Introduction
(Recommended to readers not to omit this “author’s philosophy“!!)

This short overview of Pathophysiology could serve mainly as a complementary textbook to international undergraduate students of human medicine in the Czech Republic, especially to those who came to study at Charles University - Faculty of Medicine in Hradec Králové. Although there are many textbooks of Pathophysiology existing in English, the majority of them were written in countries where Pathophysiology does not exist as a separate subject in the curricula of medical schools. Thus, they do not seem to cover fully the scope of Pathophysiology as it is traditionally instructed in the Czech Republic (as well as in some other countries of central Europe).

Reason for having Pathophysiology as a separate subject in the medical curriculum
Why to study Pathophysiology?

Pathophysiology is the study of disordered or altered functions caused by disease in a living organism. It deals with causes of diseases and dynamic disease processes. The rationale for having Pathophysiology as a separate subject is based on the prediction that good understanding to the background (causes) - Etiology - of diseases and their mechanisms (development) - Pathogenesis - represents the most important knowledge of doctors who should try to use causal therapy (not only to influence symptoms and signs of diseases but to solve the real causes of health problems) and to prevent secondary disorders (complications) of diseases. It is hardly achieved when pathophysiological aspects are only partially included in courses of physiology whilst some are separately explained in clinical disciplines (as is frequently the case). In our medical curriculum Pathophysiology represents a very integrative subject providing complex information about etiology and pathogenesis of health disorders. Since a primary problem can change homeostasis (stability of the internal environment) of the organism, it can further lead to many compensatory mechanisms and development of secondary diseases (complications) that can influence some other body systems or the whole organism. These possible changes should be understood in order to provide a reasonable effective therapy to patients. Such access is not usually ensured when problems are talked over in separate clinical disciplines. Although clinicians should cover pathophysiological background, they typically provide only description of symptoms and signs of diseases related to standard schemes of therapy. Understanding of pathophysiological background should lead to better prediction and prevention of complications. It also helps to provide an individual therapy according to differences in development of each particular case.

Recommendations for learning of Pathophysiology
How to study Pathophysiology?

With respect to the above specified characteristics of Pathophysiology, it is quite important for its successful handling to apply fully a logical approach to learning of this subject. Compared to a lot of other medical subjects it is not recommmended to learn it mechanically via memorizing of facts (names, values). It is extremely important to understand relationships between described facts - functional changes, adaptation and compensatory processes, mechanisms leading to critical dysbalance in the internal environment and death. Instead of the question "what", in the pathophysiology tests and exam you will be more frequently asked "why" and "how", to find out whether you understand the important links and relationships. It will not be so important to name correctly a disease as to explain various possible sequences of changes leading to health problems or even death, and to specify principles of their prevention or treatment. It will be verified whether you are able to understand a background of the most critical functional changes in particular diseases. For the majority of students it
will meanto changing the way of learning which was formerly oriented mainly to mechanical
description of morphological changes (memorizing of facts).

Methods for instruction of Pathophysiology

Pathophysiology consists in part of the description of general changes of internal environment
(e.g. water, mineral and pH dysbalances) and pathological processes which can take place in
any body system (like inflammation) - this is considered as General Pathophysiology.
Particular diseases influencing single body systems are the topic of Systematic (Special)
Pathophysiology. In both parts standard lectures will provide basic facts or comments to
existing literature. Seminars are included into the course of Pathophysiology to discuss the
main (most complicated) problems and to enable students to present their own ideas. Practical
classes were formerly oriented mainly to animal experiments (this was the reason why
Pathophysiology was formerly also named as Experimental Pathology) enabling to verify real
reactions of a living organism to various experimental conditions. However, nowadays where
possible animal experiments have been replaced for ethical reasons by computer simulations
that provide even larger possibilities to test some theoretical presumptions and to learn
strategies of treatment (compensation of a broken homeostasis). One of disadvantages of this
development in practical classes in Pathophysiology is the fact that students are losing
possibilities to learn some needed practical skills before they start to practice medicine on
patients.

