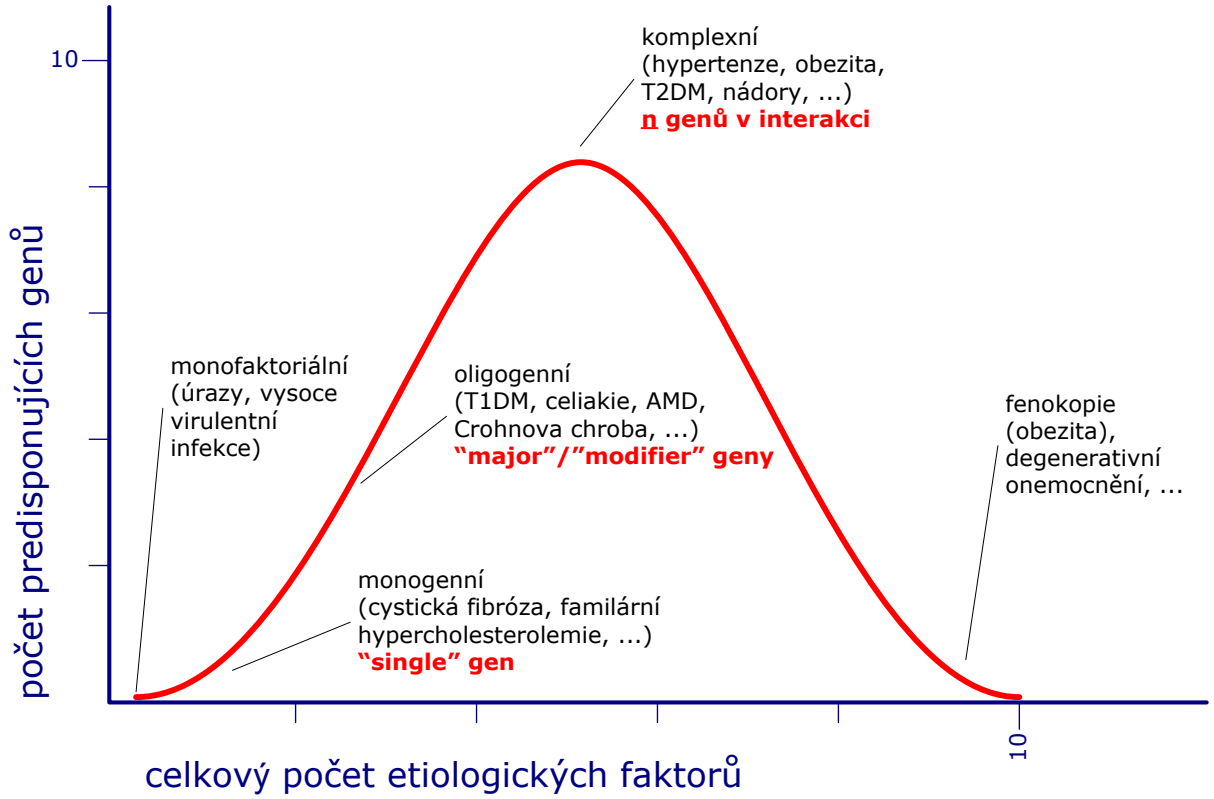
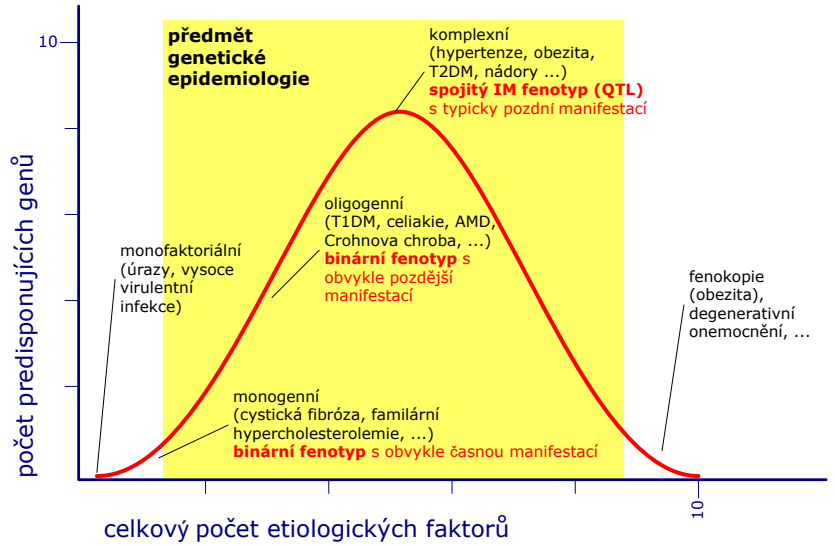
Diseases from one single cause vs. multifactorial (⇒ alternative vs. continuous model of disease)

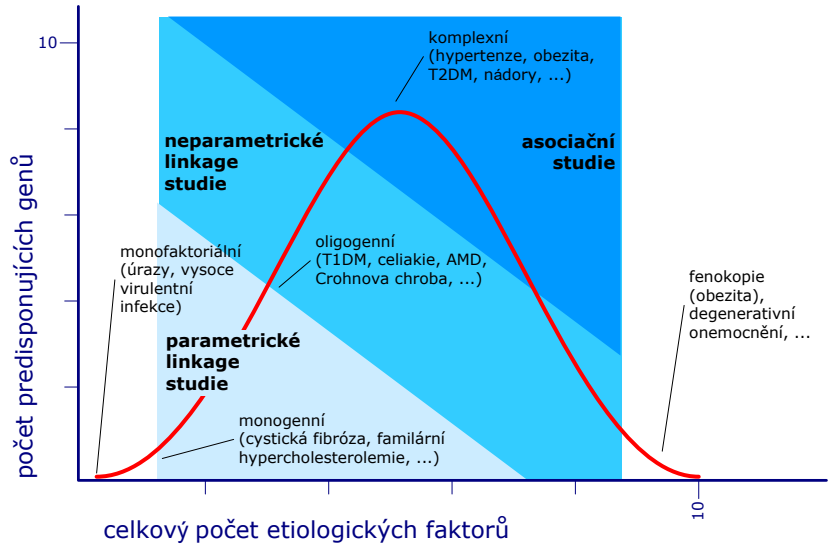
- **Monofactorial**
  - one single cause potent enough to cause disease
  - diagnosis often based on qualitative parameters
    - e.g. X-ray visible fracture, wound, malformations, …
  - easy to distinguish between health and disease
  - environment and lifestyle play generally minor role
  - examples
    - trauma
    - highly virulent infection
    - poisoning
    - monogenic disease
    - chromosomal abnormalities (i.e. aneuploidy)
      - trisomy - autosomal (Down)
      - trisomy of monosomy – gonosomal (i.e. Turner, Klinefelter)
- **Multifactorial (= complex)**
  - products of concomitant exposure to internal and external factors with typically equal role of both, so called "diseases of civilization"
  - diagnosis often based on quantitative parameters (disease is a continuum of health)
    - e.g. normal BP/hypertension, normal glycaemia/diabetes
  - often difficult to distinguish between health and disease
  - examples
    - obesity
    - diabetes
    - atherosclerosis
    - allergy
    - cancer

	Factors	
	Large effect	Small effects
Non-genetic	severe trauma, intoxications, highly virulent infections, highly penetrant population environmental exposures (e.g. nuclear catastrophe)	common environmental exposures, physical activity, dietary factors, stress, drugs, aging, …
Genetic	monogenic diseases due to rare alleles	gender, common alleles

Diseases according to the number of ethiological factors and genetic contribution







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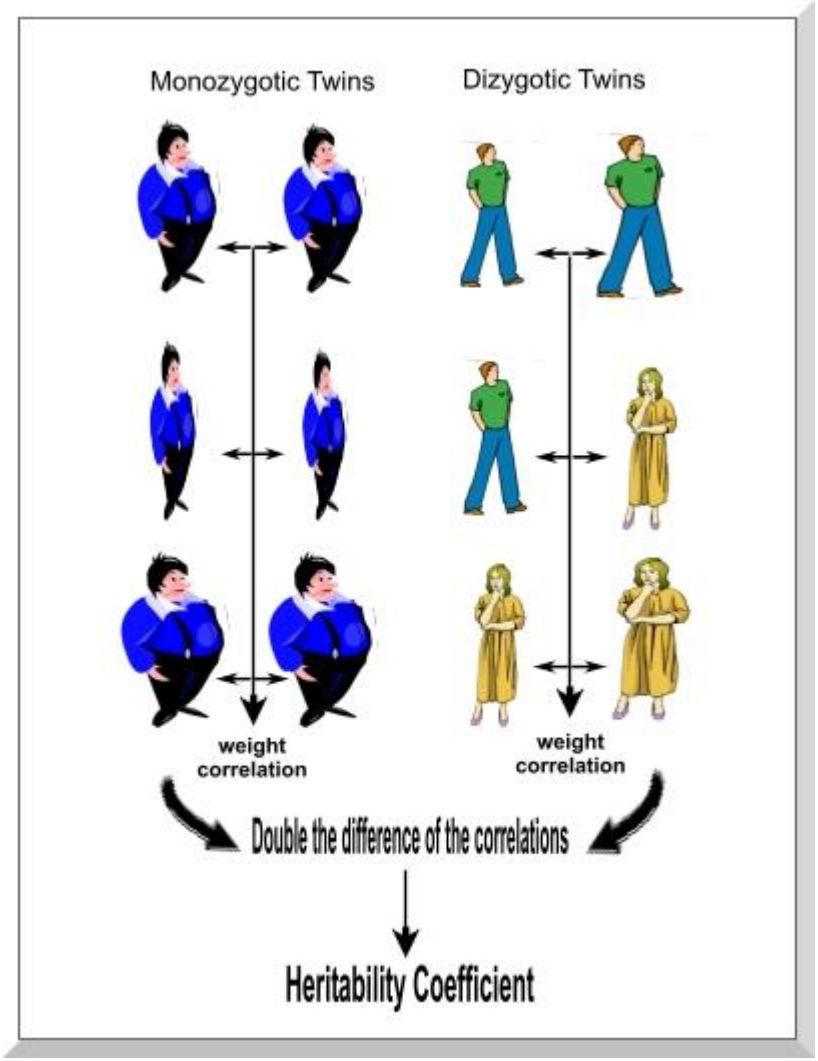
What indicates that disease is, at least partly, genetically conditioned ??



