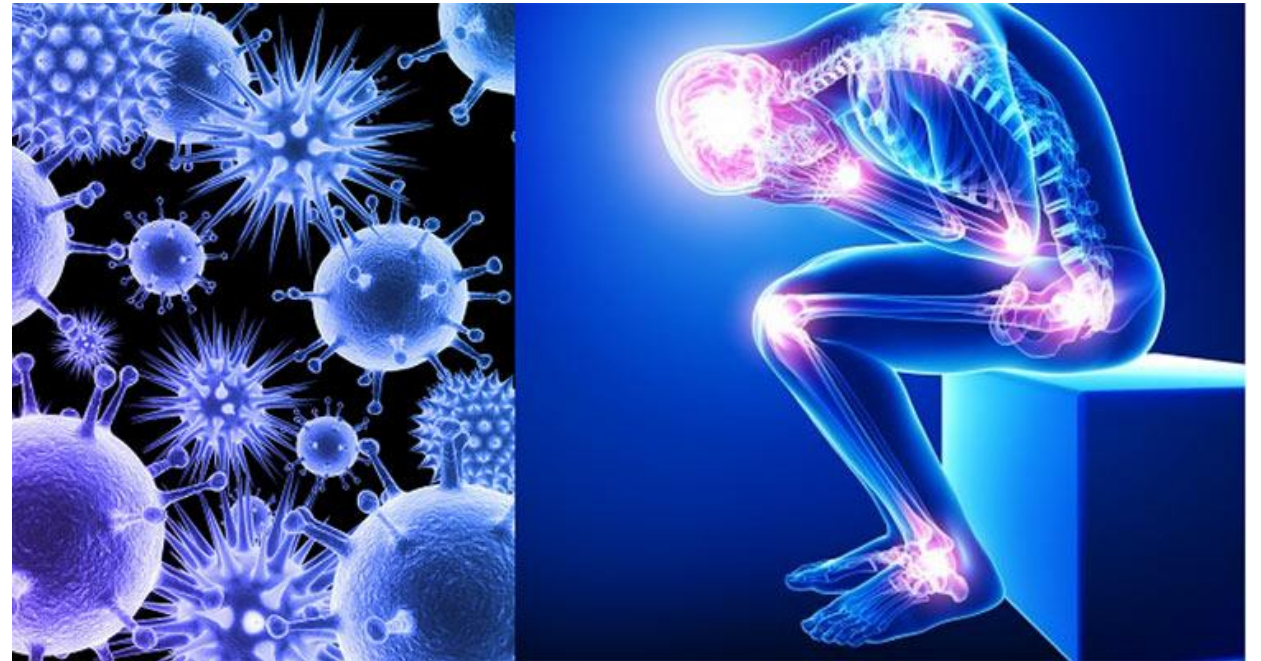


Introduction to Pathophysiology as an integrating medical discipline

- Terms and concepts
- Definition of health vs. disease/illness
- Terminology and concepts
 - in relation to aetiology and pathogenesis of disease
- Problem how to define normality in medicine



Distinction between allied disciplines

- Body has a structure and function and large capacity to maintain a **balance/homeostasis**
 - the capacity to maintain the balance gets worse as we age, therefore aging is a strong risk factor of disease
- Pathos = feeling/suffering, -ology = study of
 - **pathology** is a study of disease (structural aspects)
 - **pathology** = describes what anatomical changes disease produces
- Physis = nature/origin
 - **physiology** is a study of function
 - **physiology** = describes how the **prototypical/textbook healthy body** works
- **Pathophysiology (PP) is a study of dysfunction**
 - **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, ...
 - léčbu, ...
- Epidemiology = focuses on population/public health



Pathophysiology (PP) as a medical discipline

- PP is a 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** and, later, the disease **manifestation**)
- PP studies namely two processes
 - disease **(a)etiology** – i.e. what causes the disease to develop
 - disease **pathogenesis** – how the disease develops
- 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, ...)



How does PP 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
 - synthesize 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



PP of population = epidemiology

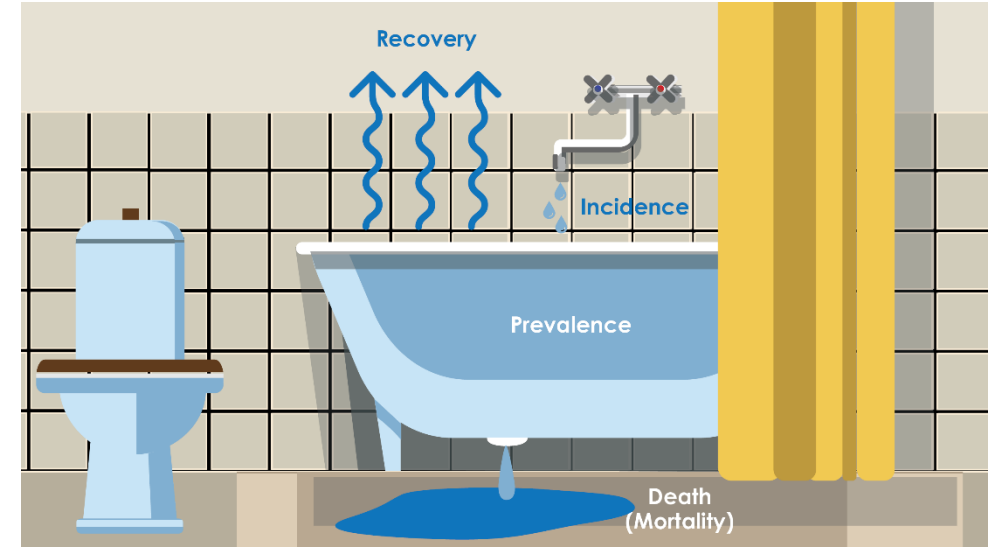
- studying diseases within populations
- **incidence vs. prevalence**
 - rate of occurrence (of diagnosing the disease) per unit of time (usually a year) for a given population unit (e.g. 100.000 subjects)
 - vs. percentage of population affected by given disease at the time in a population unit (e.g. 100.000 subjects)

$$\text{prevALence} = \frac{\text{ALL cases}}{\text{Population @ risk}}$$

$$\text{iNcidence} = \frac{\text{New cases}}{\text{Population @ risk}}$$

- **disease spread**

- endemic (regular to a small area) vs.
- epidemic (larger area, widespread) vs.
- pandemic (multiple occurrence, world-wide)



ENDEMIC



EPIDEMIC



PANDEMIC

Pathophysiology (PP) as a medical discipline

- What we are going to study?

- **General PP**

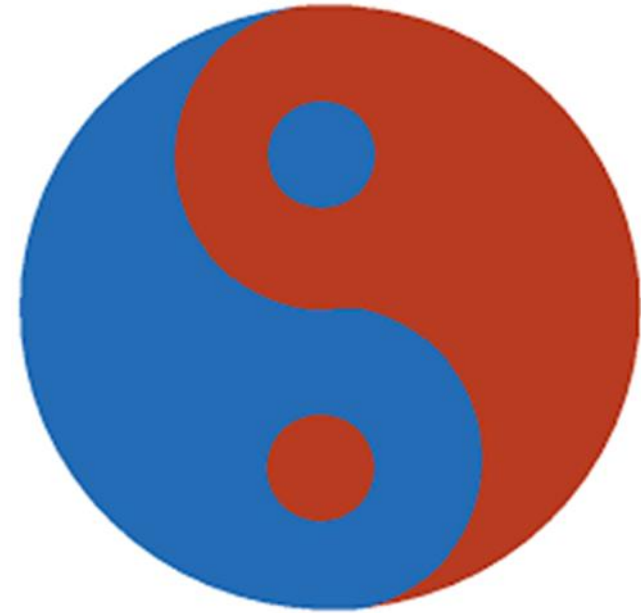
- deals with general pathologic processes and mechanisms that are involved in pathogenesis of more than one disease
 - in fact, majority of diseases are a mixture of just a few pathologic processes
 - hypoxia/ischemia, abnormal cell proliferation (too much or too little), inflammation, various metabolic 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**

HEALTH vs. DISEASE



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 **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



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**

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, pO₂/CO₂, ...) 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**

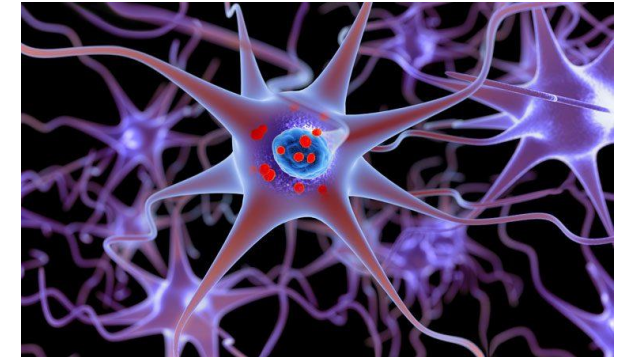
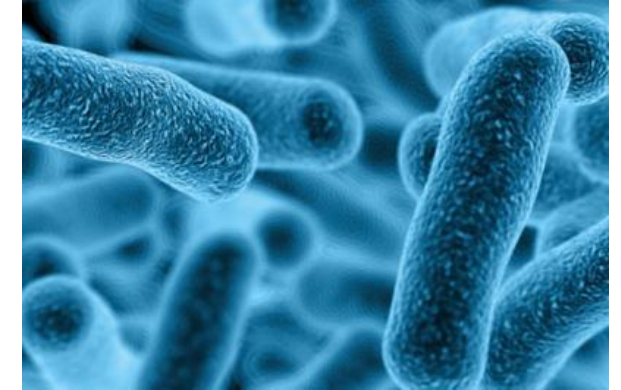
- if the person is not limited by his/her condition and **can achieve the desired goals** than he/she is healthy
 - blindness, dwarfism or autism is not a disease if the person suffering from it does not feel limited in any way

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, ...



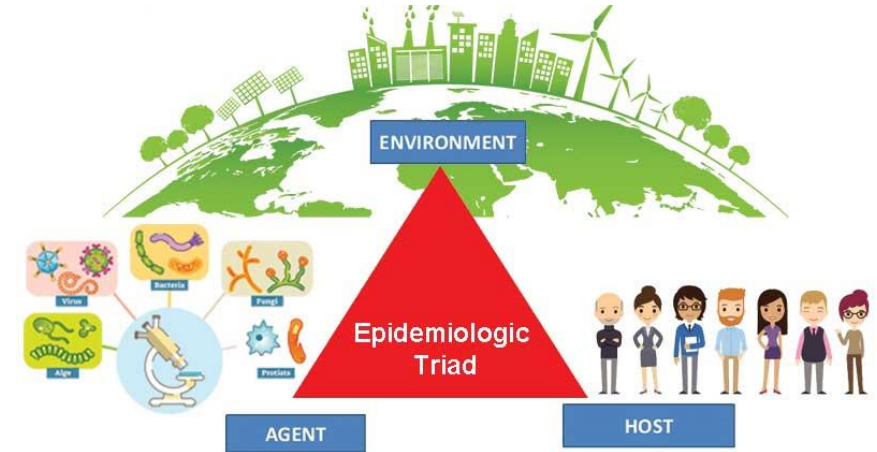
Alison Lapper (8 months) by Marc Quinn (2000). This sculpture caused controversy in UK when it was chosen as one of two pieces to occupy the vacant fourth plinth in Trafalgar Square, London.



ETIOLOGY and PATHOGENESIS OF DISEASE

Disease etiology

- endogenous = **internal factors**
 - congenital
 - genetic (monogenic as well as polygenic)
 - malformations due to prenatal exposure to viruses or toxins
 - fetal programming
 - 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
- **iatrogenic** = caused by treatment
- **nosocomial** = sick/disease acquired in health care environment
- idiopathic = no known cause



majority of diseases are multifactorial in origin and in majority of disease genetics play a certain role

Diseases from one single cause vs. multifactorial

(⇒ alternative vs. continuous model of disease)