Arrangement of this textbook

The main aim of this book is to provide a condensed overview of Pathophysiology according
to the extent of the Pathophysiology course at our Faculty of Medicine. To keep limited size,
instead of a standard essay a list of relevant items is provided with explanatory notes and
comments (without repetition of morphology, biology and normal physiology background in
the majority of chapters). Thus, it can be difficult to understand fully the mentioned problems
for those who do not participate in pathophysiology lectures and seminars. However, this
itemized overview might help students in their preparation for the final exam in
Pathophysiology, since it provides a minimized list of problems which they should
understand. In case of a need for some more detailed information (for understanding of a
particular problem), it is necessary to consult either some standard textbook of
Pathophysiology written for medical students (covering the item), or to find it on the Internet
or on the Web pages of our Dept. of Pathophysiology - http://www.lfhk.cuni.cz/patfyz/
(“Study pages”). We suppose that upgrades or appendices of this book will be continuously
appearing at our Web page.
Despite the fact that in many diseases their etiology and pathogenesis is already understood
(described) up to the subcellular level (with the use of discoveries in Molecular Biology), we
will stay (in the majority of cases) on the level of tissue, organ and system changes not only to
keep the textbook within reasonable extent for undergraduate students but also to concur with
one of the main pedagogical aims of this Pathophysiology textbook: maximum understanding,
rather than memorizing (as is the case when too many details are presented without
understandable context). This rather basic text tries to orient the reader preferably in
pathophysiological background important for a “general practitioner” than in the latest
discoveries (representing sometimes only hypotheses). We dared to simplify significantly
some very complicated topics and to condense the huge subject of Pathophysiology to about
200 pages only.
Although modern textbooks are often using a lot of graphical tools for apparently more simple
understanding of problems, we do not provide this style and we tried to replace it by a
condensed (logically??) structured text.
We hope very much that issuing this handbook of Pathophysiology will help our students to recognize better what are the most important things (at least from the point of view of their examiners) in the field of Pathophysiology representing the theoretical background of general medicine and that it will help them to better understanding of clinical disciplines, mainly Internal medicine.

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List of abbreviations (only those used throughout all chapters)

ATB - Antibiotics
ARDS - Acquired Respiratory Distress Syndrome
AS - Atherosclerosis
BP - Blood Pressure
CSF - Cerebro-Spinal Fluid
CNS - Central Nervous System
DIC - Disseminated intravascular coagulation
DM - Diabetes mellitus
EBV - Epstein-Barr virus
ECF - Extracellular fluid
GF - Glomerular Filtration
GIT - Gastro-intestinal tract (system)
Hb - Hemoglobin
HR - Heart Rate
ICF - Intracellular fluid
m. - morbus (= disease)
MV - Minute Volume (minute cardiac output)
NSAID - Non-Steroid Anti-Inflammatory Drugs
pCO₂ - Partial pressure of carbon dioxide
pO₂ - Partial pressure of oxygen
PTH - Parathormone
RAAS - Renin-Angiotensin-Aldosterone System
RV - Respiratory (minute) Volume
SLE - Systemic Lupus Erythematosus
sy - syndrome
tu - tumor

Used symbols and formatting tools

↑ - increased (increasing)
↓ - decreased (decreasing)
→ (or ⇒) - leads to (develops), forms
● - upper level of items
- - lower level of items
bold text - headlines
underlined text - lower level headlines
CAPITALS - capitals denote critical factors/mechanisms that may cause death
italic - italic text is used for giving of practical examples or for naming of some diseases/disorders
!!! - very important fact (or not commonly presented)
1. Organism and environment, adaptation

- continuous interactions between organisms and external environment
- body tries to keep constant interval environment (homeostasis) irrespective of external environment parameters via adaptation mechanisms (e.g. thermoregulatory)
- any change of external environment requires resetting of regulatory mechanisms to keep homeostasis
- each adaptation mechanism has some capacity (limited)