- binary phenotype (yes/no)
  - familiar aggregation
    - prevalence of affected probands in families >>> prevalence in general population
      - true for monogennic as well as complex diseases
  - segregation analysis
    - finding the mode of inheritance of given phenotype in families (i.e. recessive or dominant)
    - only for monogennic (“major” genes)
- continuous phenotype (how much)
  - intra-family correlation coefficient
    - proportion of overall variability in phenotype caused by variability between families
  - heritability
    - percentage of variability in phenotype due to variability in genotype (twin studies MZT, DZT)

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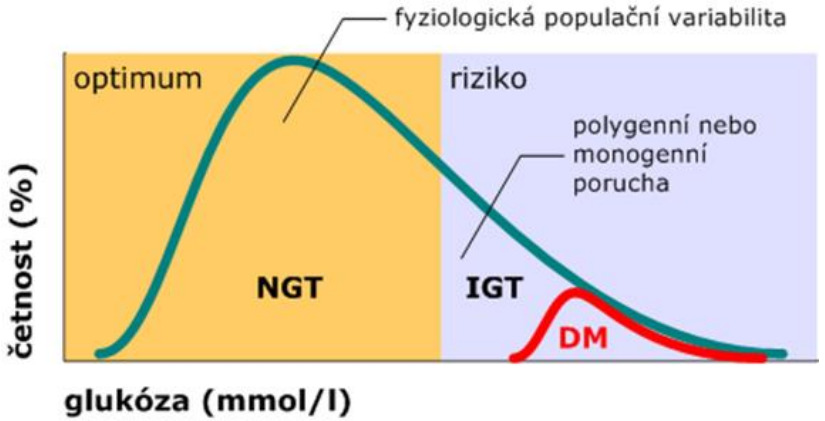
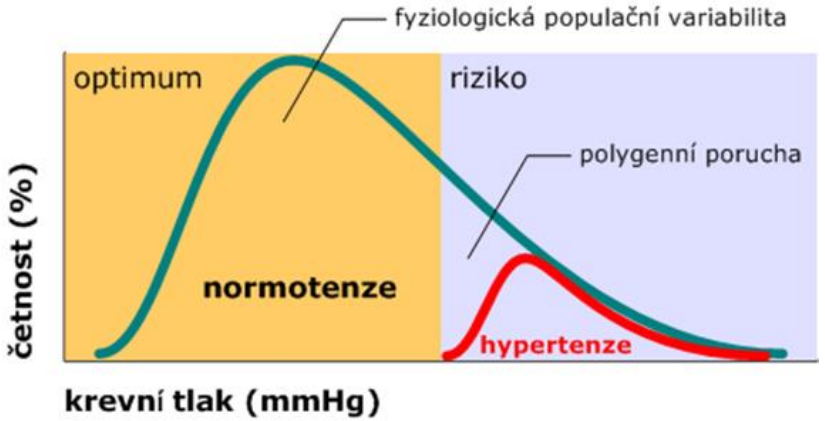
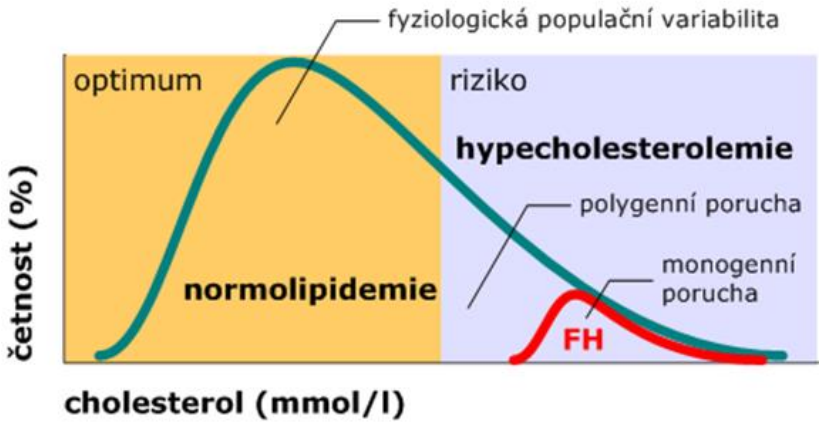
Complex diseases

typically continuous traits !!!







examples of complex diseases: essential hypertension (BP, …), diabetes (glycaemia, insuliniaemia, C-peptide, …), dyslipidaemia (TCH, LDL, HDL, …), obesity (BMI, WHR, …), allergy (provocation tests, circulating cells, cytokines, …), atherosclerosis (coronarography, …), Alzheimer disease and other types of dementia (scales, grading systems, …), others

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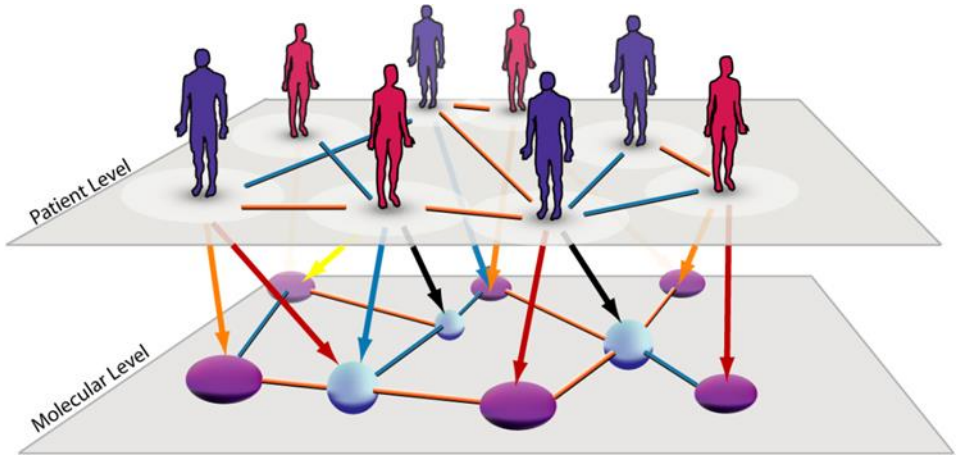
Complex diseases



- diseases developing due to the **ethiopathogenic "complex" of genetic, epigenetic and environmental factors**
  - phenotype does not follow Mendel rules (i.e. dominant or recessive mode of inheritance)
- "predisposing genes/alleles" increase probability to become affected, however, do not determine unequivocally disease development
  - effect of non-genetic factors is a necessary modifier
    - diet, physical activity, smoking, ….
  - genes interact between themselves
- typical features of complex diseases
  - **incomplete penetrance of pathological phenotype**
    - some subjects who inherited predisposing alleles never become ill if not exposed to environmental factors
  - **existence of „phenocopies"**
    - pathological phenotype can develop in subjects not predisposed, entirely due to the exposure to non-genetic factors (e.g. massive overeating leading to obesity despite the genetics)
  - **genetic heterogeneity (locus and allelic)**
    - manifestation (clinical) is not entirely specific but the same syndrome can develop as a consequence of various loci (= locus heterogeneity) in which there could be several variants (= allelic heterogeneity)
      - e.g. many loci contributing to the regulation of blood pressure = essential hypertension likely not a homogenous PF entity
  - **polygenic inheritance**
    - predisposition to disease is significantly increased only in the presence of a set of several risk alleles (polymorphisms), hence their high population frequency
      - in isolated occurrence the effect is mild, therefore no genetic selection
  - **other modes of transmission**
    - mitochondrial, imprinting (<1% of all alleles in genome), epigenetics

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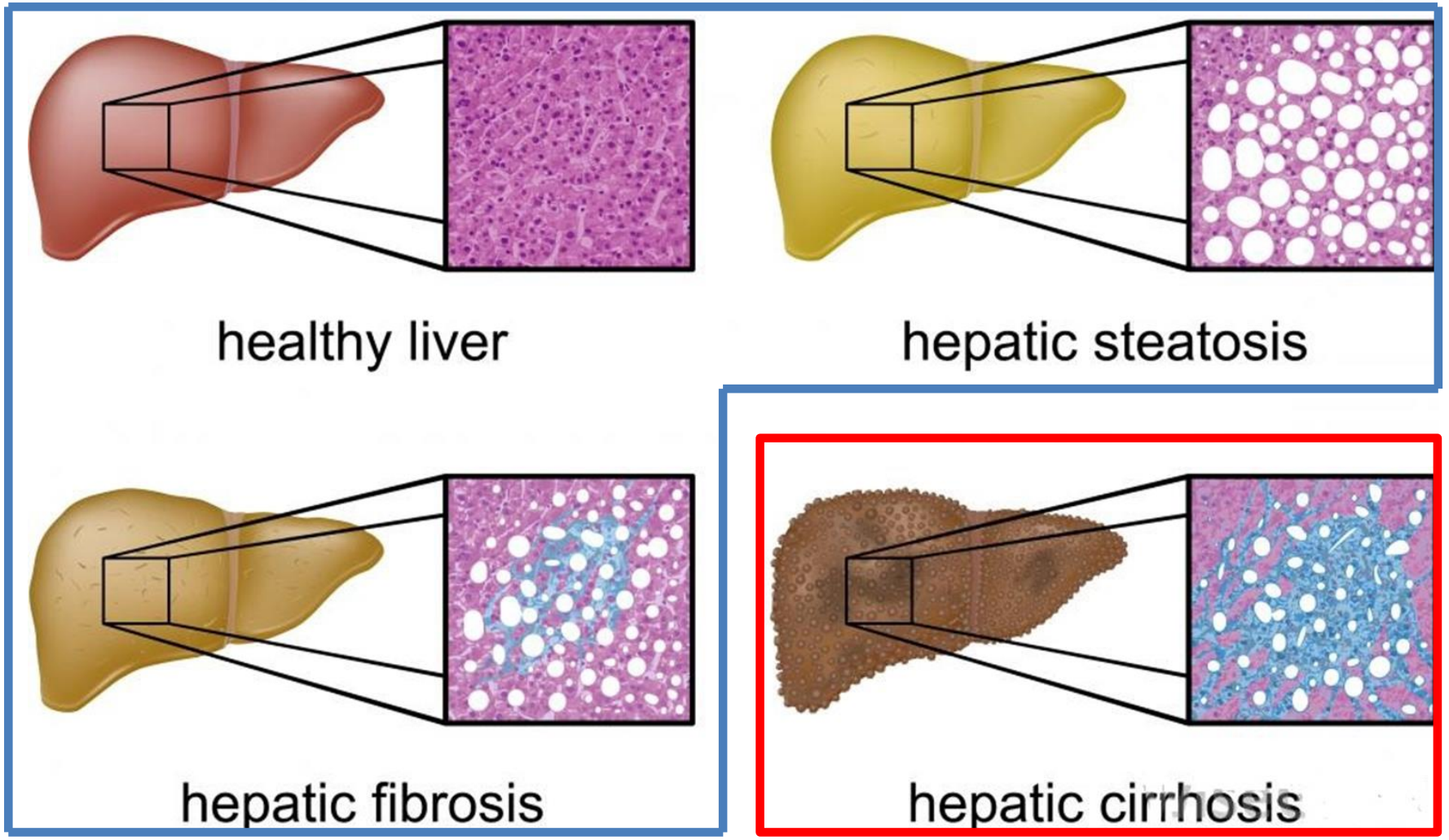
Disease pathogenesis