- **Monofactorial**

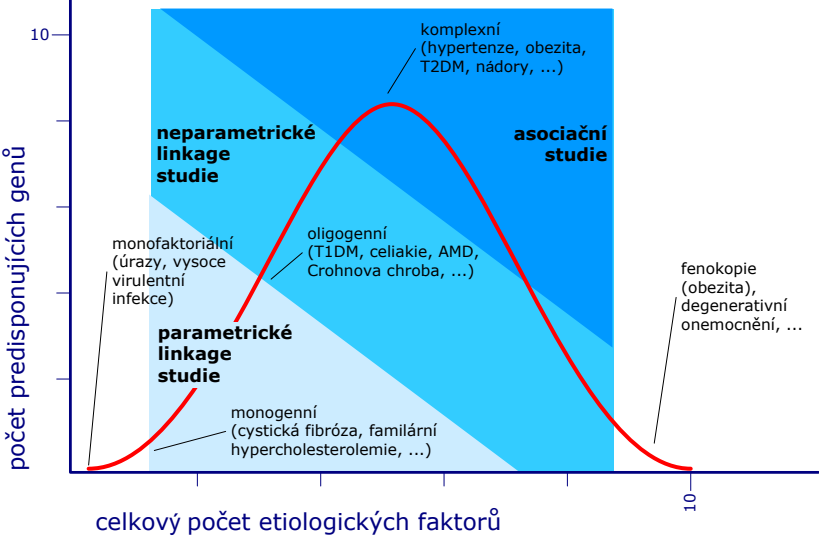
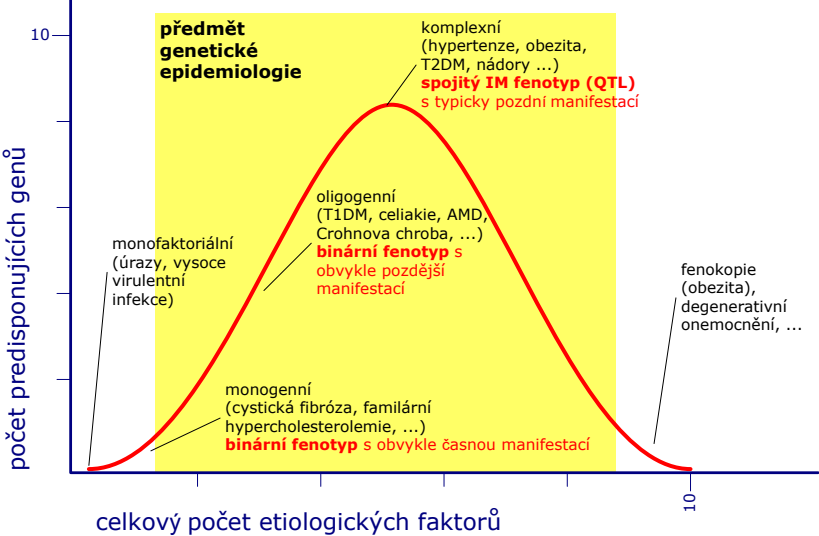
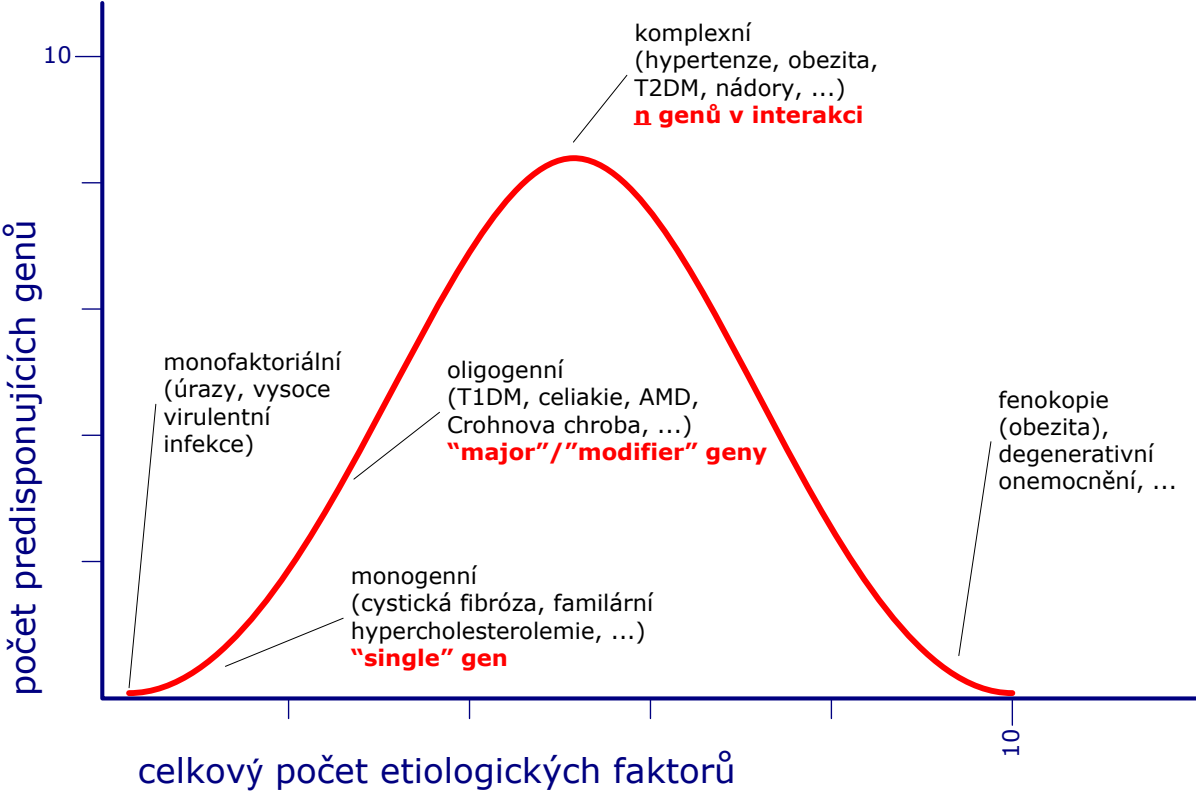
- one single cause potent enough to cause disease
- diagnosis often based on qualitative parameters
 - e.g. X-ray visible fracture, wound, malformations, ...
- easy to distinguish between health and disease
- environment and lifestyle play generally minor role
- examples
 - trauma
 - highly virulent infection
 - poisoning
 - monogenic disease
 - chromosomal abnormalities (i.e. aneuploidy)
 - trisomy - autosomal (Down)
 - trisomy of monosomy – gonosomal (i.e. Turner, Klinefelter)

- **Multifactorial (= complex)**

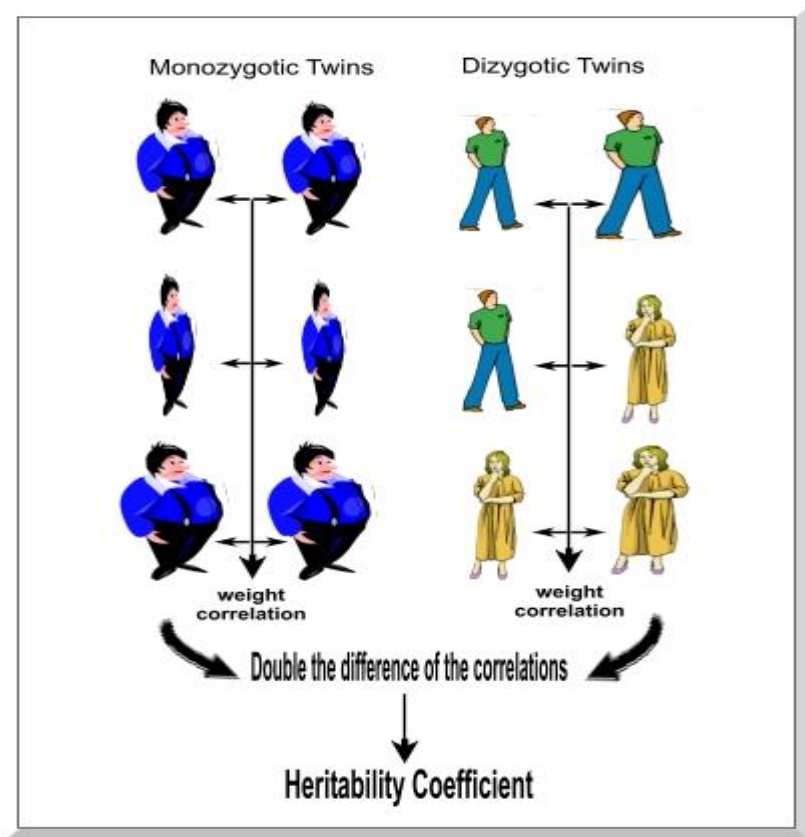
- products of concomitant exposure to internal and external factors with typically equal role of both, so called “diseases of civilization”
- diagnosis often based on quantitative parameters (disease is a continuum of health)
 - e.g. normal BP/hypertension, normal glycaemia/diabetes
- often difficult 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



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

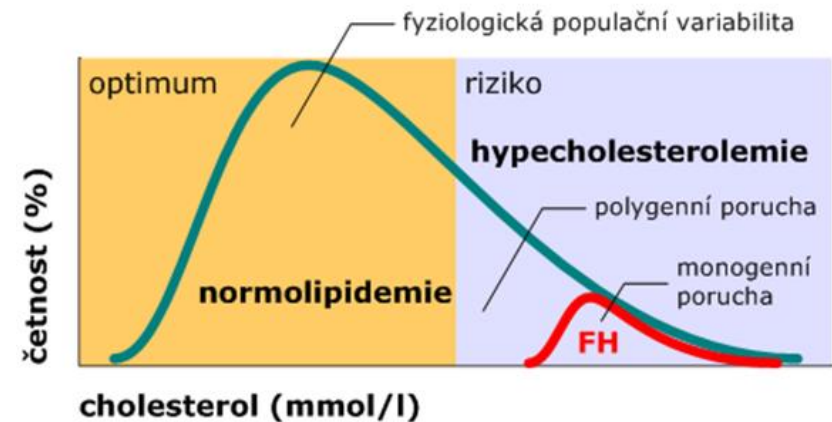
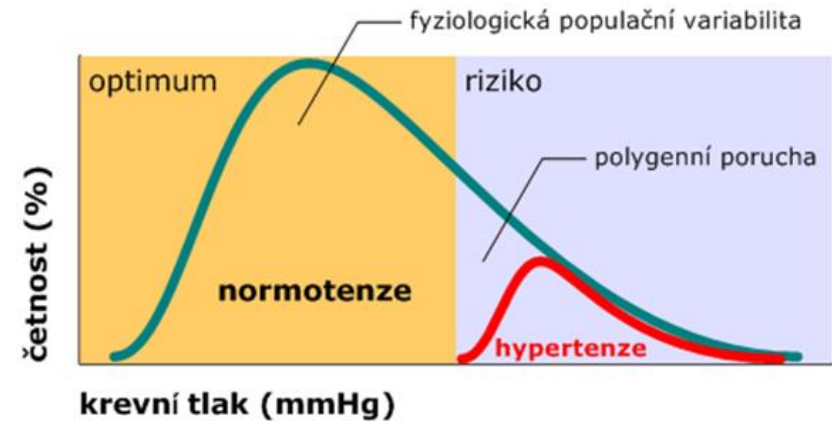
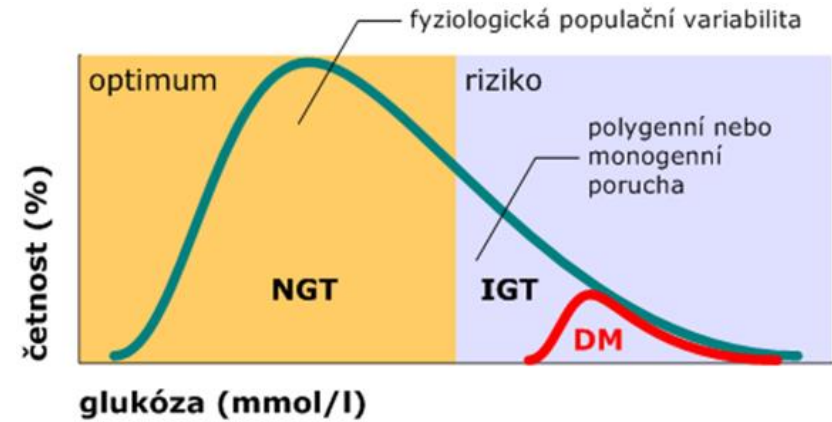


- binary phenotype (yes/no)
 - familiar aggregation
 - prevalence of affected probands in families >>> prevalence in general population
 - true for monogenic as well as complex diseases
 - segregation analysis
 - finding the mode of inheritance of given phenotype in families (i.e. recessive or dominant)
 - only for monogenic (“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)

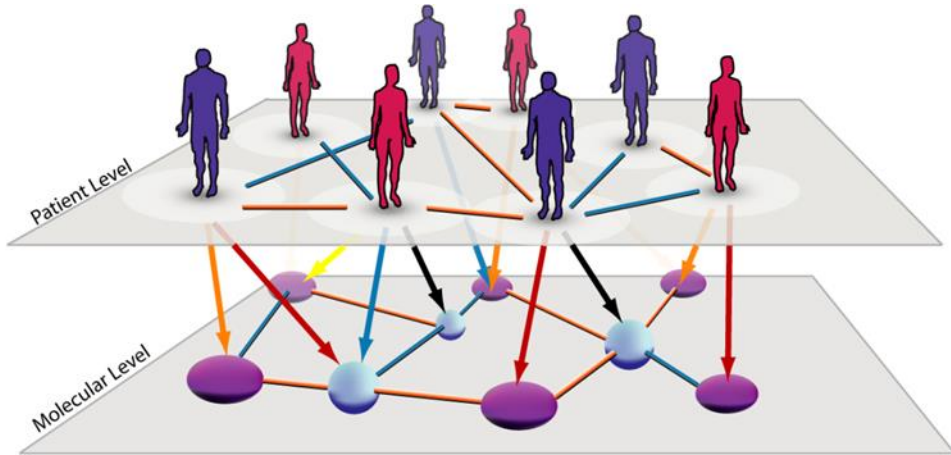
Complex diseases

typically continuous traits !!!

examples of complex diseases: essential hypertension (BP, ...), diabetes (glycaemia, insulinaemia, 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