**Adaptation capacity**
- represents adaptability of the body
- can be expressed as a range of external environment parameters within which the particular organism can keep homeostasis (survive)
- it is !!!very individual!!! - dependent on:
  - genetic disposition
  - age
  - functional reserve of the body systems responsible for the adaptation to a particular change (dependent on the previous life style - nutrition, physical activity etc.)
- extreme (or too quick) changes of the external environment or failure of adaptation mechanism (due to failure of some organ) → change in internal environment (broken homeostasis) → disease
- border changes of external environment leading to survival only of individuals with best adaptation facilities are causing natural selection (Darwin theory), when Medicine does not interfere
- high external temperature requires thermoregulatory response based on peripheral vasodilatation → ↓ BP - to keep adequate BP requires ↑ MV, people with chronic heart failure do not have sufficient heart reserve→ COLLAPSE (unconsciousness) (typical for old people)

**Factors influencing organism**
- not-changeable
  - genetics, gender, ethnic, age
- changeable
  - nutrition, life style, personal habits
- factors from environment
  - viral and microbial
  - chemical (toxins, drugs, allergens)
  - physical (irradiation, temperature, sun exposure, altitude - pO₂)
- psychological factors (family background, stress, religion etc.)

Disease may be dependent:
- exclusively on genetic factors without any possibility to influence its appearance:
  - autosomal dominant (Adult polycystic kidney disease, Familial hypercholesterolemia, Osteogenesis imperfecta, Spherocytosis, von Willebrand's disease)
  - autosomal recessive (Color blindness, Cystic fibrosis, Phenylketonuria)
  - X - linked recessive (Hemophilia, Bruton-type hypogammaglobulinemia, Duchenne's dystrophy)
- largely dependent on environment or life style
  - Colon cancer - low in developing countries (e.g. Africa), high in "westernized" populations (USA, Europe) - due to different intake of dietary fibers and fat
  - Lung cancer - due to smoking (low in Mormons and Seventh day Adventists with code against use of tobacco – but non-smokers also can have lung cancer!!)
- Skin cancer - due to ultraviolet light
- Malaria - only in countries with mosquitoes transmitting Plasmodium
- dependent on combination of genetic predisposition and factors of environment or life style influencing manifestation of the disease = most frequent case
- early coronary heart disease - due to predisposition to hypercholesterolemia and simultaneous high animal fat intake and/or smoking, low physical activity, stress factors etc.
- obesity and insulin non-dependent diabetes mellitus - combination of genetic predisposition with nutritional habits and low physical activity
2. Health versus disease, Clinical and biological (somatic) death

Concept of normalcy (health):
- all parameters of the human body have a certain amount of interindividual variation and it is important to know the range of values considered as normal (this can differ among ethnic groups, sexes and is usually age dependent)
- in normal (standardized resting) conditions a healthy subject should display all measurable parameters in the normal range, however, any single measurement (laboratory result, observation) that seems to indicate abnormality must be always judged in the context of the entire individual and its conditions (e.g. a single reading of elevated blood pressure does not make and individual hypertensive or single elevated blood glucose does not mean that the person is diabetic)
- the concept of normalcy (especially in the field of mental abilities) may be dependent on cultural values, which may differ in various populations (e.g. dyslexia - reading disability could not be considered as a defect of a central nervous system function in a primitive culture (analphabets))
- the 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.” - seems to be a very comprehensive definition, but given the almost general frustration of people at least in some aspects of their life, this definition does not seem to apply to too large part of the human population (the more intelligent person, the worse: the intelligent person cannot be happy (in social well-being) for a long time because he/she will realize very soon some problem he/she has.)

Concept of disease
- can be defined as any situation which changes the internal environment (impaired homeostasis) - its parameters are not within the normal range
- since formerly there were almost no changes of intrinsic factors measurable in psychiatric diseases, it would have looked as though the above specified definition of disease did not cover psychic disorders - however, nowadays it is well evident that at least subtle biochemical (neurotransmitter) changes are already detectable in many psychic disorders as well
- the subjective feeling of an ill person is that "he/she loses ability to continue in normal daily activities"
- in some chronic diseases homeostasis can be kept but the organism has decreased adaptation capacity - the body can survive in a very limited range of environmental conditions
- health and disease are not strictly separate, there are some border states