- Response of the body to the action of etiological factor(s)
  - **adaptation** = no change in functional abilities = no disease
  - **dysadaptation** = impairment of function = 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/systemic from the very beginning

Liver Disease



ORGAN-SPECIFIC

SYSTEMIC

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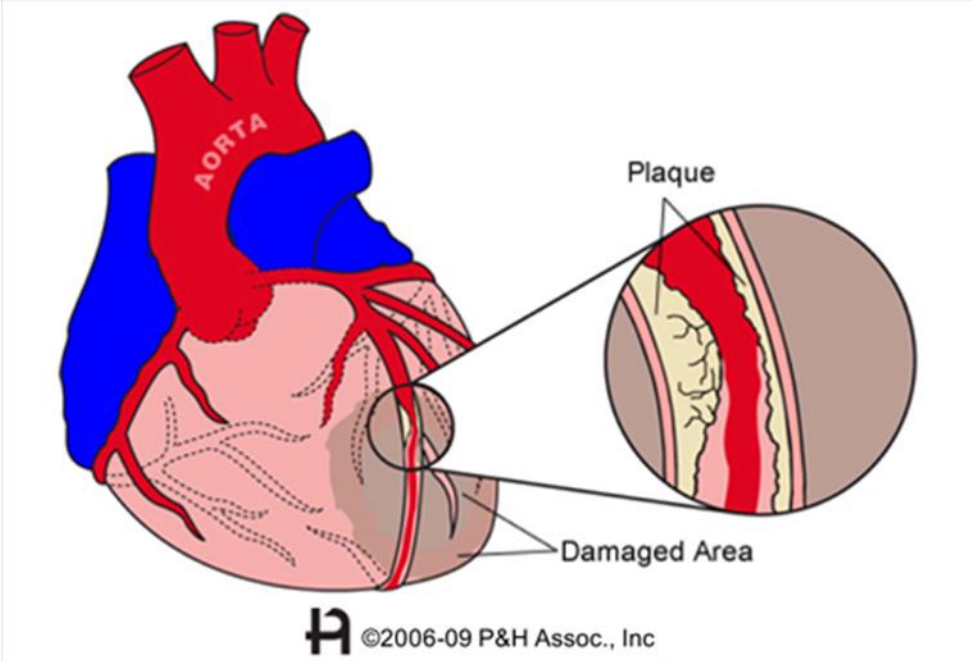
Common misconceptions

- Atherosclerosis might be cited as a etiology of coronary artery disease (CAD)
- 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 (risk factors)
  - external – diet, exercise, smoking,
  - internal – genetic susceptibility, metabolic, inflammation, …
- CAD is therefore late clinical manifestation of atherosclerosis



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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

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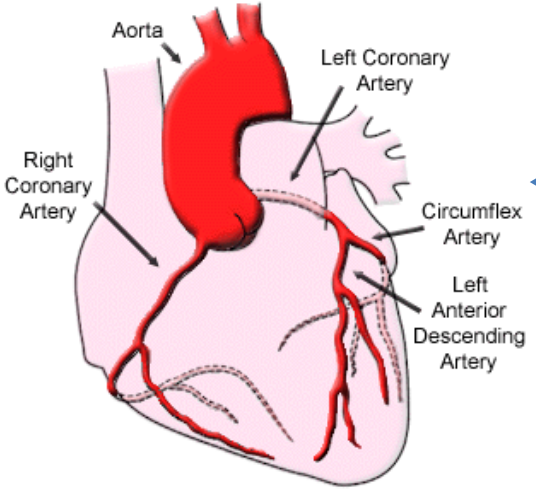
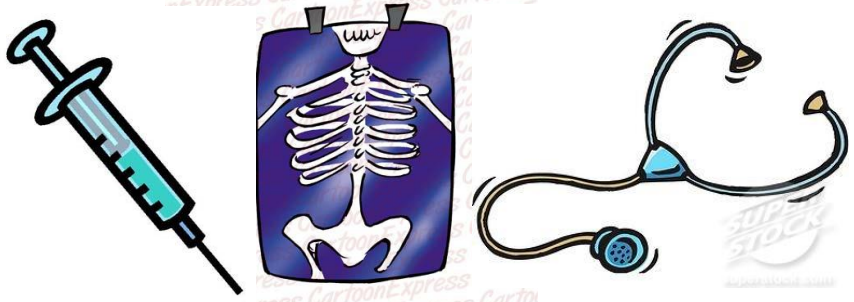
Pathophysiology vs. clinical medicine

pathophysiology is inductive



clinical medicine is deductive



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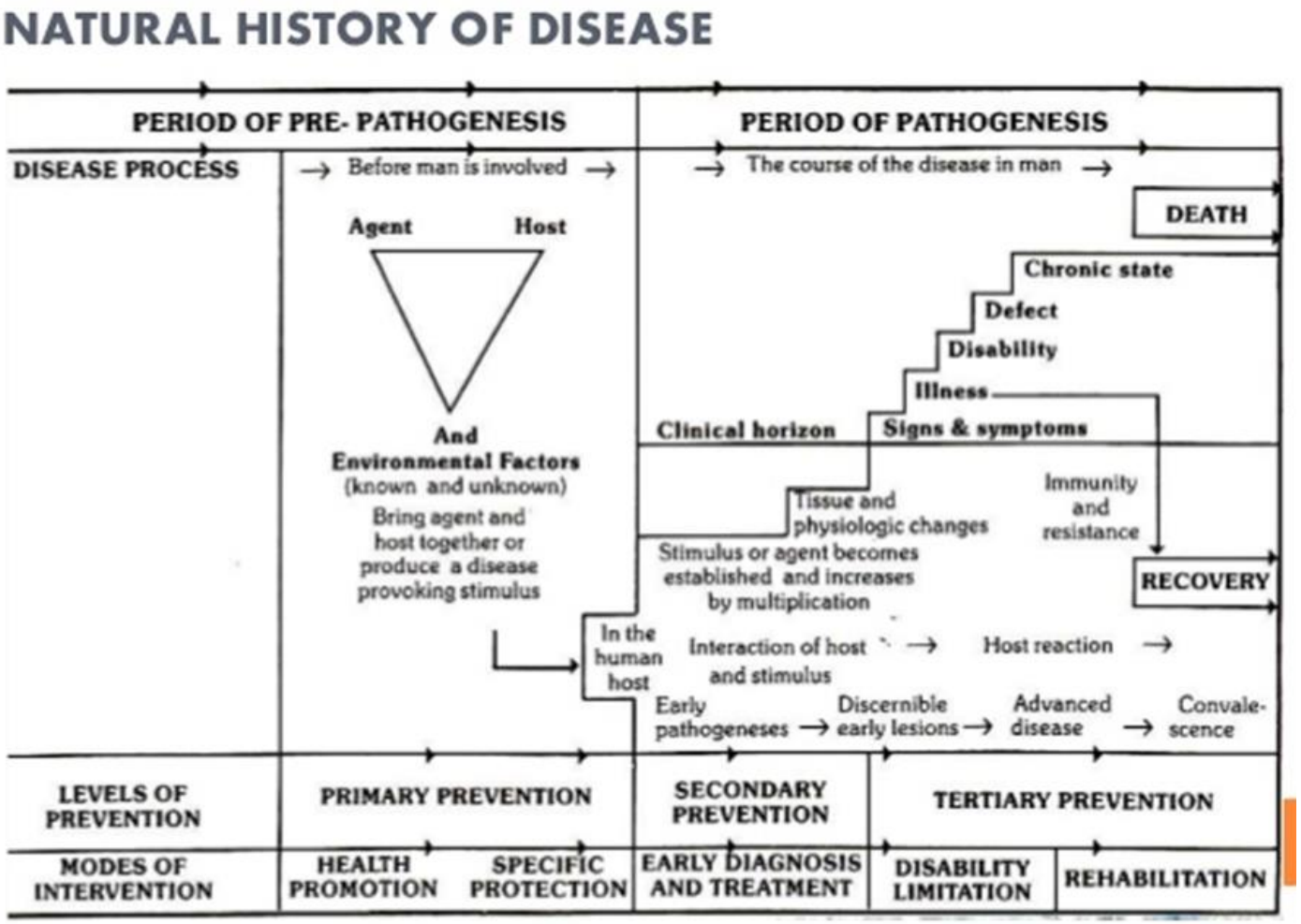
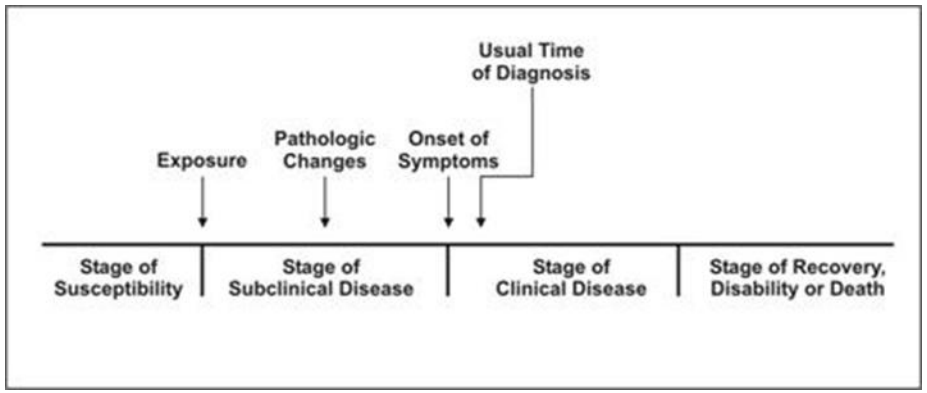
Natural history of disease