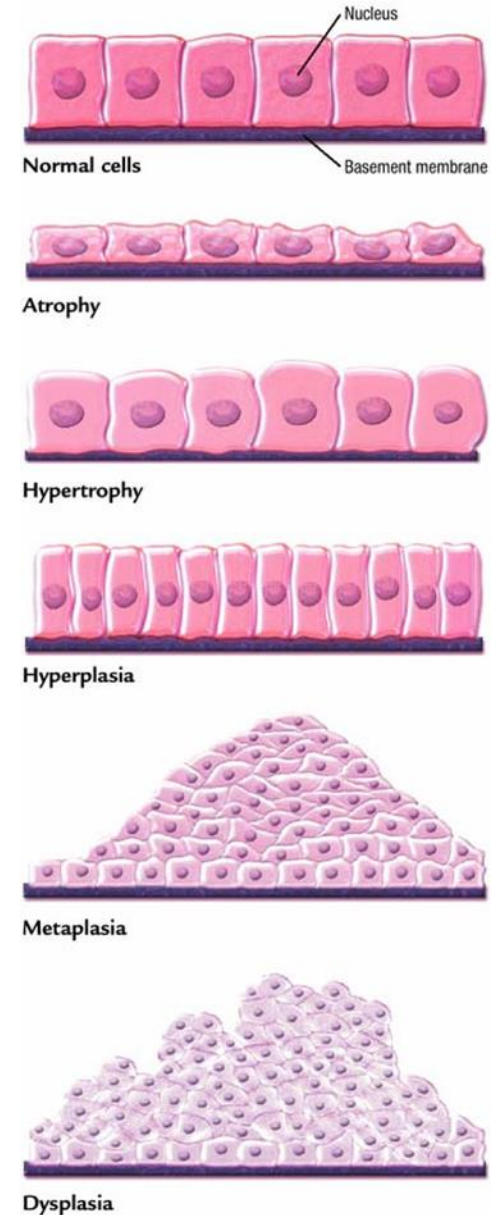
Complex diseases



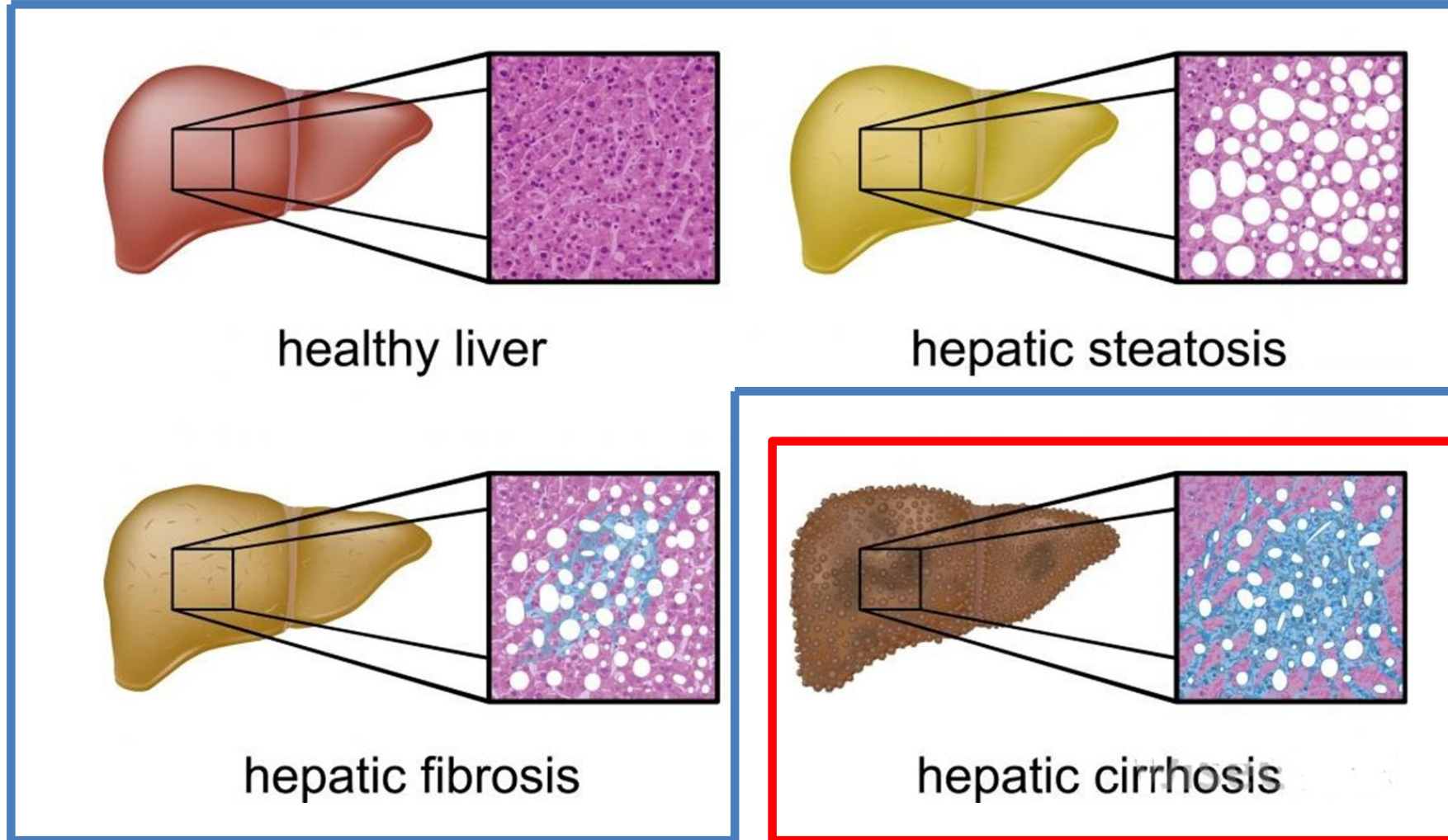
- diseases developing due to the **etiopathogenic “complex” of genetic, epigenetic and environmental factors**
 - phenotype does not follow Mendel rules (i.e. dominant or recessive mode of inheritance)
- “predisposing genes/alleles” increase probability to become affected, however, do not determine unequivocally 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

Disease pathogenesis

- Response of the body to the action of etiological factor(s)
 - **adaptation** = no change in functional abilities = no disease
 - tissue atrophy / hypertrophy
 - BUT brain atrophy in Alzheimer disease is late, however, very significant disease stage
 - lie and dissimulation could be considered protective mechanisms of a kind
 - adaptation to a new situation
 - **dysadaptation** = impairment of function = disease
 - dysplasia, metaplasia
- 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



Example – liver disease and its manifestations (initially adaptation, later dysadaptation on organ and then systemic level = a disease)

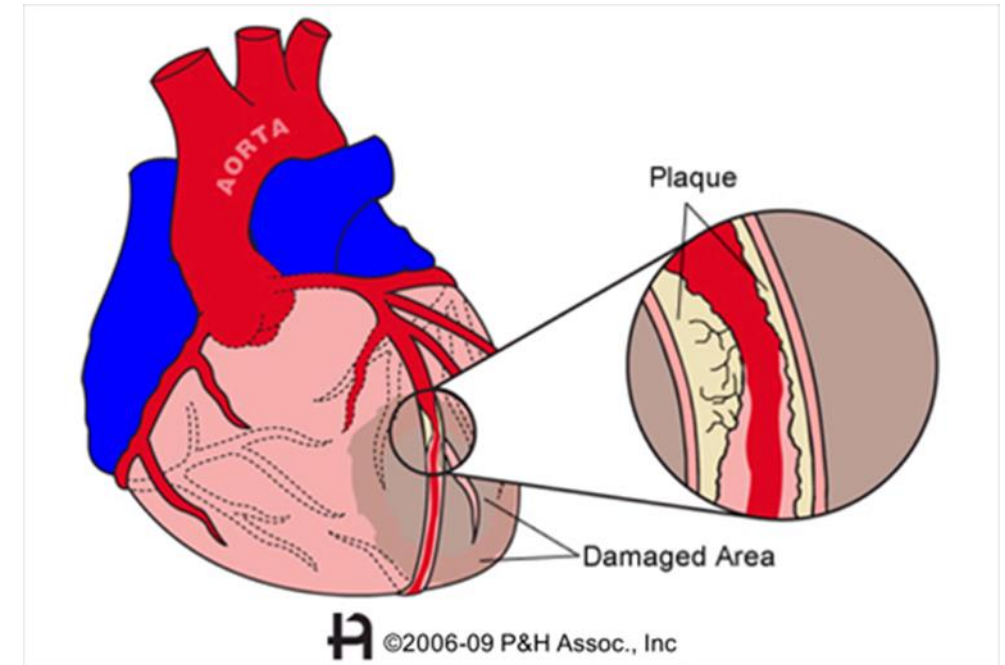


ORGAN-SPECIFIC

SYSTEMIC

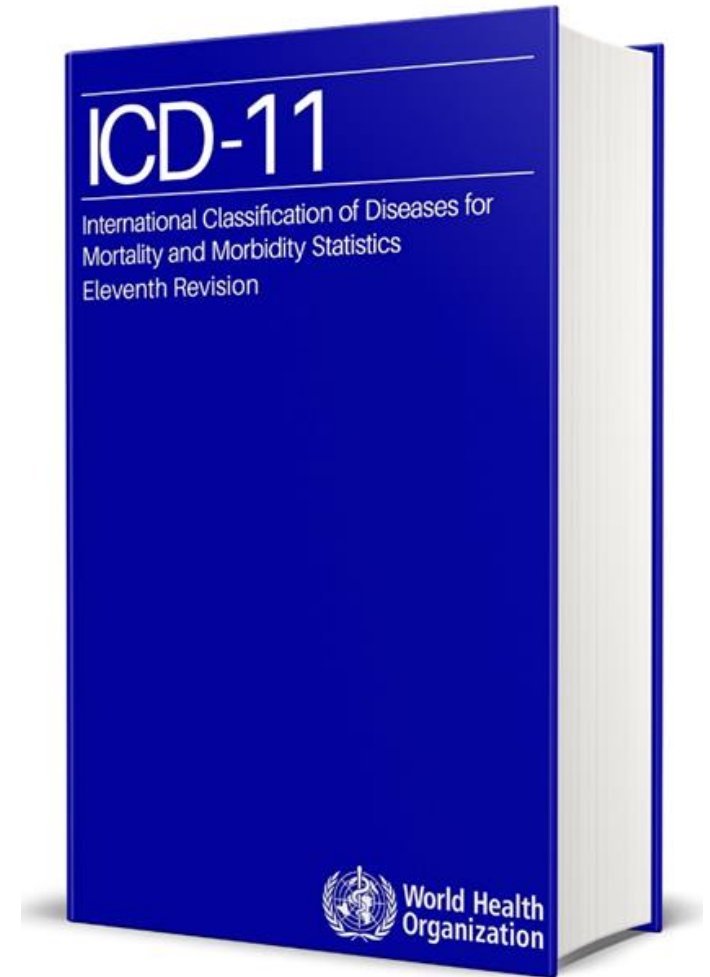
Common misconceptions

- 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

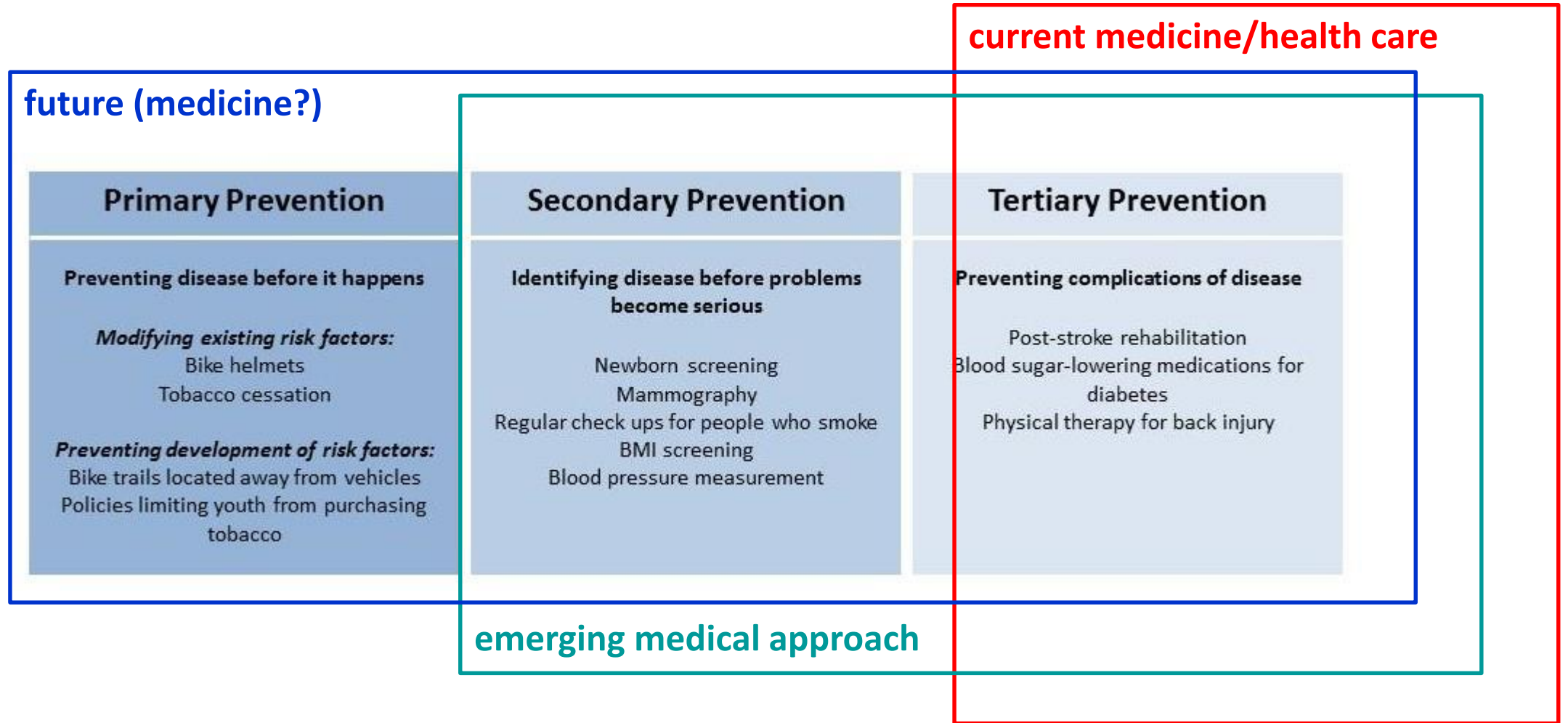


Clinical manifestation of diseases

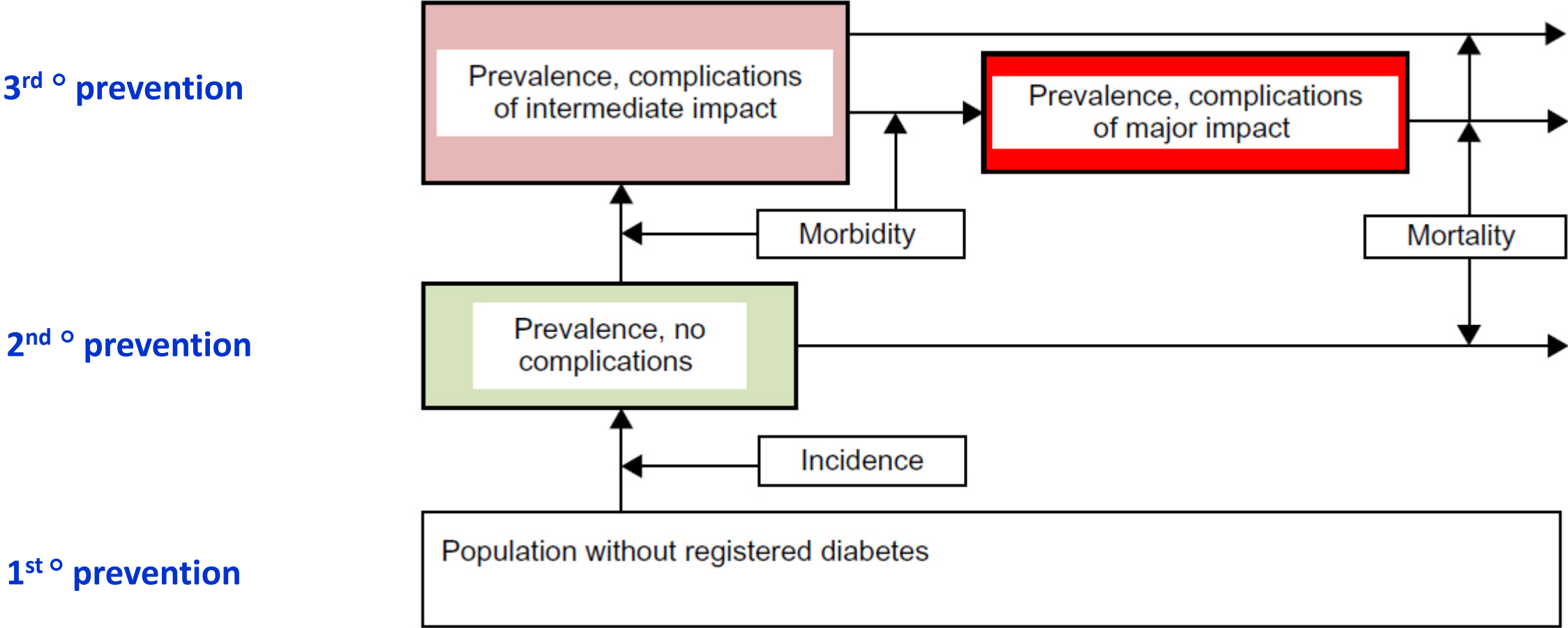
- **diagnosis** = giving a label to disease or illness
 - based on the recognition and proper interpretation of symptoms and signs at diseases manifestation
 - **prevention*** aims to recognize and interfere earlier (see the next slide)
 - **symptom** = feature recognized subjectively by the patient
 - e.g. pain, anxiety, dyspnoea, nausea, ...
 - **sign** = objective (by physical examination), measurable (by diagnostic method such as laboratory, X-ray, ultrasound, ...)
 - e.g. temperature, fracture, vomiting, swelling, hyperglycaemia, ...
- 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**