Pathological state
- not a fully normal organism - e.g. after amputation of a limb - but having normal homeostasis

Symptoms and signs of diseases
- symptoms - subjective manifestations of a disease (e.g. nausea, headache, fatigue) that cannot be verified objectively
- signs - objective measurable manifestations (e.g. fever, tachycardia, edema, hypertension)

Phases of diseases
1. latent phase - period between exposure to causal factor(s) and first symptoms/signs (in infectious diseases it is incubation period) - no manifestations of diseases are recognizable
2. prodromal phase - usually only non-specific symptoms and signs are manifested (e.g. fatigue, fever, increased FW reading (sedimentation of erythrocytes) that are not sufficient for recognition (diagnosis) of the disease
3. manifest phase including also some specific signs and symptoms (some typical location of pain, typical efflorescences on the skin, changes in plasma concentrations of minerals and other substances)
4. Reconvalescence - gradual recovery of normal functions of the body
5. Final phase - resolution includes the following possibilities
   - "resolution ad integrum" = total recovery of the organism without any consequences or recovery with some chronic consequences of the disease (e.g. decreased vital capacity after some respiratory processes)
   - "development of chronic variant" of the disease with remissions (improvement of the clinical state) and exacerbations (repeated worsening of the clinical state)
   - death

Death
- clinical - represents stop of vital functions (breathing, heart activity); there is possible resuscitation within about 5 minutes (before some irreversible brain cortical changes) - this interval for resuscitation can be longer in cases of decreased body temperature causing lower metabolic rate and postponing irreversible changes due to hypoxia
- biological - means loss of cortical brain functions (can be proved via recording of brain electric activity or reactions of brain vessels) - proper statement of biological death is very important especially in cases where organs for transplantation are to be removed from the dead person

Age related diseases
- some diseases or health influencing consequences of some events appear typically at certain ages:
   - Birth - 14 years: congenital disorders, allergy, childhood infectious diseases, some tumors (e.g. Wilm's tumor, leukemia), accidents, early onset Diabetes mellitus
   - 15 - 30 years: Allergy (asthma) endocrine disorders, accidents (suicide), venereal diseases
   - 30 - 40 years: peptic ulcer, hypertension, breast cancer, alcoholism
   - 40 - 60 years: hypertension, heart diseases, myocardial infarction, liver cirrhosis, lung cancer, colon cancer, breast cancer
   - 60 - 80 years: heart failure, cancerogenesis
   - 80 - 100 years: cancerogenesis, osteoporosis, infections, heart failure, ictus, accidents (fracture), Alzheimer disease
3. Etiology and pathogenesis

Etiology - describes causes of diseases
- formerly (on the border of 19. and 20. centuries) moncausal etiology of diseases was typically recognized - e.g. etiology of Tonsillitis is Streptococcal infections
- nowadays mainly polycausal etiology (multifactorial) is stated in majority of diseases - e.g. appearance of Streptococcal tonsillitis is not dependent on an exposure to Streptococcal infection only but its development is also dependent on the state of immunity, which is substantially influenced by nutrition, rest (sleep), physical and psychic exhaustion, exposure to cold (causes peripheral vasoconstriction and lower input of leukocytes to tonsils)
- usually one etiological factor can be recognized as the main factor and the others as contributing
- it is extremely important (but difficult) to specify correctly the etiology of a disease, otherwise it is not possible to state proper causal therapy - symptomatic therapy is not so efficient and it is risky because it can eliminate some important manifestations of the disease (loss of information) - e.g. use of analgesics may eliminate pain which could signal some critical problems like acute abdominal events (appendicitis)
- very complex understanding of etiology is necessary ("causes of causes" should be known) in order to recognize correctly the real background of health problems - providers of “alternative/complementary” medicine misuse the recent situation in standard (allopathic) medicine in which many doctors are not able or willing to spend time on enough detailed search for the etiology including detection of various social frustrations
- "idiopathic" (essential) diseases - such disorders in which the real etiology is as yet not known