- 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
- classifies the modes of prevention



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Clinical course of the disease

- **susceptibility** ("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**
  - **latent/asymptomatic/silent** – manifest only in increased load/demand
  - **prodromal** – usually unspecific signs of upcoming disease
    - e.g. fatigue, weakness, nausea, anorexia, pain, fever, dizziness
- **acute** illness (limited number of days, can be 1 day to 1 month)
  - severe but self-limiting
- **chronic** illness (longer than 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, persistent injury)
  - chronic from the very beginning
    - e.g. due to pathogen making itself inaccessible, or targeting the very means od body defense, auto-aggressive

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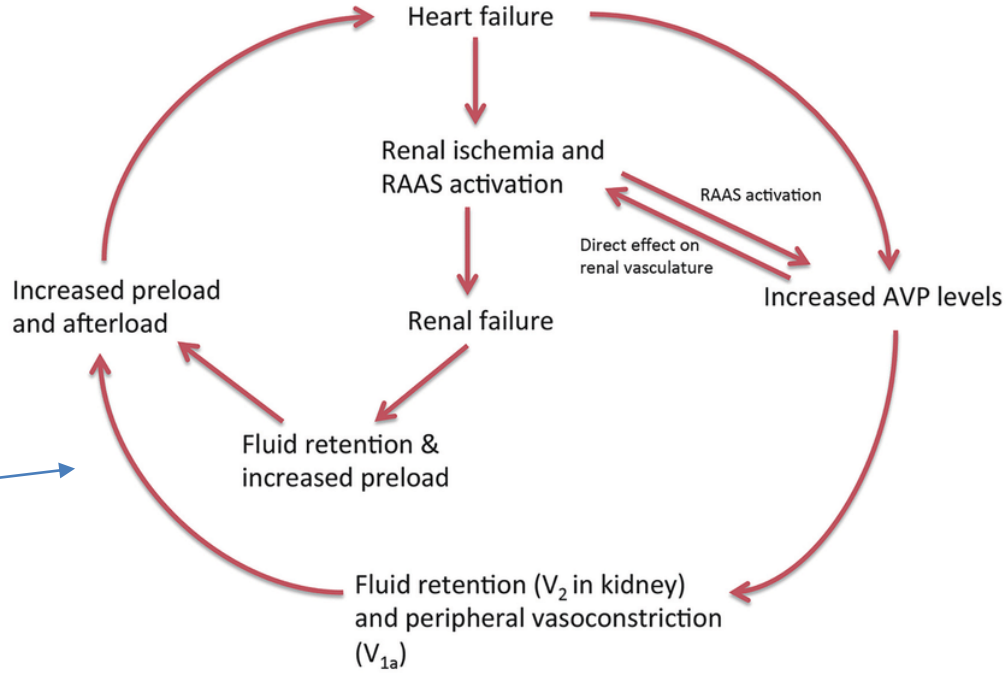
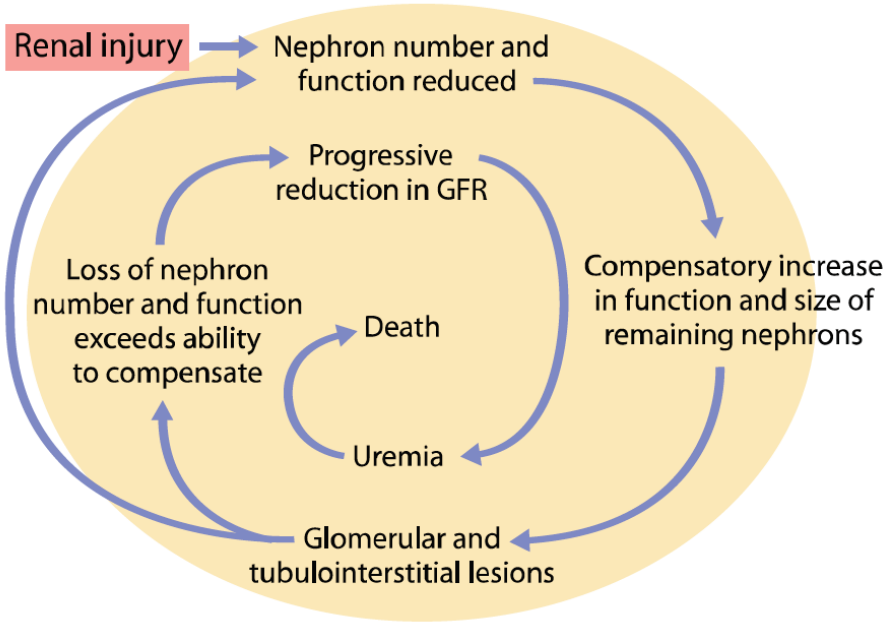
Chronic disease - intensity

- Exacerbation = aggravation of symptoms, signs and severity of disease
- Remission = lessening of severity or disappearance of a clinical disease induced by treatment
  - however with the risk of reoccurrence = relaps
  - 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

Vicious cycle

- A situation in which the apparent solution of one problem in a chain of circumstances creates a new problem and increases the difficulty of solving the original problem
- Many examples in PP





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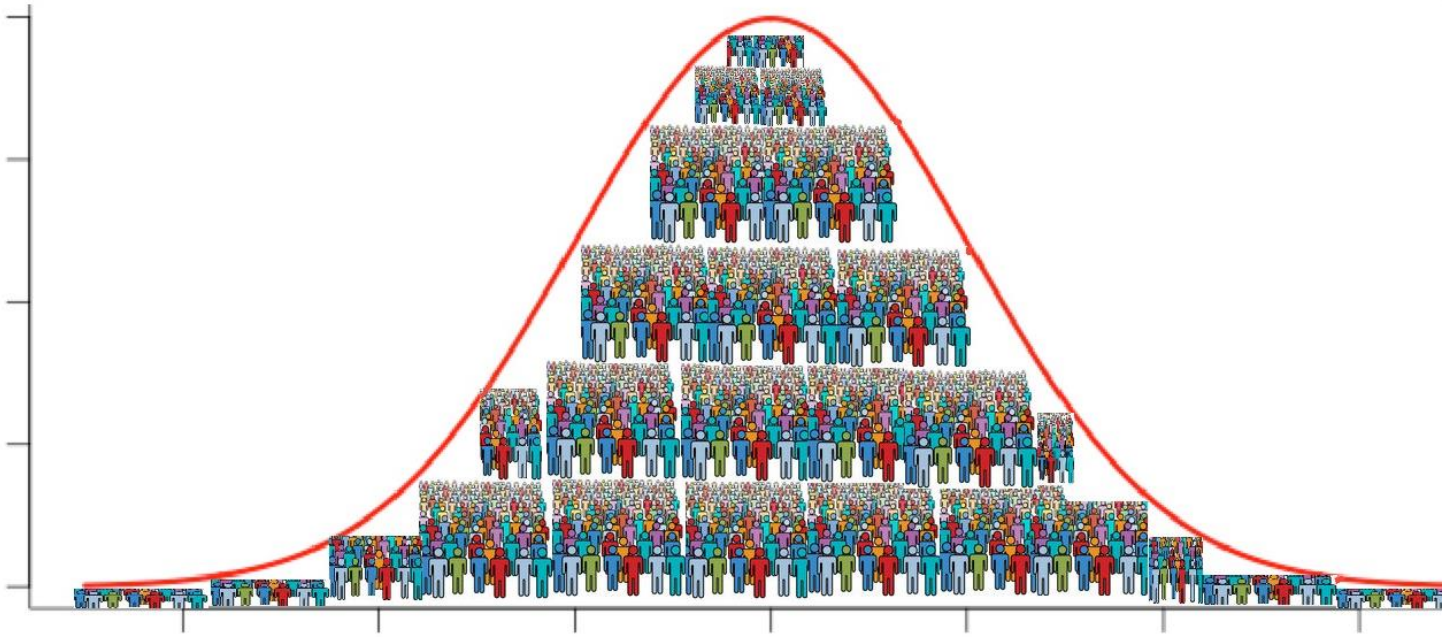

Problem with normality in medicine

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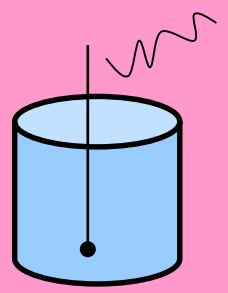
Inter-individual variability makes definition of normality (and therefore distinction between health and disease) problematic