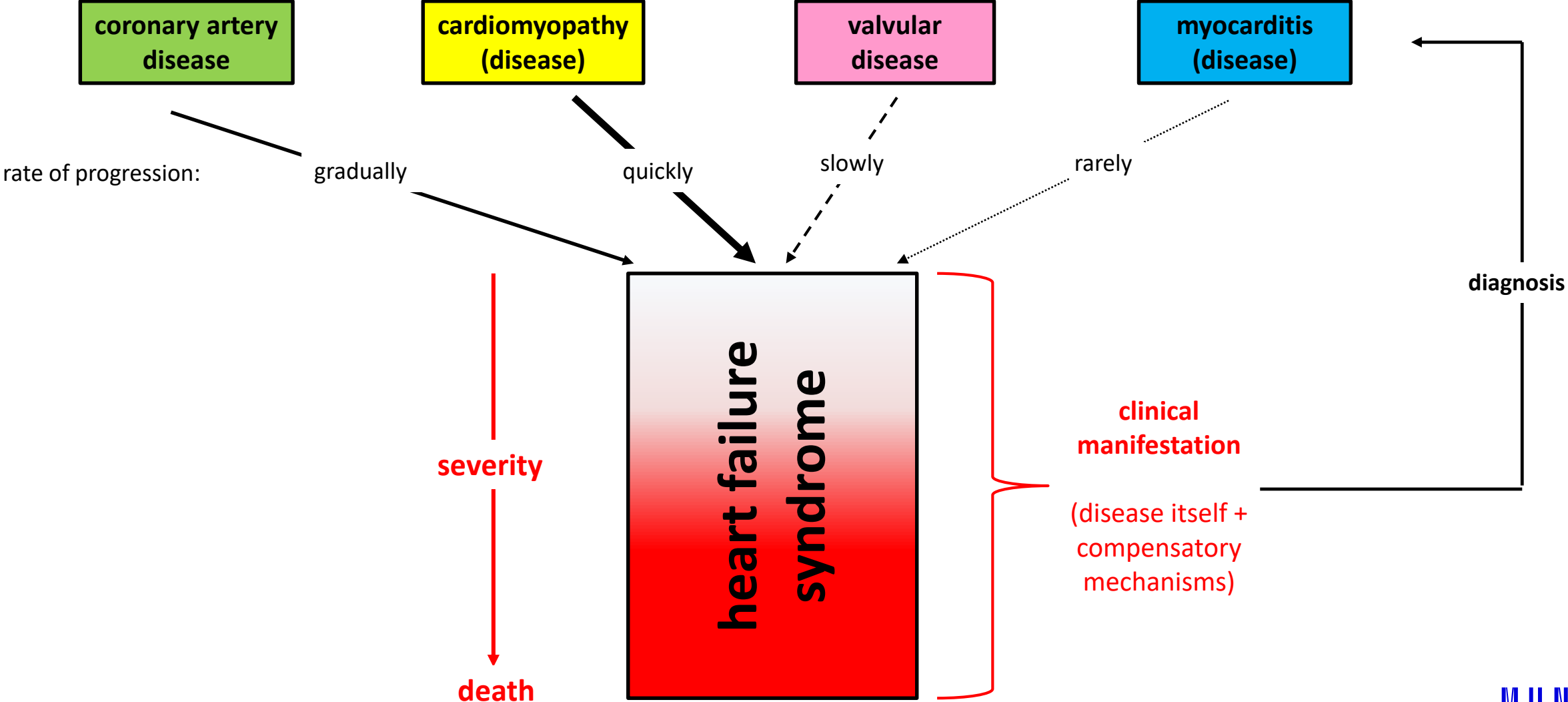
*Disease prevention



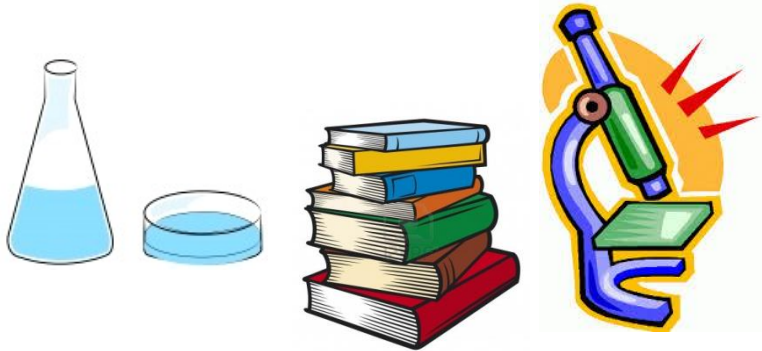
Example - diabetes



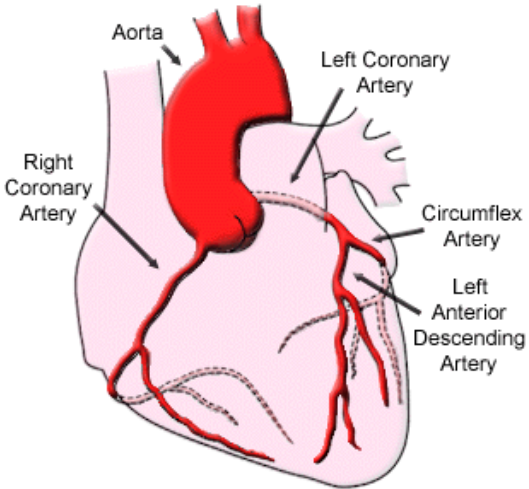
**Disease vs. syndrome



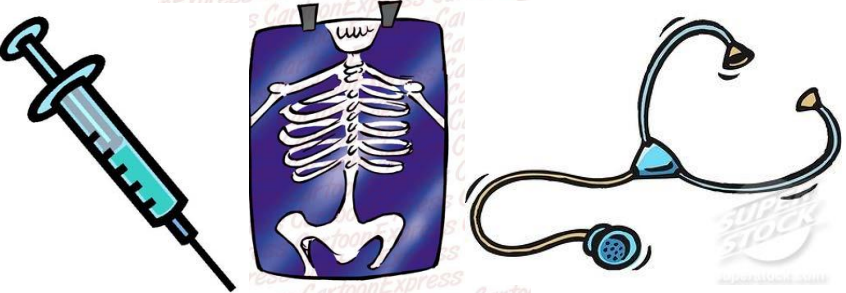
Pathophysiology vs. clinical medicine



pathophysiology is inductive

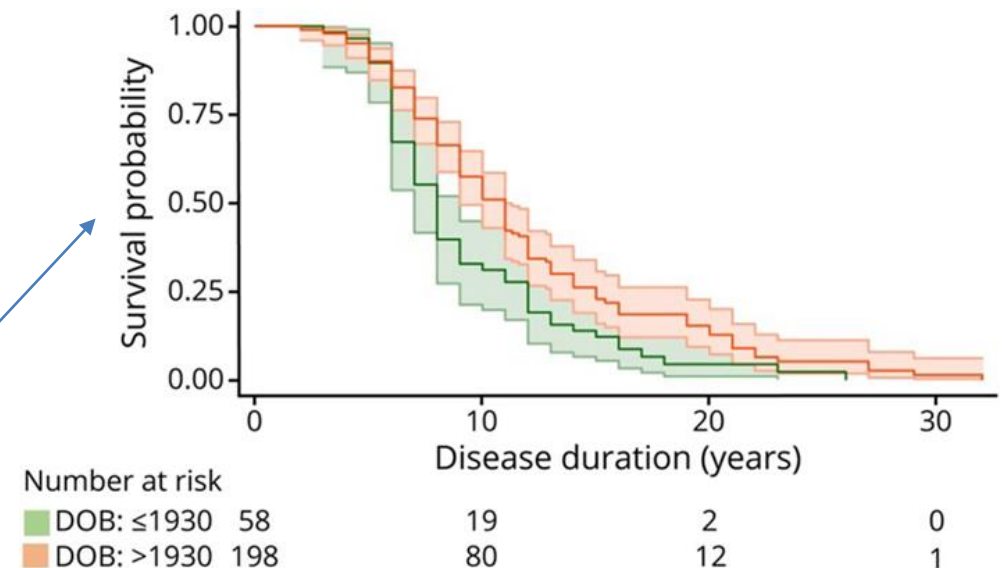
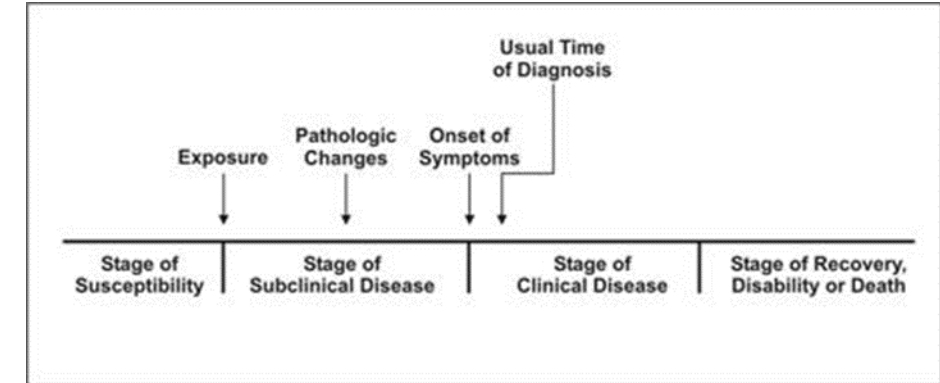


clinical medicine is deductive



Natural history of disease (clinical course)

- 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
 - also classifies the modes of prevention
- **(1) 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.
- **(2) pre- or subclinical stage**
 - **asymptomatic** – no symptoms but disease has started
 - **latent/silent** – manifest only in increased load/demand
 - **prodromal** – usually unspecific signs of upcoming disease
 - e.g. fatigue, weakness, nausea, anorexia, pain, fever, dizziness
- **morbidity** = disease rate
 - diagnosed disease contributes to population morbidity
 - polymorbidity = the patient suffers from multiple disease
 - comorbidity = one disease is clinically more significant, the rest are comorbidities
- **prognosis** = forecasting the outcome based on current knowledge and means
 - evidence-based medicine (EBM)
 - no guarantee of the actual outcome, but probability/likelihood (EBM)



Natural history of disease - the length/duration

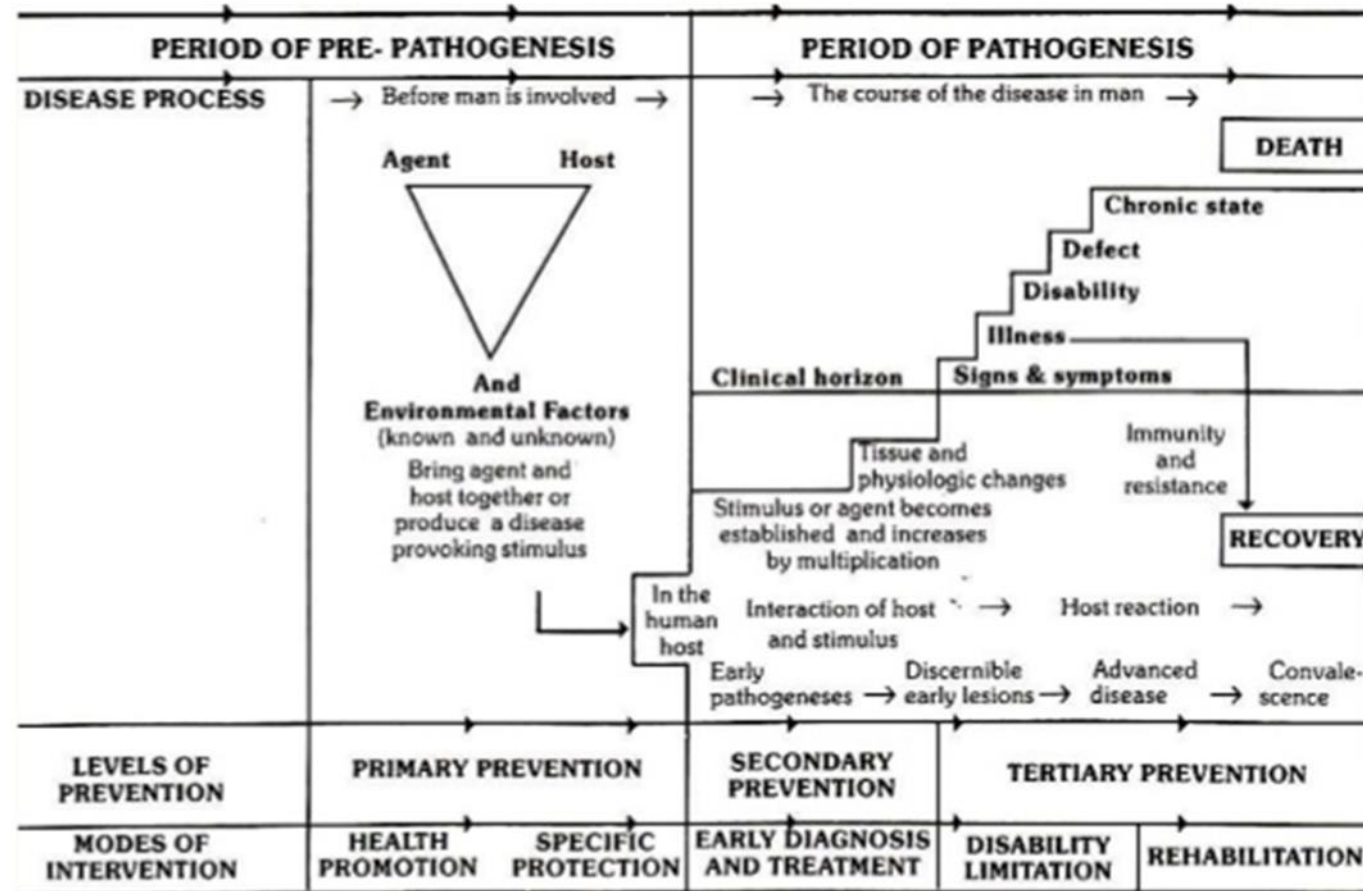
- **clinical manifestation**

- **acute** illness (limited number of days, can be 1 day to 1 month)
 - could be severe or abrupt (fulminant) but self-limiting
 - it can lead to death or restitution
 - convalescence could be prolonged
- **chronic** illness (longer than typical pro given disease)
 - long term, continuous process (with variable intensity)
 - it can follow 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 (intracellular), or targeting the very means of body defence (immune deficit), auto-aggressive (autoimmune) or the damage is perpetual (mechanical damage, chemical irritation, smoking ...)