Pathogenesis
- description of pathogenesis of diseases represents explanation of mechanisms of a disease, its development, constitution of compensatory mechanisms, and the appearance of complications - secondary diseases
- good knowledge of pathogenesis enables prevention of complications of a primary disease (e.g. prevention of hypocalcemia and bleeding disorders in primary biliary problems which lead to malabsorption of fats and the fat soluble vitamins D and K, and consequently lead to the problems with Ca and the vitamin K-dependent coagulation factors)

Both etiology and pathogenesis are presently described up to the sub-cellular level. Although this is necessary for development of new kinds of causal therapy, for a “general-practitioner”, who cannot be specialized in all diseases, it is more important to achieve competence in the prevention of diseases and the principles of appropriate therapy, based on understanding of clinical (organs and systems) manifestations.
4. Pathologic changes in immunoreactions - immunodeficiencies, autoimmune disorders, post-transplantation reaction, allergies

**Immunodeficiencies**

- **Inborn immunodeficiencies**
  - cell mediated (decreased phagocytes)
  - quantitative (leukopenia, agranulocytosis)
  - qualitative (syndrome of "lazy leukocytes")
  - cell mediated (T-lymphocytes)
    - Di George syndrome (thymus aplasia, deficiency of T-lymphocytes - severe infections in children)
  - humoral – antibody-mediated (complement)
    - C1 angioneurotic edema
    - C2 opportunistic infections
    - C3 - sepsis
  - humoral (B- lymphocytes)
    - hypogamaglobulinemia in all classes (IgG, IgM, IgA, IgE) - under 2mmol/l = agammaglobulinemia
    - Bruton's - newborn' type dysgammaglobulinemia
  - combined

- **Acquired immunodeficiencies**
  - endogenous - represent complication of some other primary disease influencing immunity
    (e.g. via development of hypoproteinemia (e.g. nephrotic syndrome, liver cirrhosis, malabsorption), bone marrow depression, Diabetes mellitus)
  - exogenous - due to irradiation, cytostatic therapy, malnutrition, etc.)

**AIDS**

- immunodeficiency caused by virus HIV (HTLV3, LAV)
- transmission via blood transfusions, transplacentar, sexual act, professional - health care staff
- manifestations - fever, enlargement of lymphatic nodes, infections

**Autoimmune disorders**

- deficiency of autoimmune tolerance
- probability increases with aging
- primary disorders on the basis of genetic change
- own tissues with changed structure
- can be activated by exogenous factors - bacterial, viral, chemical substances, irradiation

Mechanisms of secondary intolerance:
- change in immune non-accessibility (normally without contact with the immune system)
- eye lens without direct blood supply
- non-transferable membrane - sperms
- Hashimoto thyroiditis
- crossed reactivity
- sensitization by antigen that is very similar to own body structures
- sequestration of clones - appearance of lymphocytes that are not immunologically controlled
- prohibited clones - formed by mutation (intolerant to own tissues)
- autoimmunity on the basis of immunodeficiency (proliferation of surface antigens in lymphocytes sensitized against own antigens)

Examples:
- organ specific - Hashimoto thyroiditis, Grave's thyreotoxicosis, m. Bechtërev, m. Sjögren, m. Crohn, Atrophic gastritis, Myasthenia gravis
- organ non-specific - SLE, Polyarteritis nodosa, Scleroderma, Wegener's granulomatosis, Rheumatoid arthritis

**Post-transplantation reactions**
- transplanted graft is exposed in the body of a recipient to attack of his HLA immune system (set of genes coding large number of antigens on the plasmatic membrane) representing immunologic identity of the individual
- the velocity of the immunological reaction (rejection of the graft) depends on:
  - pre-formed antibodies in the body of the recipient - due to former transfusion or transplantation, pregnancy
  - compatibility in the HLA system (mainly HLA2)
  - immune suppression of the recipient (necessary use of glucocorticoids, cyclosporin A and other immunosuppressive agents)
- development of the rejection
  - hyperacute - patient has already pre-formed antibodies → microthrombotization, ischemia, necrosis of the graft - "white graft" (already evident during the transplantation procedure)
  - acute – cell-mediated or antibody-mediated
  - chronic - based on reactions of vessels
- the graft does not function after rejection - ectomy of graft is necessary
- also reaction of the graft against the recipient is possible (influences mainly bone marrow)