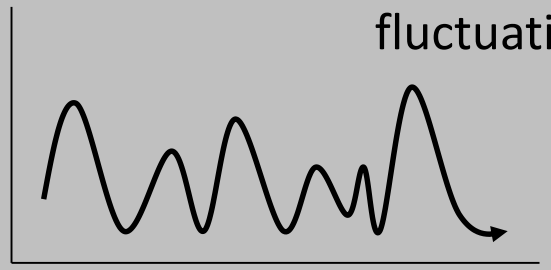
repeated measurements of temperature



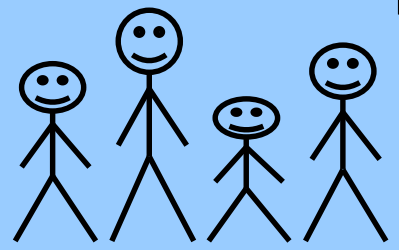
18.2°C
18.5°C
19.1°C
18.7°C

diversity in biological populations
inter-population or ethnical differences
= BIODIVERZITY

temporal changes/ fluctuations



variability of height in population



180 cm
175 cm
165 cm
157 cm

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Interindividual variability

- physiological interindividual variability of phenotypes/traits is a **consequence of genetic variability and variable exposure to external factor**s
  - higher the number of independent factors affecting the given trait the more likely “normal” the population distribution is
  - if the effect of one factor dominates over the others or there are significant interactions the distribution becomes asymmetrical
- interindividual variability of a given trait is present in the whole population incl. healthy as well as diseases subjects!
  - both all healthy and all ill people are not the same
  - disease as a “continuous function of the trait”
- etiology of diseases (see earlier)
  - “monofactorial” incl. monogenic
    - even here the subjects affected by the same disease are not the same
      - allelic heterogeneity – e.g. familiar hypercholesterolemia
      - mosaicism vs. classical Down syndrome
  - complex (“multifactorial” incl. polygenic diseases)
    - classical example of interindividual variability and „disease as a continuation of the continuous trait“ model

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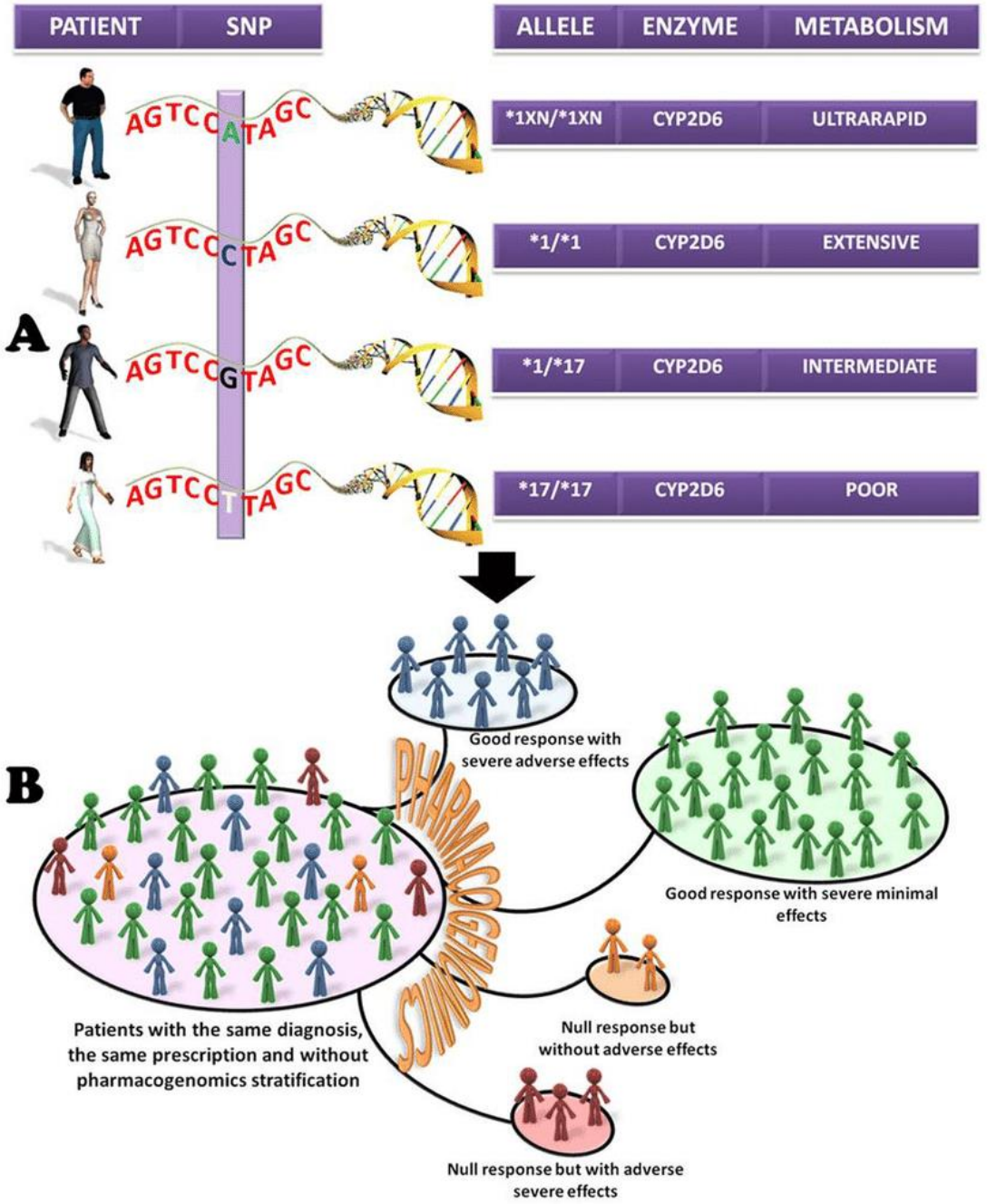
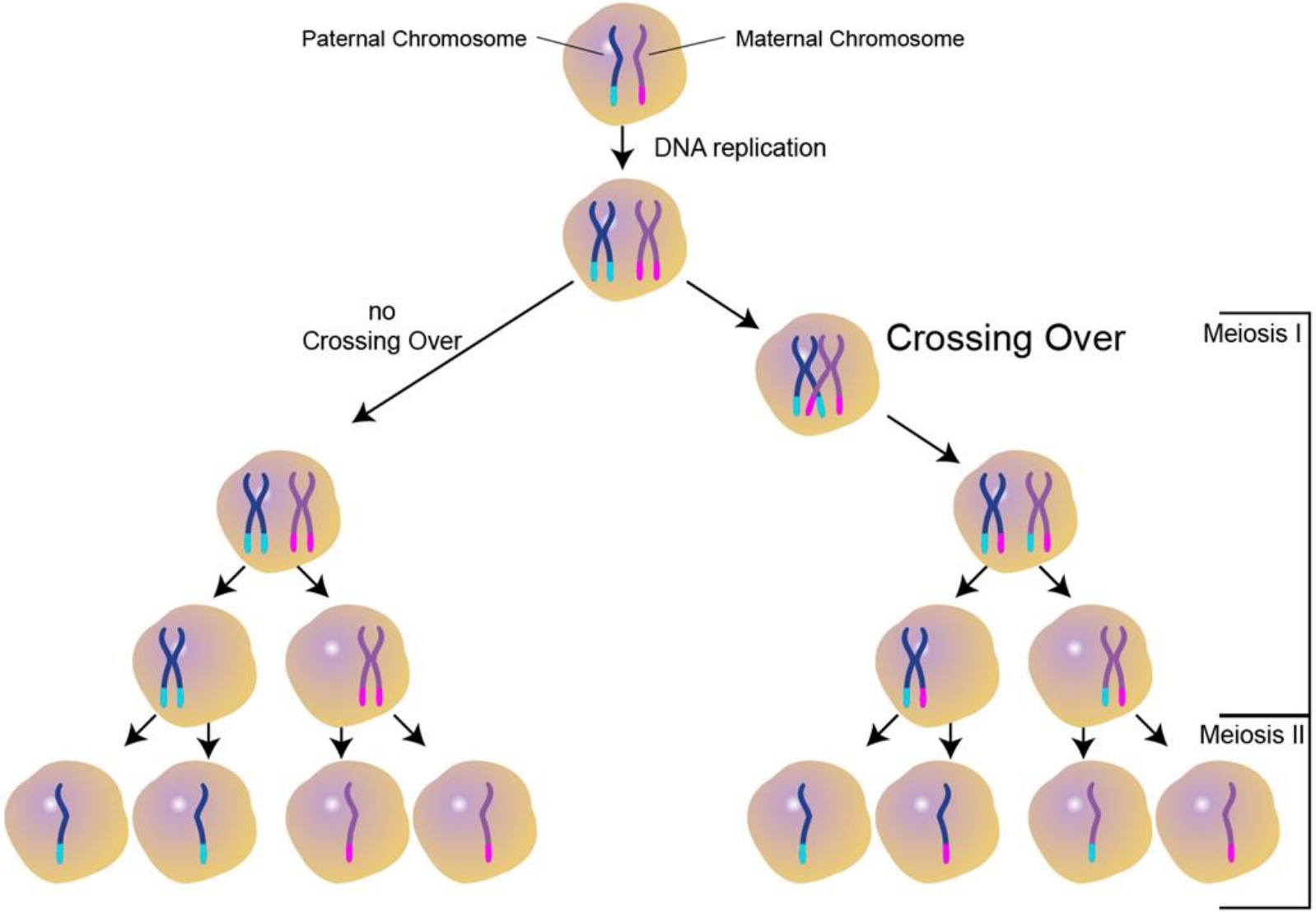
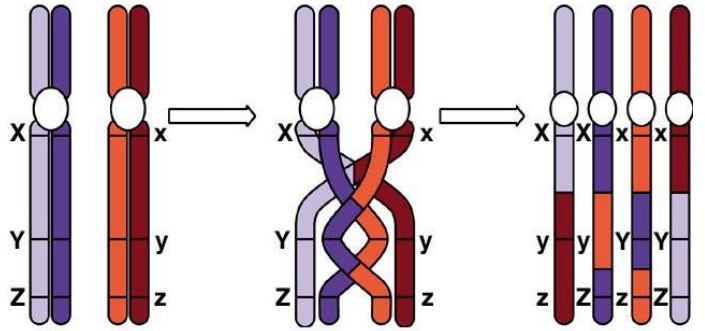
Genetic variability