	Acute Illness	Chronic Illness
Duration of disease	Short	Long-term—may be lifelong
Goal of treatment	Cure—return to normal life	► Adapt to a changed life ► Manage day-to-day symptoms
Patient's role	Comply with the treatment plan	Self-manage treatments, diet, medications, etc.
Staff's role	Provide medical care	► Provide medical care ► Prepare patients to self-manage

28 – subacute = between acute and chronic

NATURAL HISTORY OF DISEASE



Chronic disease - intensity

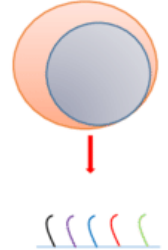
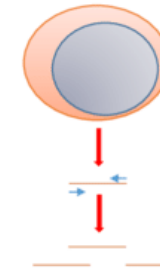
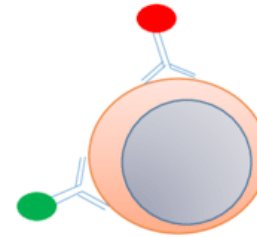
- **Exacerbation** = aggravation of symptoms, signs and severity of disease
- **Remission** = lessening of severity or disappearance of a clinical disease induced by treatment
 - however with the risk of reoccurrence = **relapse**
 - e.g. cancer – with current methods we cannot be sure we eliminated 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

MRD modality

Multi-parameter flow cytometry

Quantitative PCR

Next generation sequencing



Advantages

- Fast turnaround
- Can be used in majority of patients

- Highly sensitive
- Can be compared with previous results
- Dynamic quantitative range
- Routinely established in many labs with standardisation

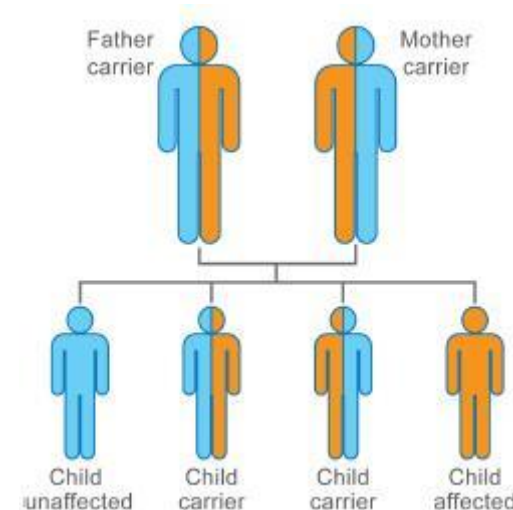
- Can be used in many subtypes of AML

Disadvantages

- Reliant on expertise and skills of reporting lab
- Phenotype of leukaemic cell may change during monitoring period

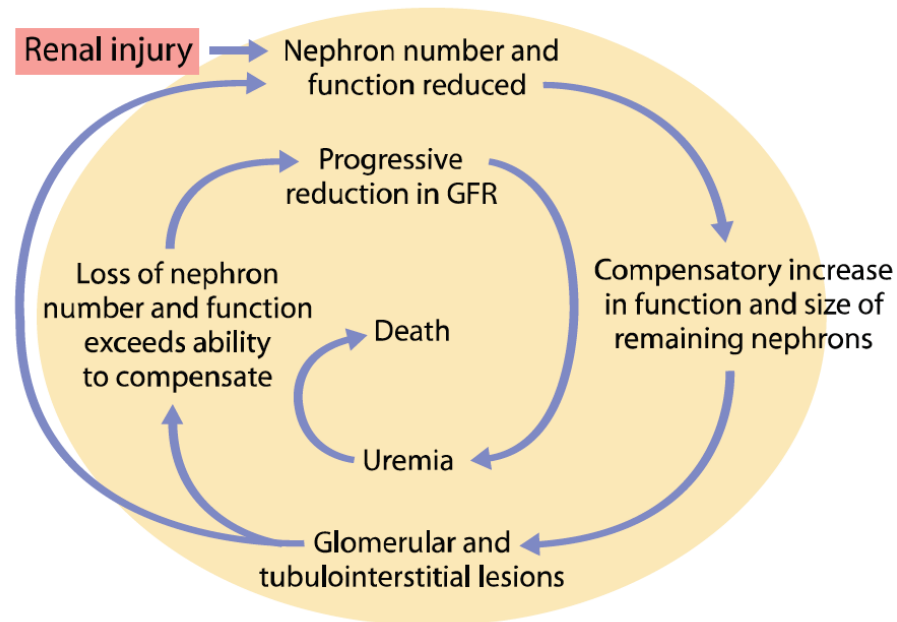
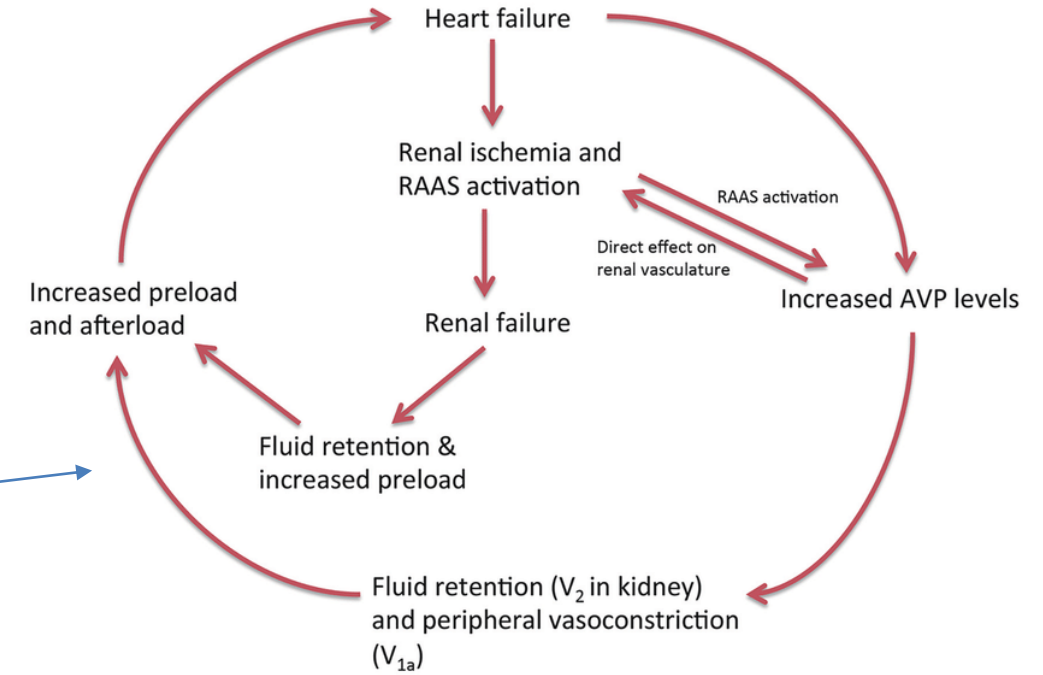
- Restricted molecular targets (e.g. core-binding factor fusion protein, NPM1c mutant)
- Requires expertise

- In ongoing development and interpretation, dependent on many factors including gene in question
- Sensitivity limited at present but is improving
- Requires expertise



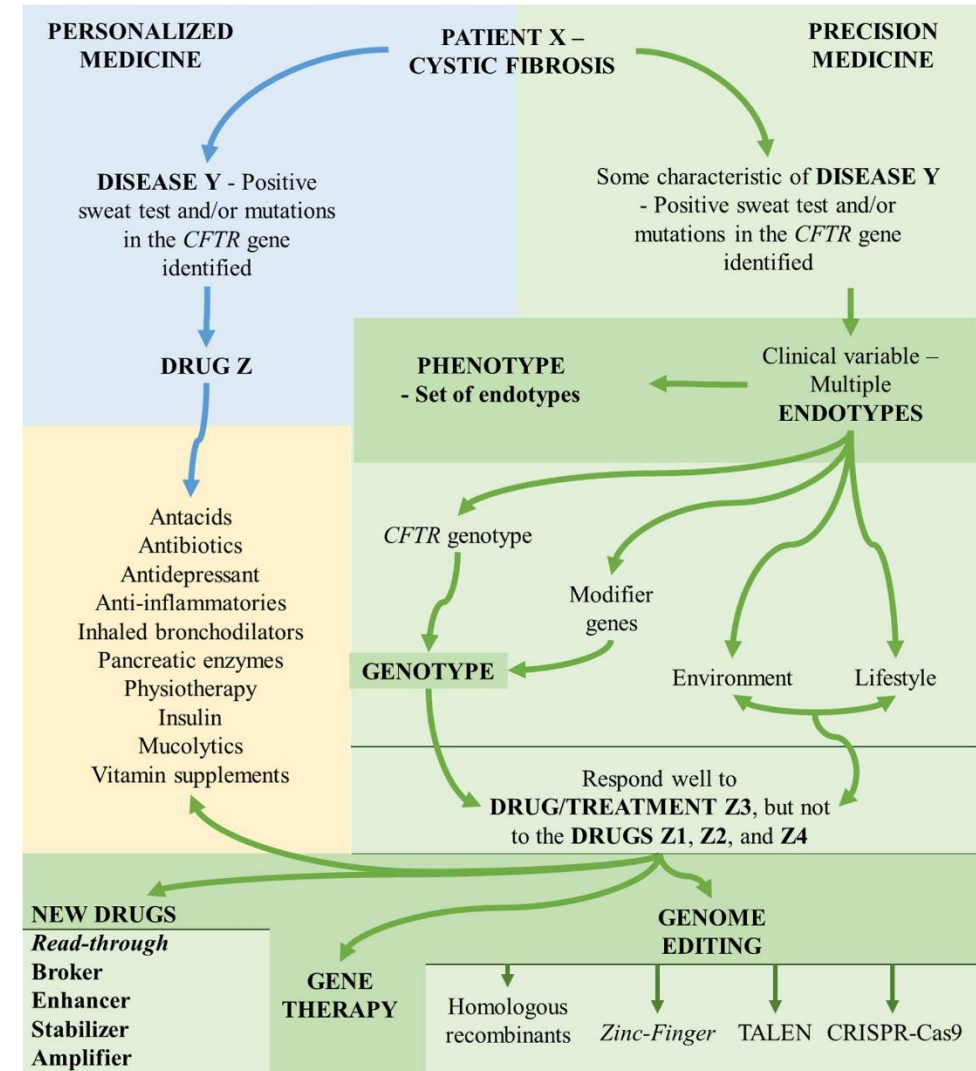
Vicious cycle

- 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



PP typically presents a prototypical disease course unaffected by treatment

- reality is of course much more complex
 - diagnosis at different time points/disease stages
 - different mode of treatment (EBM)
 - interind. variability
 - comorbidities
- „complex patient“** concept
- personalised vs. precision medicine**
 - historically synonyms
 - undesired interpretation of the word „personalised“ („tailored“)
 - there is still EBM paradigm!!!
 - moreover, economically unfeasible
 - recently dominance of the term „precision“
 - personalisation = for the patient (his/her symptoms)
 - considering age, gender, comorbidities, personal preferences
 - precision = for the disease (choice of treatment modalities)
 - gene expression, mutations, pharmacogenetics, ...

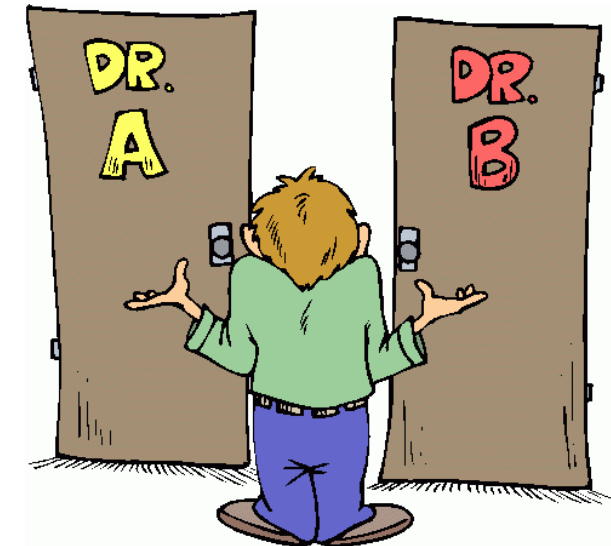
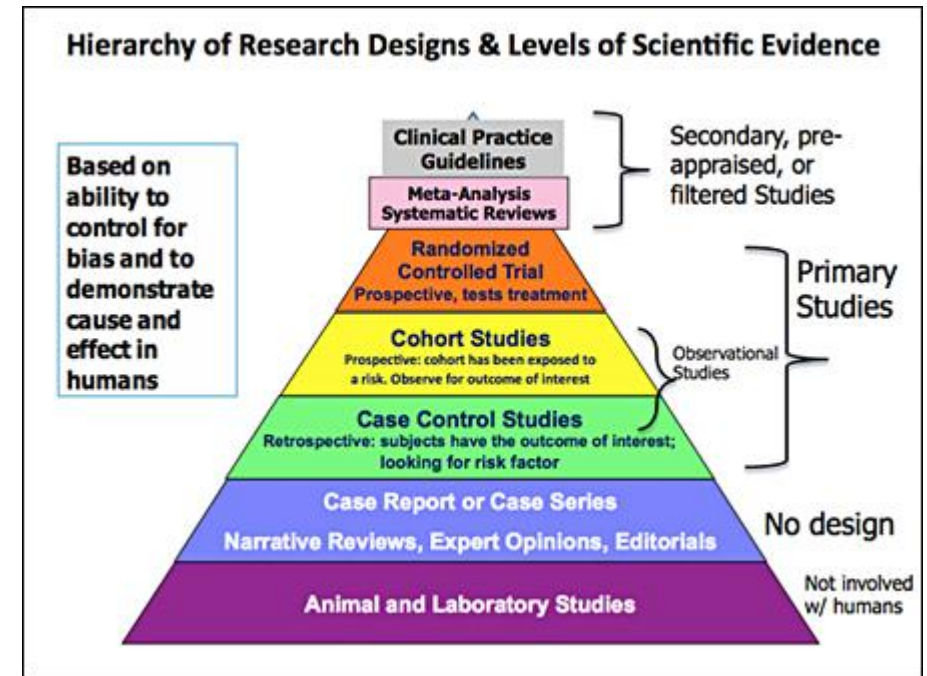