**Allergies**
- inappropriate immune reactions to allergens - substances that are indifferent for another organism

**I. type** - anaphylactic reaction
- antibodies IgE - accumulated in mast cells (mainly in epithelium of respiratory and gastrointestinal system)
- degranulation of mast cells releases:
  - histamine → vasodilation, ↑ permeability → edema, bronchoconstriction, increased mucus production
  - serotonin
  - arachidonic acid
- manifestations depend on:
  - type of antigen
  - individual sensibility - atopic reaction in the case of overproduction of IgE
- forms of allergic reaction
  - localized anaphylactic reaction
  - generalized anaphylaxis – 1° contact - antibodies sensitize basophils
  - 2° contact - degranulation
- Examples: Bronchial asthma, hay fever, most critical is ANAPHYLACTIC SHOCK = circulatory shock with acute respiratory failure due to bronchoconstriction

**II. type** - cytotoxic reaction
- circulating antibodies react with antigens on the surface of cells → destruction of cells
- Examples: post transfusion reaction, Fetal erythroblastosis

**III. type** - formation of immune-complexes (activation of complement) - deposits into the vessel wall → tissue injury
- Examples: Glomerulonephritis, serum disease, rheumatic process
IV. type - reaction mediated by cells - delayed type
- appearance of sensitized lymphocytes T (effect of some infections, allergens - e.g. penicillin)

V. type - stimulus hypersensitivity - formation of functionally interfering antibodies →
- blockage or activation of target tissues
Examples: Grave's thyreotoxicosis, Myasthenia gravis

VI. type - cytotoxicity mediated by cells dependent on antibodies (ADCC - antibody dependent cellular cytotoxicity) - mediated by T^K lymphocytes

**Immunoproliferative states**
- lympho- or myeloproliferative states after benign infections (e.g. Infectious mononucleosis)
- can cause chronic lymphatic leukemia or lymphosarcoma
- non-Hodgkin lymphoma, multiple myeloma, Waldenström macroglobulinemia
- accompanied by immunodeficiency

**Regulation of immune responses**
- active and passive immunization
- increase of non-specific immunity
- desensitization
- immunosupression

**Immunity in elderly**
- thymus deficiency - decrease T^H, T^S
- B - lymphocytes are hyperactive - increase of para-proteins and auto antibodies
- immunity dependent on the level of nutrition
5. Neoplasia, neoplasm-host interaction (effects)

Definition - tumorous process characterized by loss of cell differentiation (loss of normal functions) and loss of cell growth control (is not coordinated, expansive)
- normal cell has no telomerase, thus the shortening of telomeres allows max. ca 50 reproductions (∴ apoptosis)
- tumorous cell with telomerase has unlimited reproduction, is less dependent on oxygen, and has increased utilization of glucose

Benign tumors
- similar to original tissue, partially differentiated, keeps function
- slow growth, localized, without metastases, rare necrosis
- can cause death just as can malignant tumors, if in some critical location - e.g. intracranial, airways

Malignant tumors
- low differentiation, loss of normal function but possibility of paraneoplastic syndrome - e.g. secretion of substances imitating various endocrine effects - paraendocrine sy
- quick expansive growth, formation of metastasis, frequent necrosis

Etiology
- genetic mutations either activate proto-oncogens and/or inactivate tumor suppressive genes
- for malignant tumorous process more (at least 6) is necessary
- decreased immunosurveillance (due to chronic catabolic state, hypoproteinemia - possibly caused also by long-lasting starvation)

Carcinogens - genotoxic, irreversible changes of DNA:
- chemicals - asbestos, benzene, benzpyrene, aniline, insecticides, fungicides
- food and drugs - smoked foods, aflatoxin, estrogens, cytostatics
- radiation, UV waves
- viruses - EBV, herpes virus, retroviruses