- one particular **gene/locus** is typically present in several **variants/alleles in population** which can be variably frequent
  - genetic variability is a result of several processes
    - 1) sexual reproduction
      - inbreeding as risk factor for monogenic diseases
    - 2) independent meiotic segregation
      - 23 chromosome pairs → 2^{23} combinations = 8,388,608 different gametes
    - 3) meiotic recombination (crossing-over)
      - there is a >> combinations than 8 millions
    - 4) de novo mutations
      - replication errors
        - » proof-reading ability of DNA polymerase and mismatch DNA repair are not 100% error free)
      - exposure to mutagens (more typical for somatic cells, but germinal cells exposed as well)
    - 5) genetic drift
    - 6) natural selection
      - cave eugenics!
- the terminology genetic mutation vs. polymorphism is based on population allele frequency
  - genetic polymorphism = existence of several (at least 2) alleles for given gene, in which less one common has a frequency at least 1%
  - mutation = population frequency <1%
- types
  - genomic
    - alteration of the number of chromosomes or of the whole sets (aneuploidy, polyploidy)
  - chromosomal aberrations
    - structural anomaly of individual chromosomes (duplication, deletion, insertion, inversion, translocation)
  - genetic (mutations or polymorphisms)
    - shorter changes (1 – thousand base pairs)
    - SNPs – single nucleotide polymorphisms



Meiotic recombination (crossing-over)





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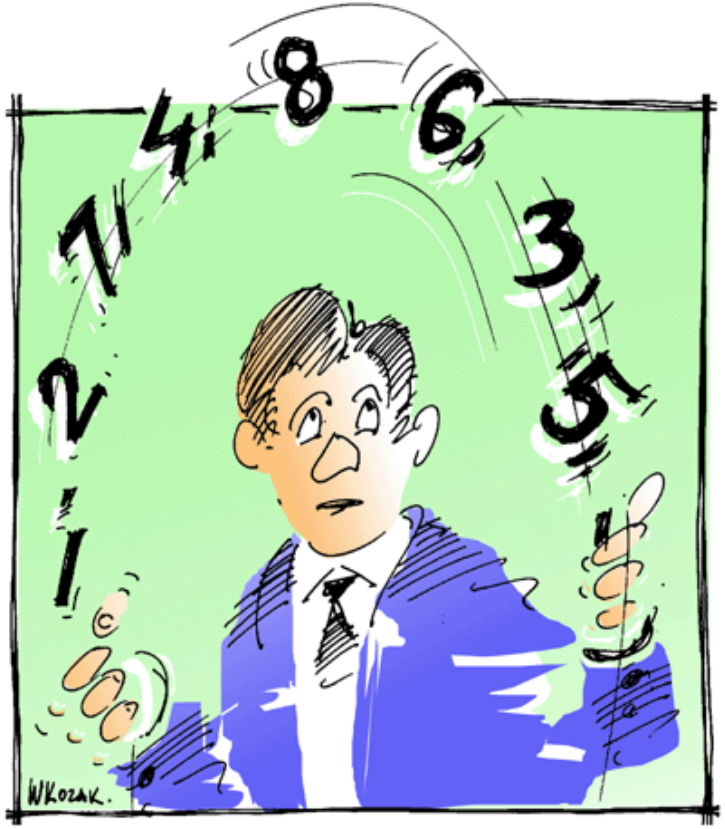
Statistical approach to defining normality / health

(1) simple lie

(2) treacherous lie

(3) statistics



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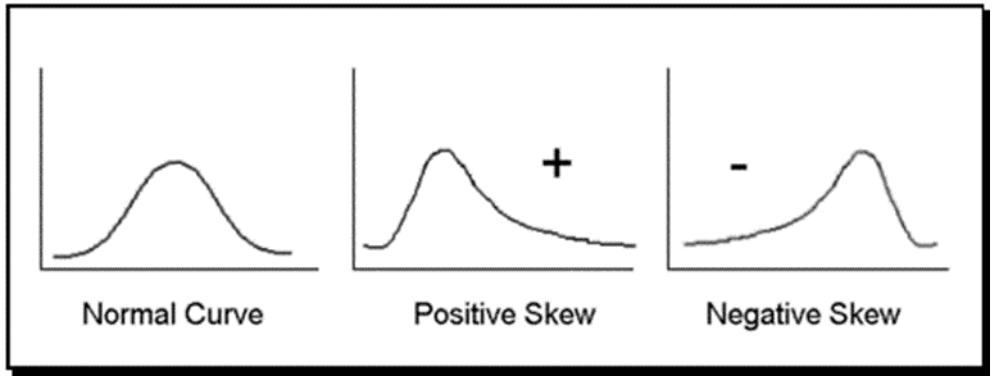
Diagnosis of disease – problem with “normality”

- parametrs/traits used as diagnostic parameters might be
  - 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
- alternative vs. continuous model of disease
- practical approach = reference intervals
  - mean ± 2 SD (for normally distributed parameters)
  - 95% of values in a given population



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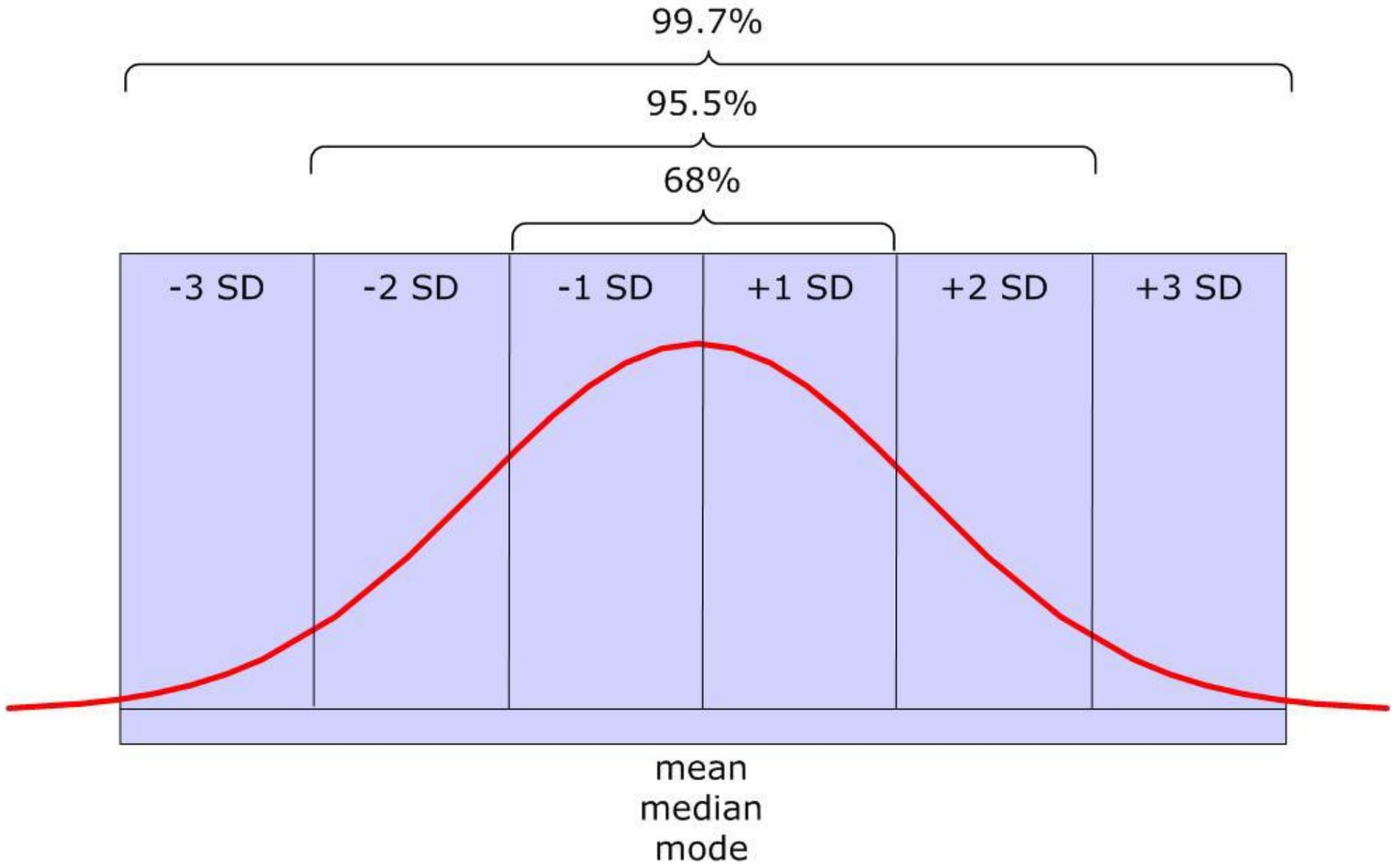
Normal distribution is rare in biology/medicine