(Front. Pharmacol., 20 June 2017 | <https://doi.org/10.3389/fphar.2017.00390>)

Evidence-based medicine (EBM)

- **EBM** = the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients
 - EBM guidelines for the therapy of given disease/condition
 - to select the best option among available approaches with the strongest evidence for efficiency
 - evidence is provided by most commonly by randomised, controlled (placebo or else) multicentre studies and their meta-analyses
 - in order to judge the evidence one needs to grasp at least the essentials of biostatistics!!!
- However, **real-world data** (RWD) and **real-world evidence** (RWE) are playing an increasing role in health care decisions
 - for example FDA uses RWD and RWE to monitor post-market safety and adverse events and to make regulatory decisions
 - RWD and RWE can support clinical trial designs (e.g., large simple trials, pragmatic clinical trials)
 - the use of computers, mobile devices, wearables and other biosensors to gather and store huge amounts of health-related data has been rapidly accelerating. This data holds potential to allow us to better design and conduct clinical trials and studies in various settings to answer questions previously though infeasible. In addition, with the development of sophisticated, new analytical capabilities, we are better able to analyze these data and apply the results of our analyses to medical product development and approval.
 - RWD can come from a number of sources, for example:
 - Electronic health records (EHRs)
 - Claims and billing activities
 - Product and disease registries
 - Patient-generated data including in home-use settings
 - Data gathered from other sources that can inform on health status, such as mobile devices

- **Personalised vs. precision medicine**



Mortality (death rate) vs. lethality (case fatality rate)

- **mortality** = death rate in the population or sub-population (age group, geographical area, gender, ...)
 - when particular disease occurs often it might increase mortality
- **lethality** = proportion of deceased from the group of affected by given event
 - for example disease or traffic accident

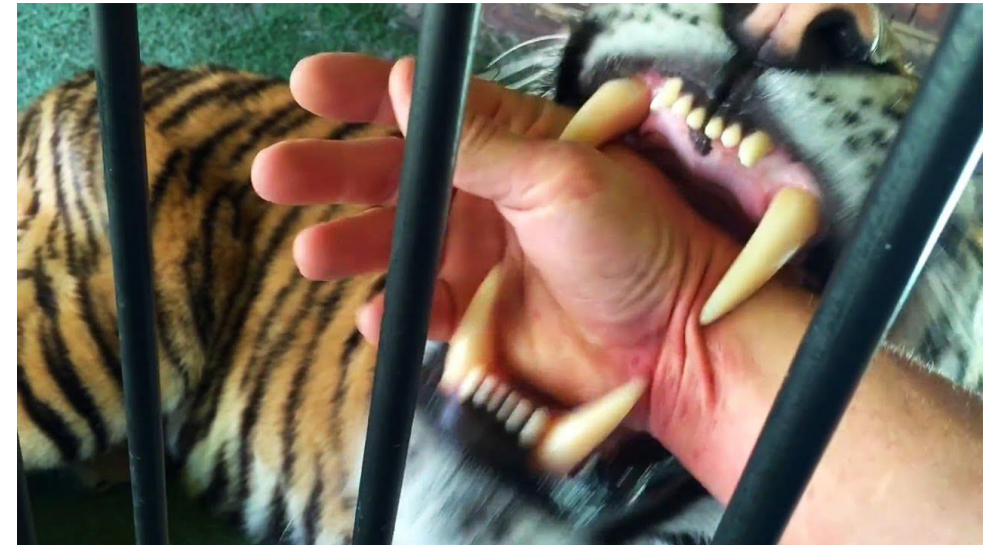
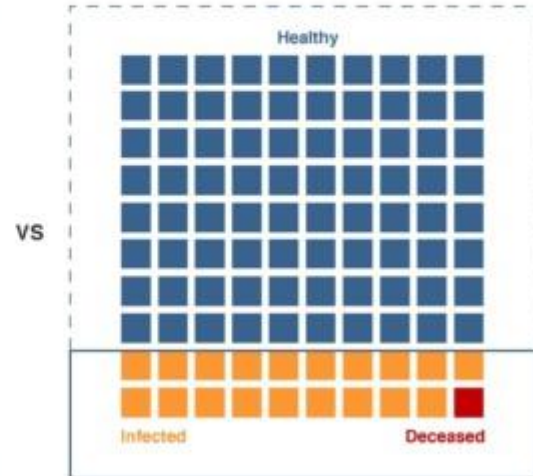


Mortality Rate vs Case Fatality Rate

$$\text{Mortality Rate} = \frac{1 \text{ Deceased}}{100 \text{ People}} = 1\%$$



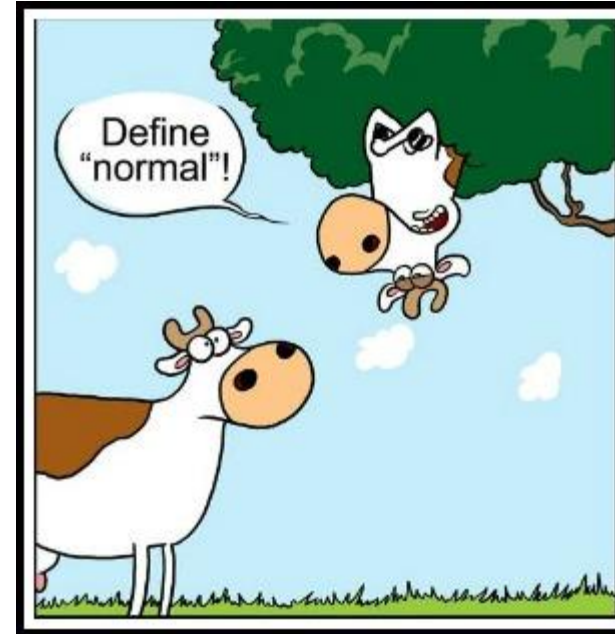
$$\text{Case Fatality Rate} = \frac{1 \text{ Deceased}}{20 \text{ People}} = 5\%$$



Death (exitus) – definition and terminology

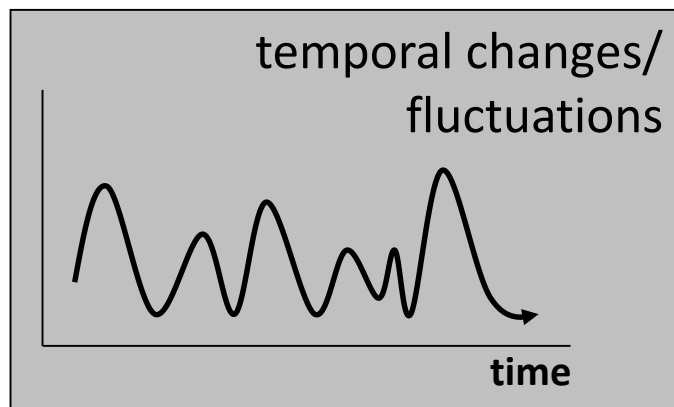
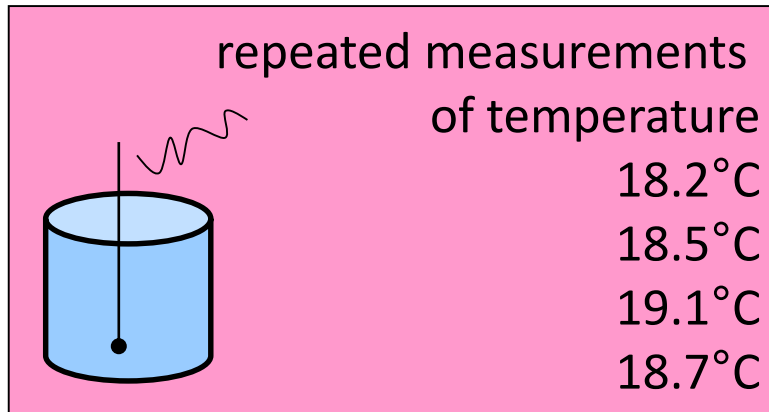
- **Death** (of organism) - is **the permanent, irreversible cessation of all biological functions that sustain a living organism**
 - inevitable fate of all living organisms
 - cardiac and respiratory arrest plus **brain death** (no spontaneous EEG activity) is sometimes used as a legal definition of death
 - can be problematic – for example neo-cortical death (**apalic syndrome**) due to hypoxie affecting evolutionary younger parts
 - apnoe test
 - cardiac and respiratory arrest leads to **clinical death** (a potentially reversible state with CPR)
 - partial death - tissue (infarction) or **cell death** (necrosis, apoptosis and other types)
- **dying** is a gradual process leading to death
 - subjects of **palliative medicine/care**
 - **thanatology** – science of dying and death
- causes of death
 - natural
 - consequence of aging
 - starts after puberty (see theories of aging – mutations, senescence, telomers, ...)
 - life span is characteristic for each species and reflects the genetics and environment
 - » longevity as an exception
 - life expectancy of humans is getting longer in most parts of the world (nutrition, health care, hygiene and healthy lifestyle)
 - succumbing to (lethal) disease/injury
 - unnatural
 - predation (by man or other predator)
 - execution (death sentence)
 - suicide
 - euthanasia – passive, active



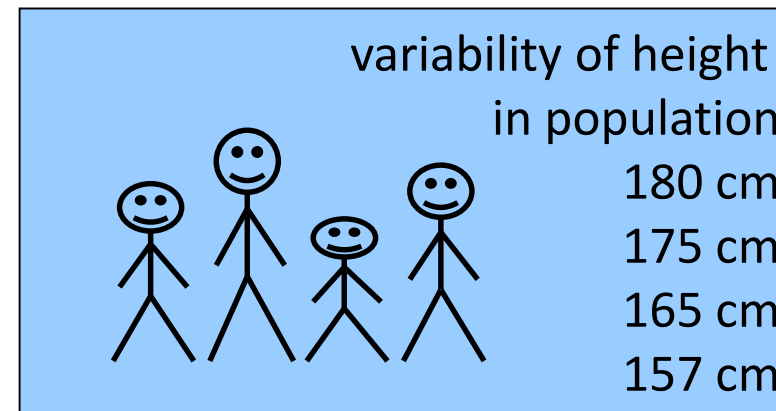


PROBLEM WITH NORMALITY IN MEDICINE

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



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



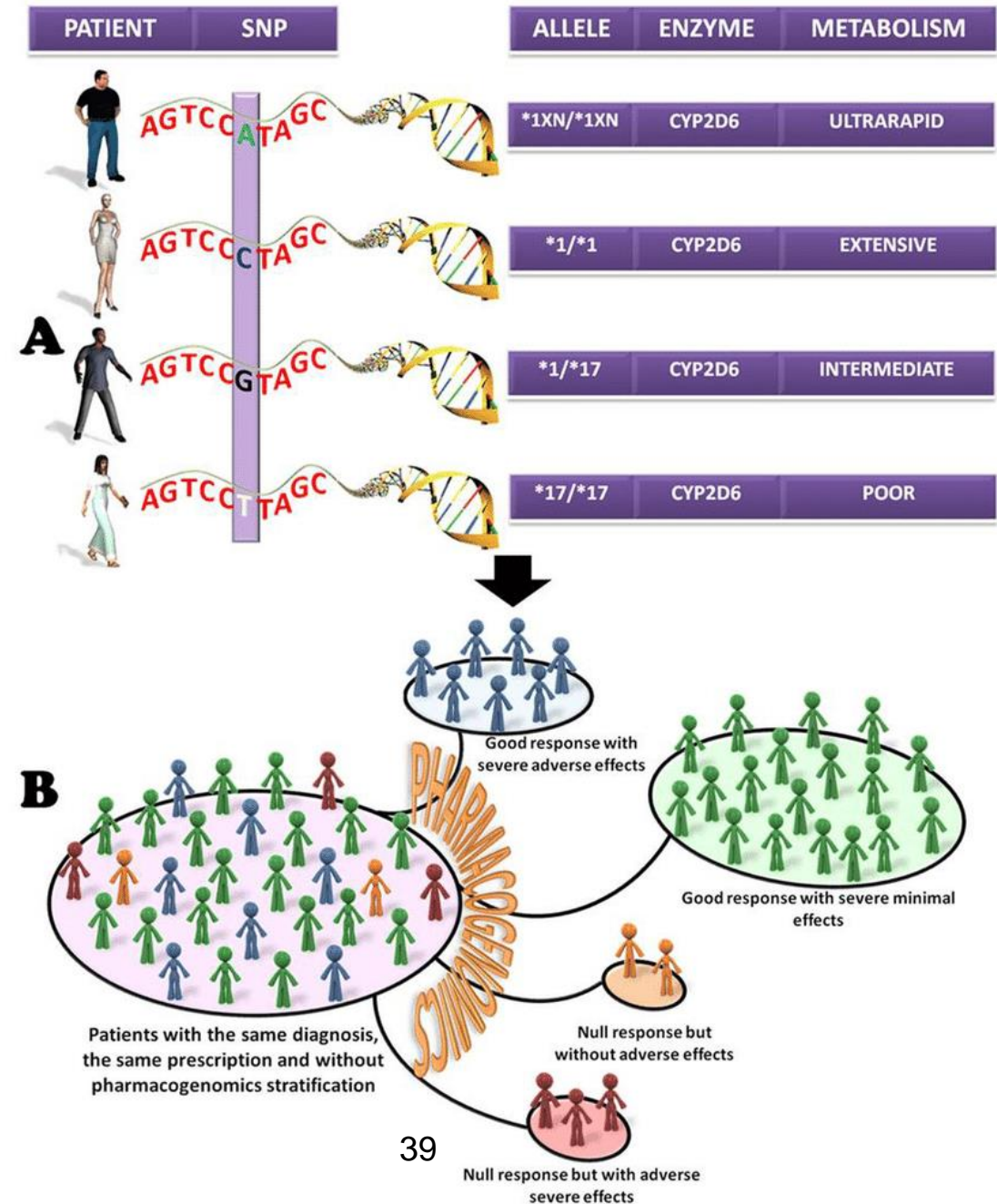
Interindividual variability

- physiological interindividual variability of phenotypes/traits is **consequence of genetic variability and variable exposure external factors**
 - higher the number of independent factors affecting the given trait 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. familial 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