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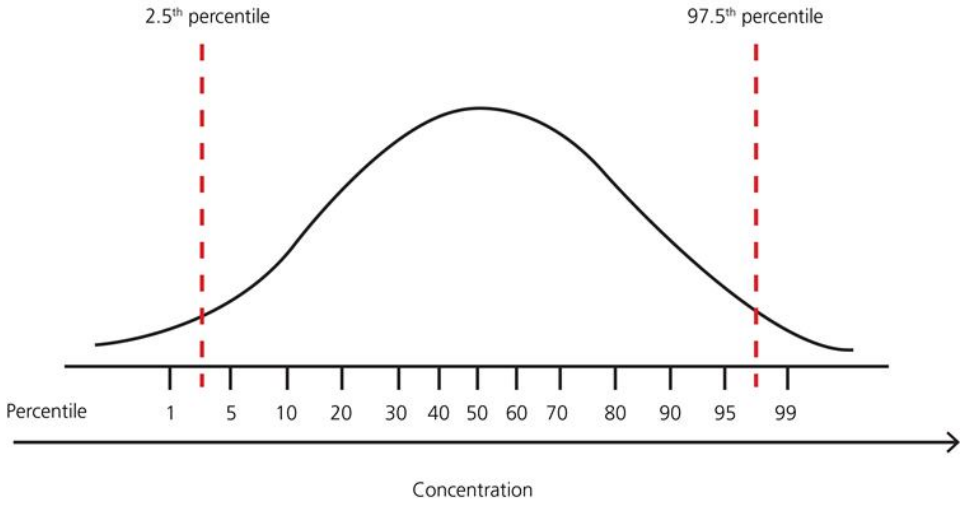
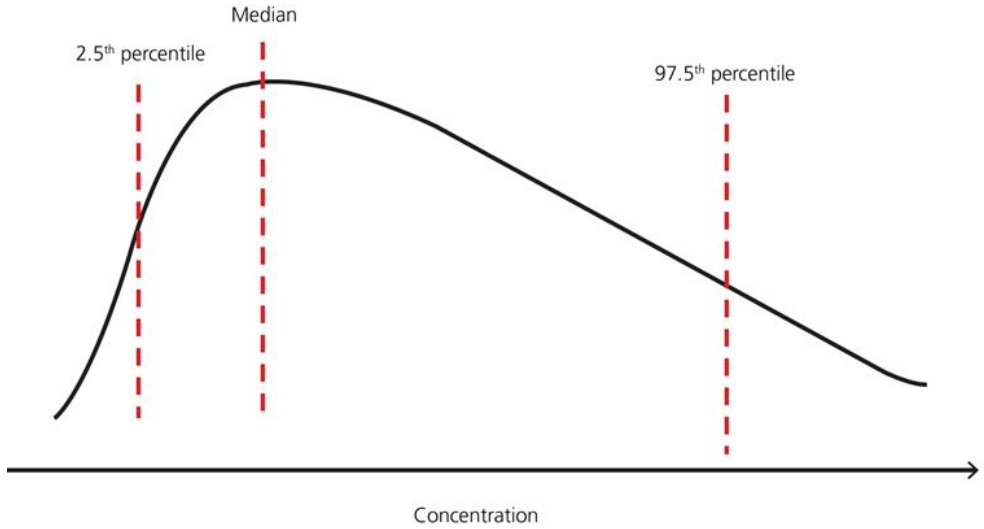
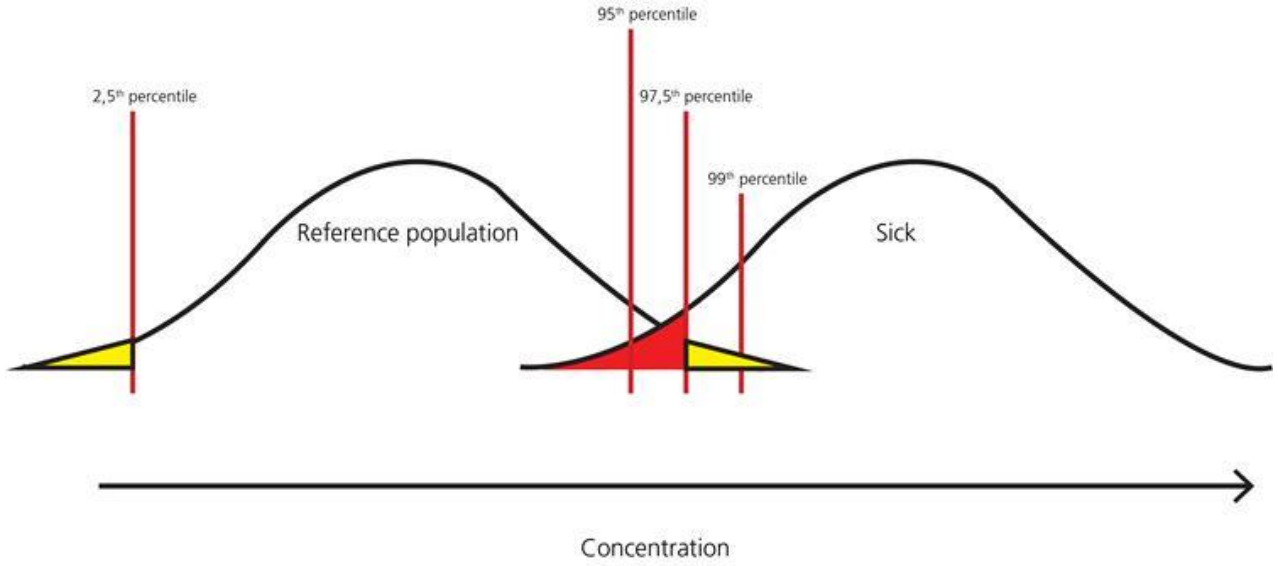
Reference interval („normal range“) - implications of eliminating extreme results from reference intervals







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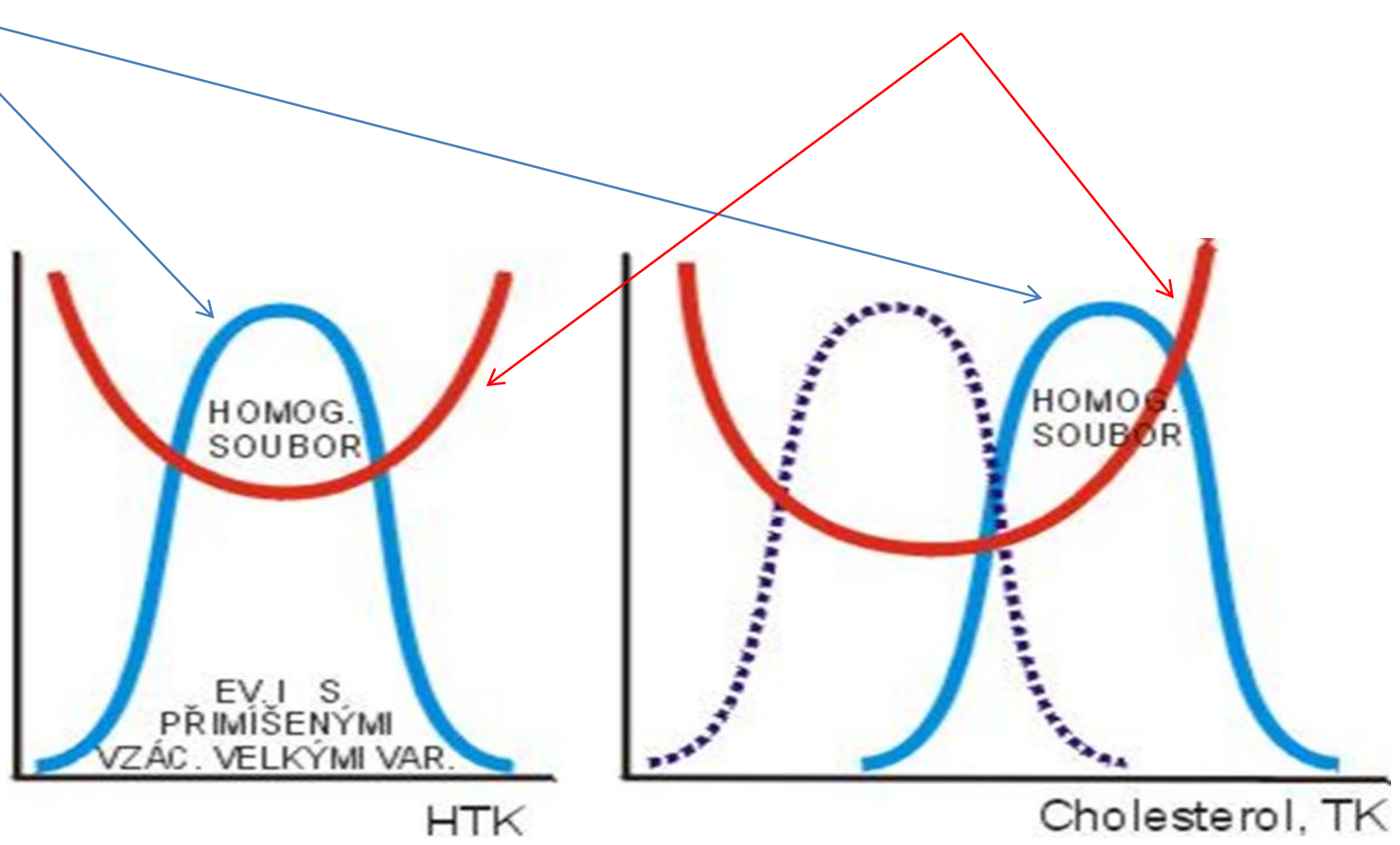
Distribution vs. selection (mortality)



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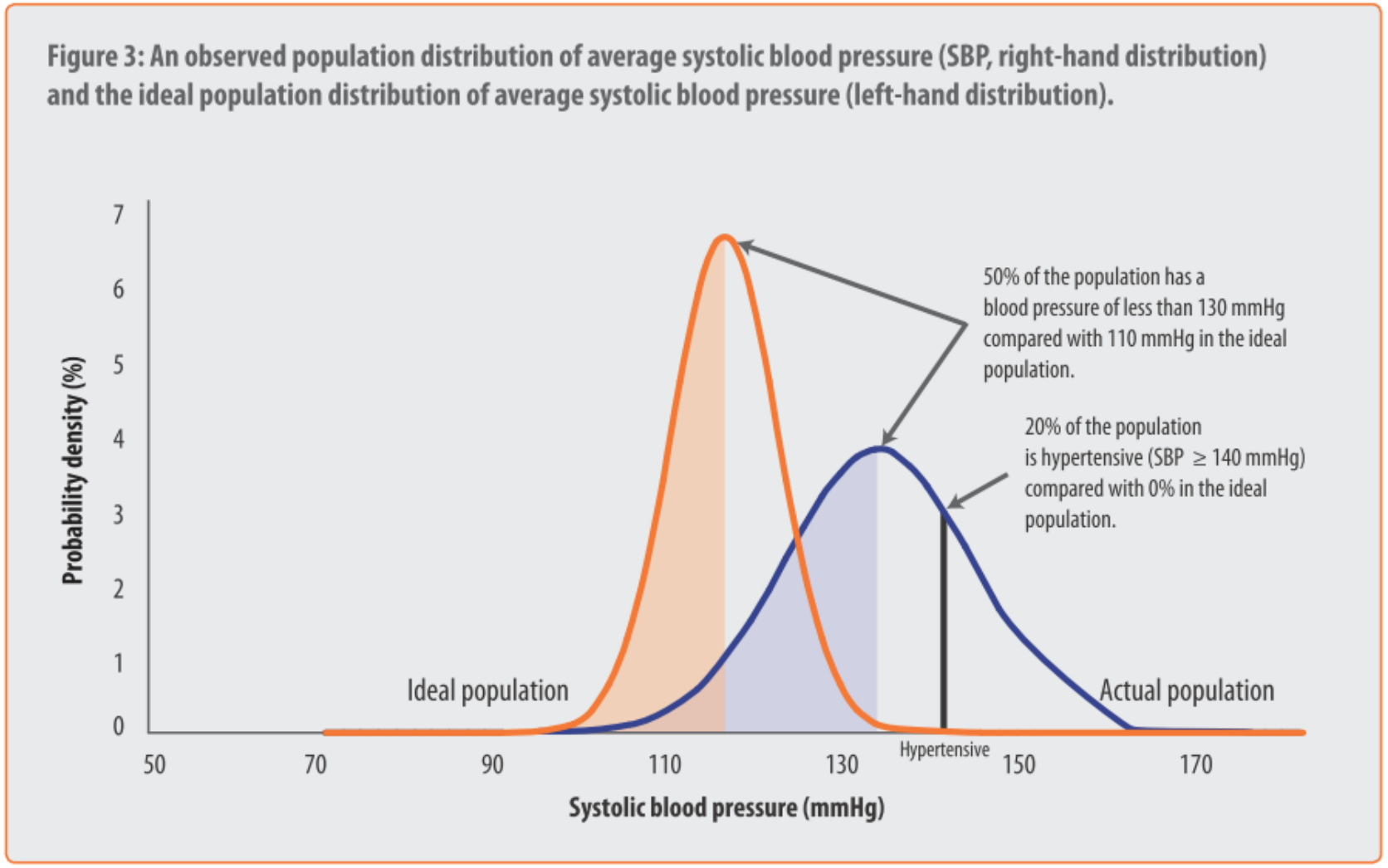
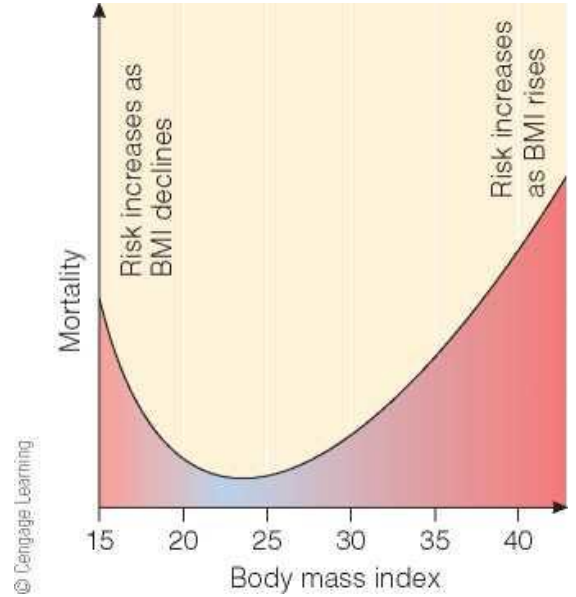
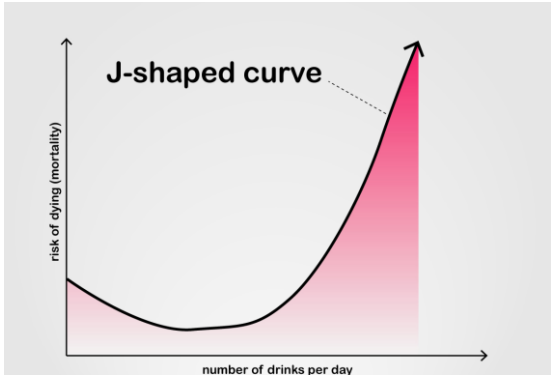
Reference range (or upper or lower cut-offs) can be further modified by mortality/morbidity data







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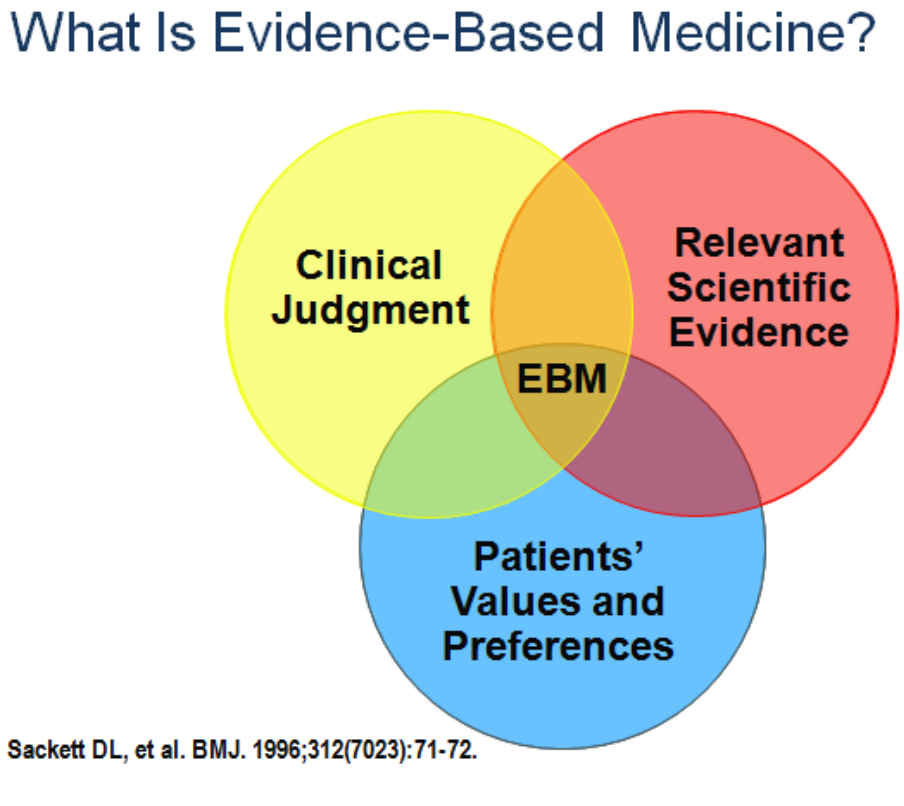
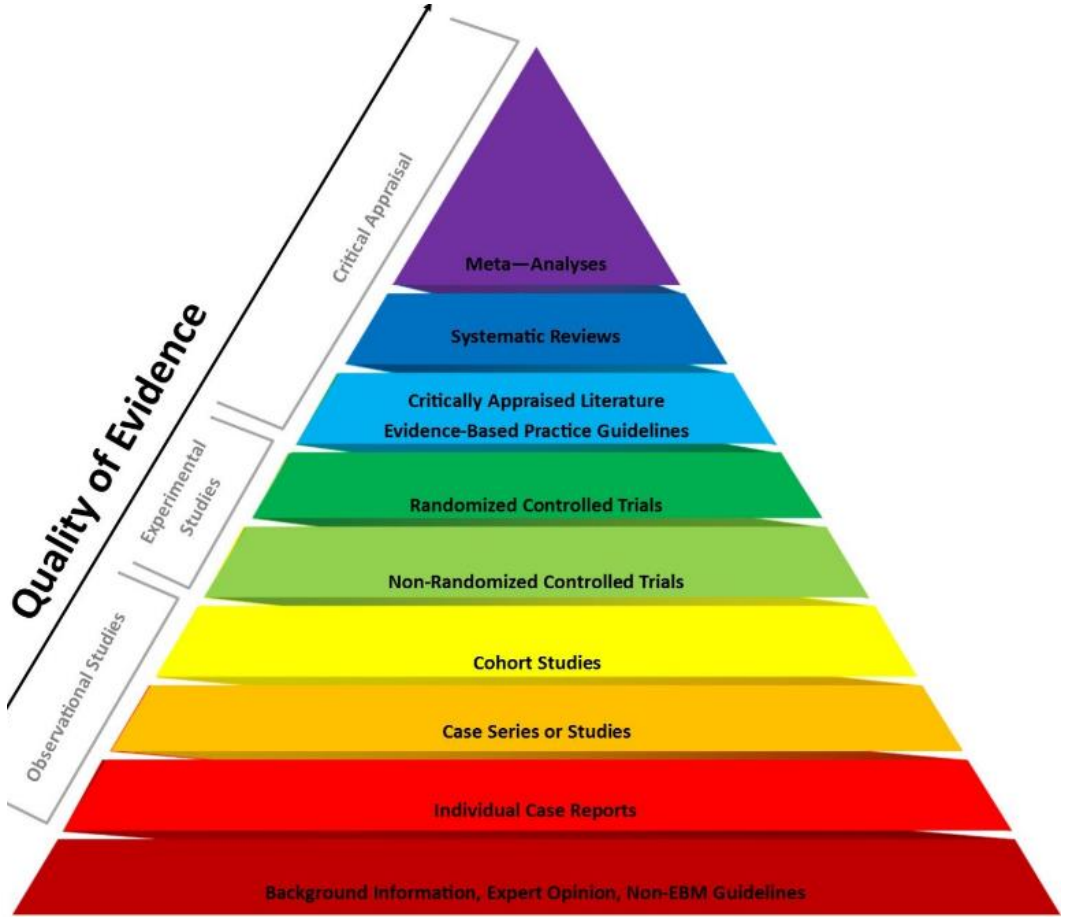
PP as part of the evidence-based medicine paradigm





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Summary - why is pathophysiology important for medical students and physicians

- It helps them to find answers to important questions related to disease processes:
  - What is the **cause/causes** of the disease, and why the disease is developing
  - What are the **mechanisms** responsible for disease onset, progression, and recovery
  - What are the mechanisms responsible for development of **symptoms and signs** of disease
- If doctors are able to understand the causes and mechanisms of the disease, then they are able to find the way how to influence them rationally

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