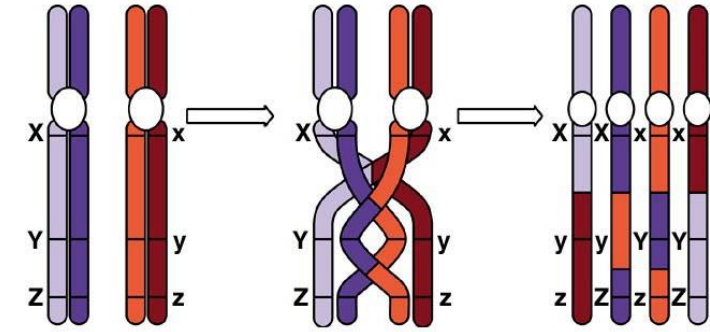
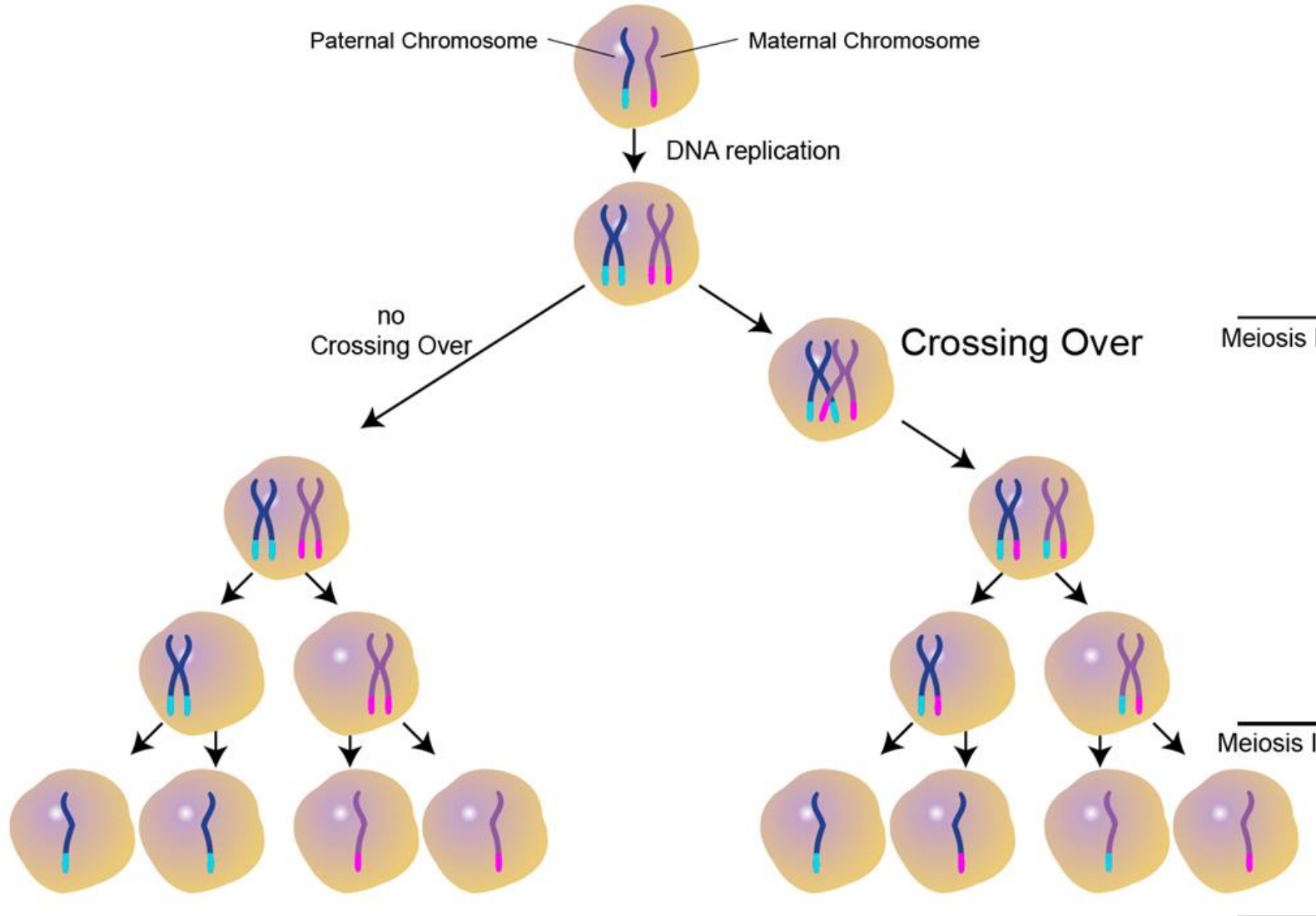


Genetic variability

- 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

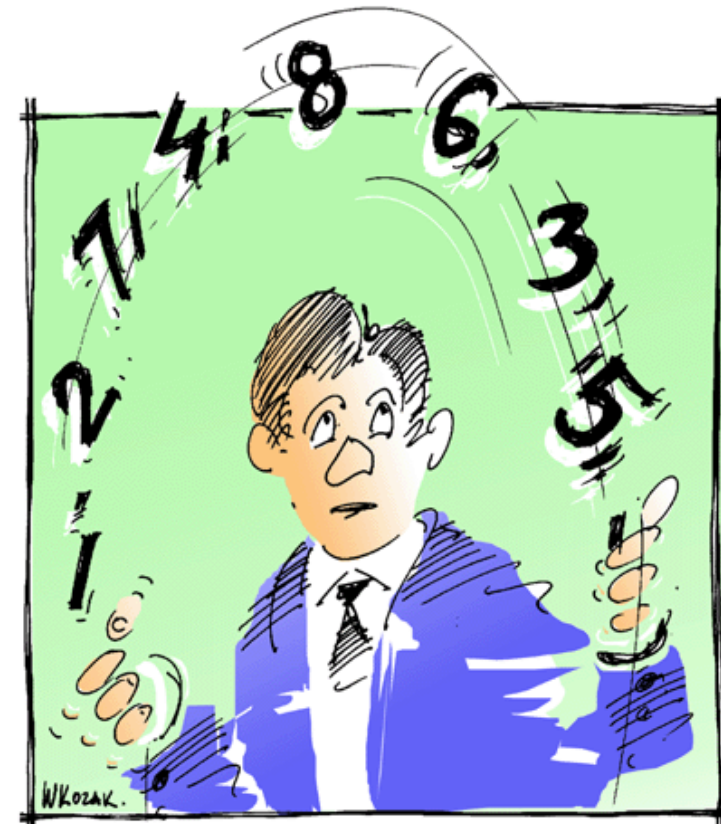


Meiotic recombination (crossing-over)



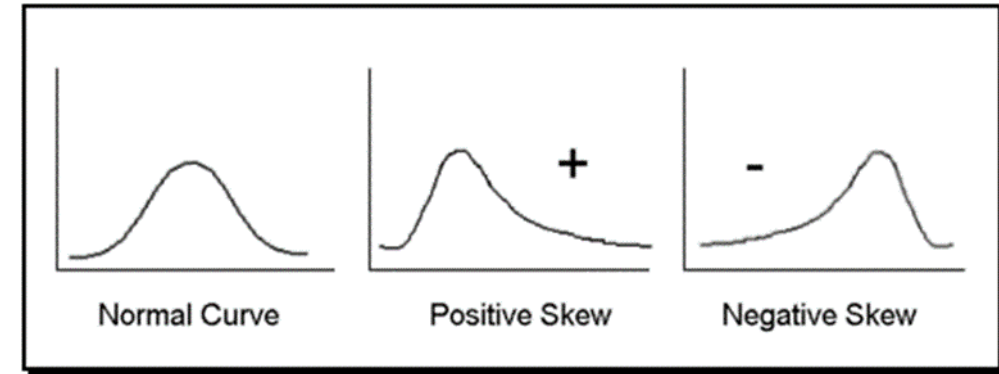
Statistical approach to defining normality / health

- (1) *simple lie*
- (2) *treacherous lie*
- (3) *statistics*

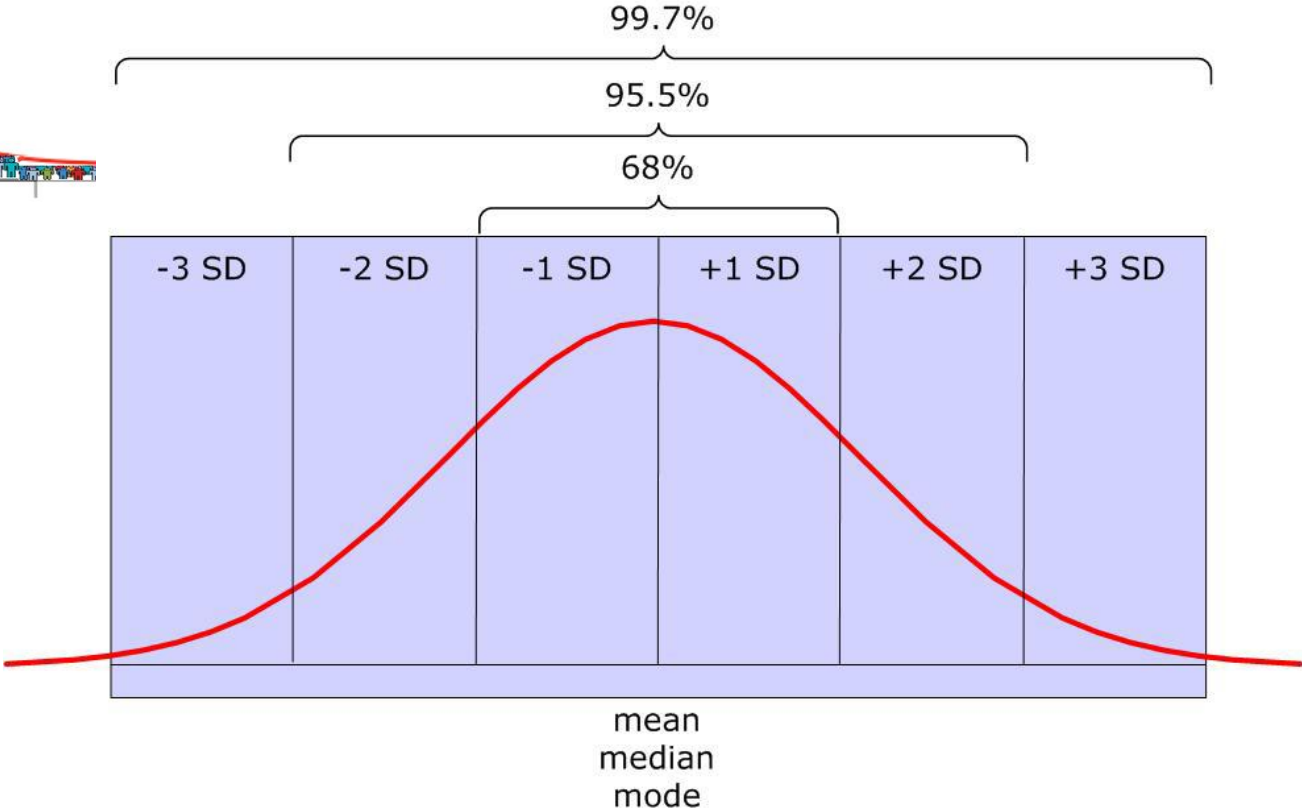
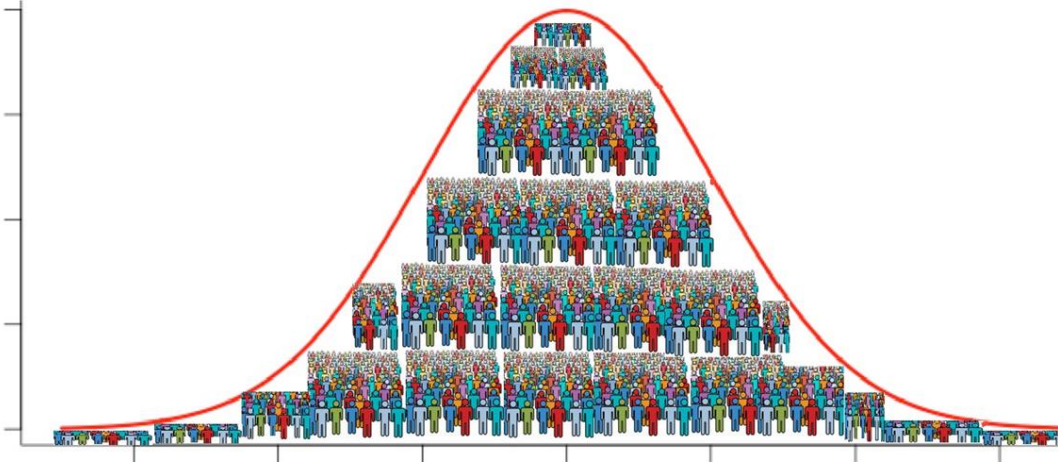


Diagnosis of disease – problem with “normality”

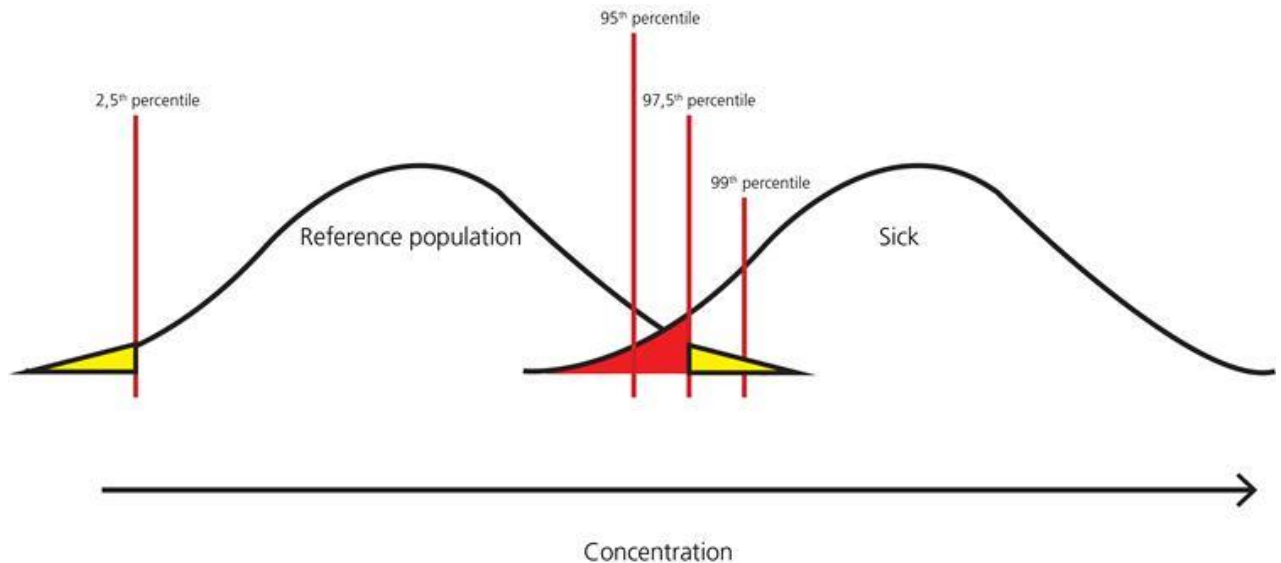
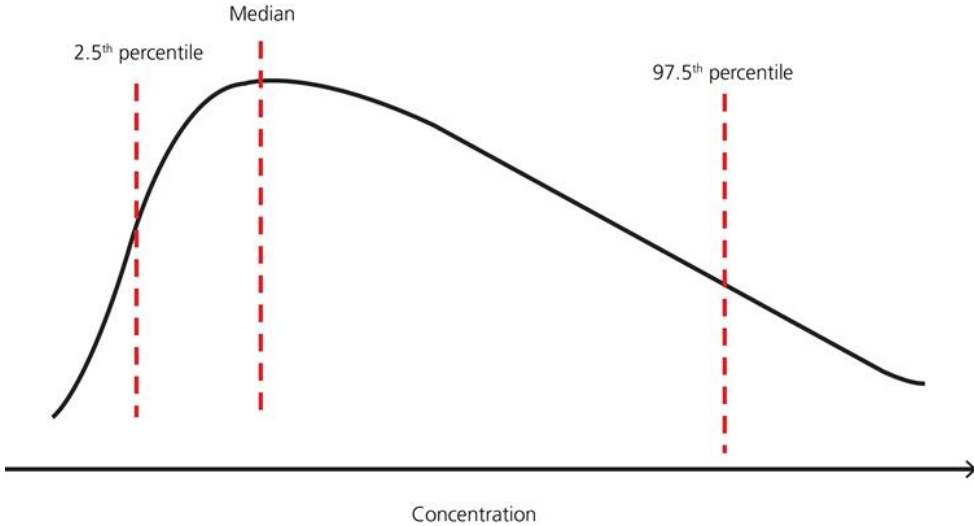
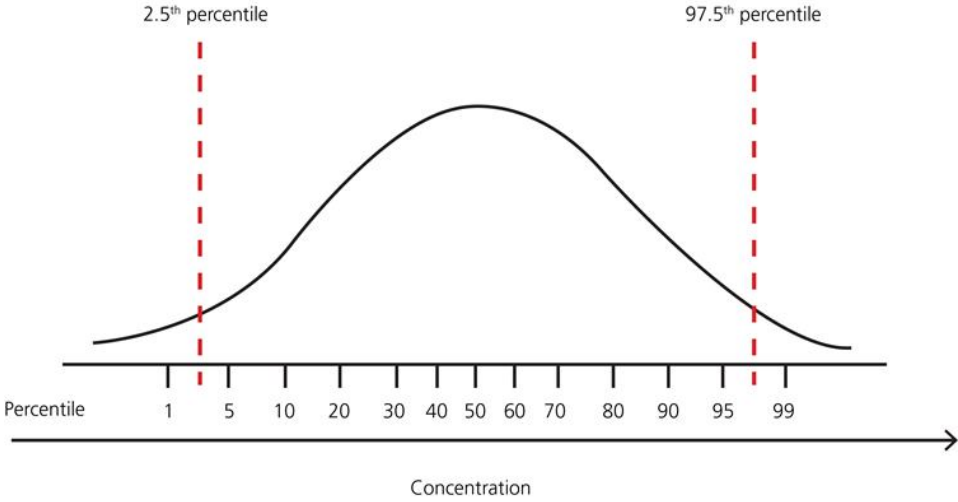
- parameters/traits used as diagnostic parameters might be
 - qualitative
 - alternatives yes/no
 - e.g. cleft palate, congenital valve disease etc.
 - quantitative
 - measurable
 - continuous distribution in population
 - typically influenced by many factors
 - problem to distinguish what is normal and what is not
- alternative vs. continuous model of disease
- practical approach = reference intervals
 - mean \pm 2 SD (for normally distributed parameters)
 - 95% of values in a given population



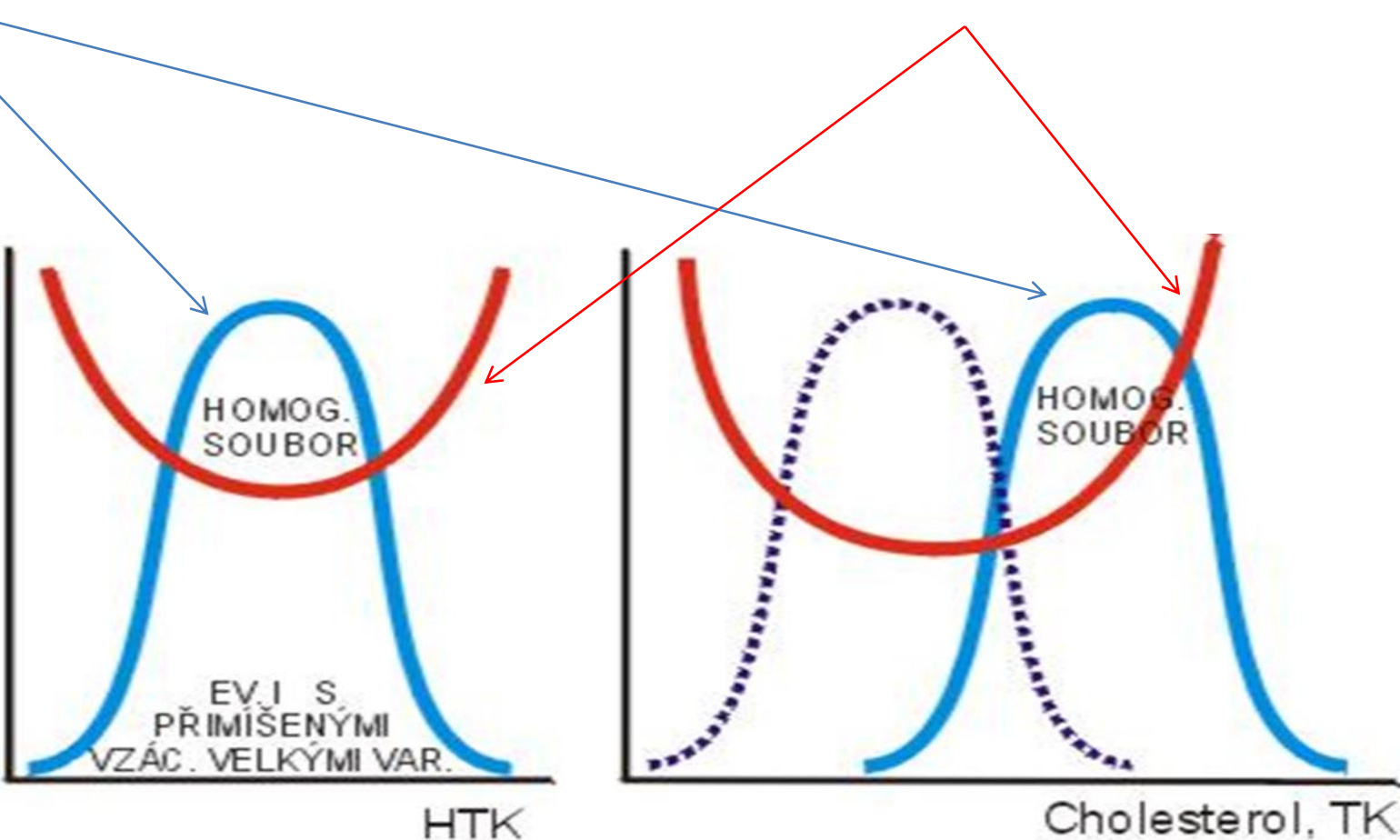
Normal distribution is rare in biology/medicine



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

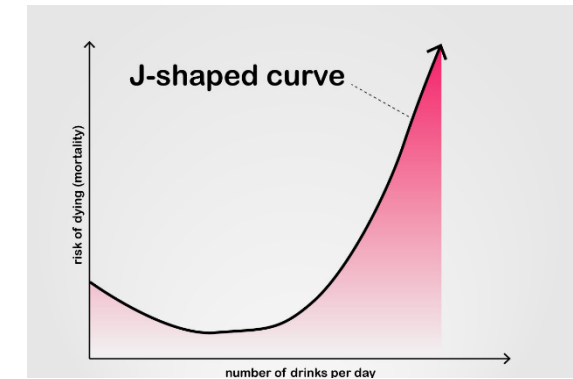
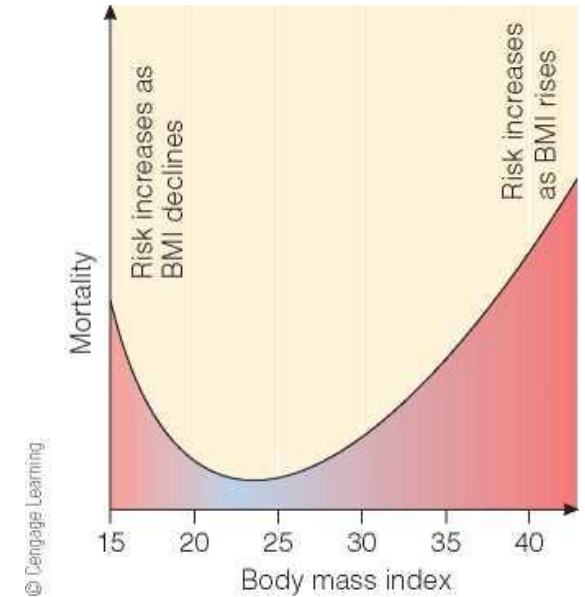
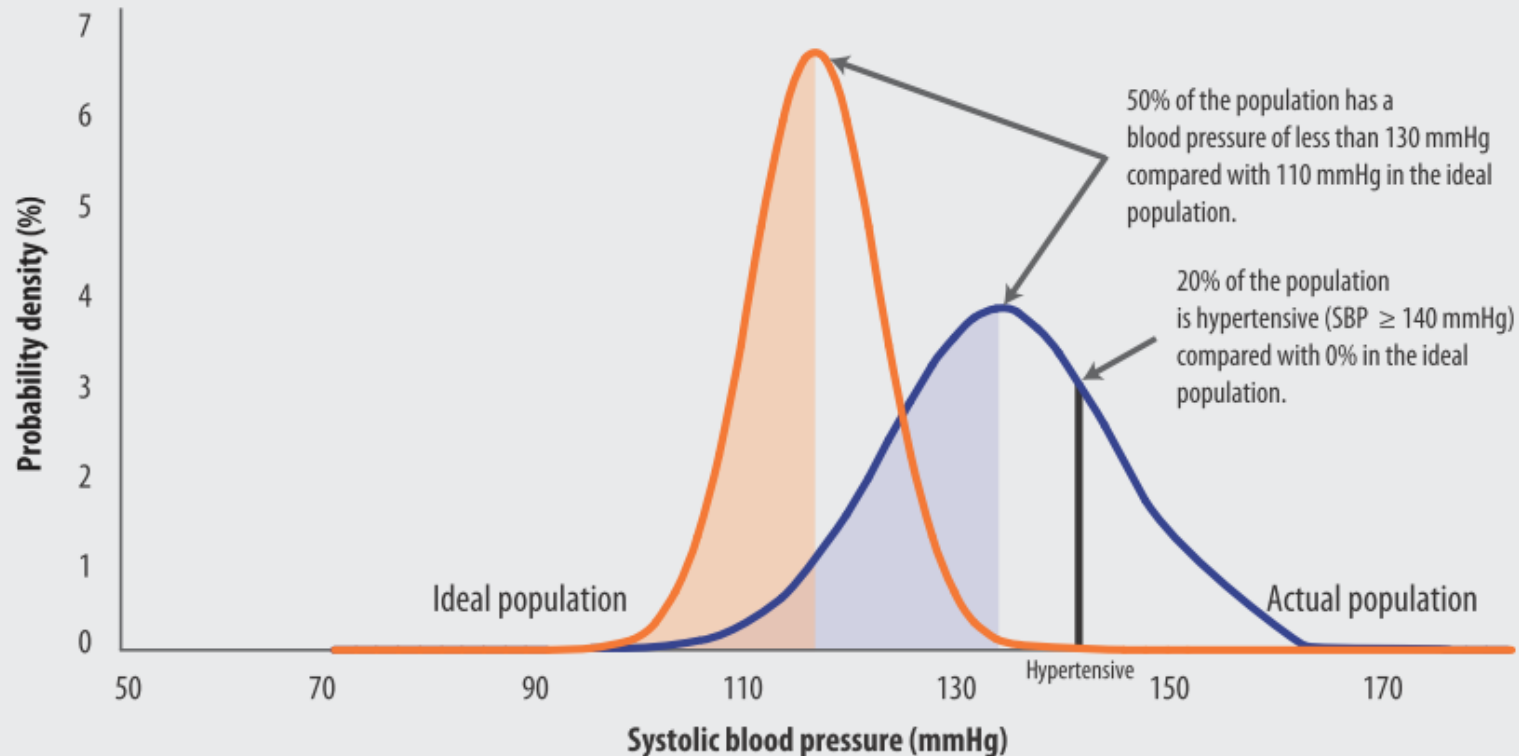


Distribution vs. selection (mortality)



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

Figure 3: An observed population distribution of average systolic blood pressure (SBP, right-hand distribution) and the ideal population distribution of average systolic blood pressure (left-hand distribution).



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