Tumor suppressive genes
p53 - causes transient stop of reproductive cell cycle, reparation of DNA and in cases of its failure activates apoptosis → only health cells are reproduced
- activity is changed according to needs
- in case of dysfunction even defective cells can reproduce

Pathogenesis
- expansion of tumorous cells
- formation of metastasis via circulation, lymphatic system, via implantation (during surgery)
  - most frequent localization - liver (from abdominal tumors), lungs, brain - distant, bones, prostate - late metastatic process
- angiogenesis - formation of new capillaries

Tumor markers
- substances released by tumors into blood, cerebrospinal fluid, urine
- specific for particular tumor, thus helpful in diagnostics and monitoring
Examples: antigens, hormones, enzymes (alcaline phosphatase in bone tumors)
Generalized effects of tumorous processes (end stage)
- initial phase usually asymptomatic, thus patients come frequently too late to doctor (in the phase of metastasis)

**Pain** - caused by the following mechanisms and forced by stress (decreased threshold):
- pressure of the tumor, destruction of tissues
- ischemia (compression of vessels, embolisation by tumorous cells
- inflammation, necrosis
- iatrogenic effect of therapy

**Cachexia** (extreme loss of weight) - causes:
- loss of appetite, problems with nutrition in tumors of GIT, release of TNFα (cachectin)
- nausea, vomiting (either peripheral - direct irritation of stomach, ischemia or central - due to circulating substances released by tumor or iatrogenic from cytostatic therapy
- increased metabolism by tumorous process → catabolic state - loss of muscle proteins
- ↑ gluconeogenesis, insulin resistance, ↑ lactic acid
- released toxins from tumorous cells

**Bone marrow depression**
- due to invasive growth of tumor (metastasis)
- decreased nutrition (catabolic state, hypoproteinemia)
- in cytostatic therapy
Consequences - anemia (with all consequences), leukopenia (with immune effects)

**Bleeding disorders**
- due to thrombocytopenia, low formation of coagulation factors (hypoproteinemia)
- chronic or acute bleeding
- in some cases increased thrombogenesis can appear - production of coagulation factors by tumors, obstruction of vessels, immobilization

**Immunodeficiency**
- due to leukopenia, hypoproteinemia (↓ Ig), cytostatic therapy
- causes a lot of infections in terminal states of tumorous processes - most frequent cause of death
- causes decreased immunosurveillance (elimination of first existing tumorous cells mainly by T<sub>K</sub>- possibility of some other tumorous processes)

**Edemas**
- compression of vessels, ↓ oncotic pressure, increased permeability (acidosis, tumor substances and inflammatory mediators)
- elephantiasis - limb edema in infiltration of lymphatic nodes and obstruction of lymphatic system
6. Alterations in fluid volume

Regulation of fluid volume
- dependent mainly on "RAAS" activated in hypoperfusion of kidney (decrease of pressure in vas afferens increases production of renin in juxtaglomerular apparatus)
  Because this system is activated also e.g. in heart failure or atherosclerosis of renal arteries, it can lead to dysregulation of fluid volume
- since aldosterone increases simultaneously reabsorption of sodium and water, there is no distinct change in osmolarity
- ADH system primarily regulates osmotic changes because it is influenced by osmoreceptors in the hypothalamus, however, it also contributes to volume regulation because loss of volume (usually hypotonic fluid - like sweat) is accompanied by hyperosmolarity
- atrial natriuretic peptide produced in heart atria in case of increased preload does not influence circulating volume too much (nevertheless its function is tested in failing heart)

Dehydration – fluid volume deficit
Causes
- Inadequate fluid intake
  - unconsciousness or inability to express thirst
  - impaired thirst mechanism (in some CNS disorders, in very old people
  - oral trauma or inability to swallow
  - withholding of fluids for therapeutic reasons
- Excessive fluid losses
  - Skin losses – fever, exposure to hot environment, physical activity (loss of 1l/hour), dry environment (extremely low humidity on board planes during long flights), burns and wounds (loss of plasma!)
  - Gastrointestinal losses – vomiting, diarrhea (critical mainly in newborns), GIT suction
  - Urine losses – diuretic therapy, osmotic diuresis (hyperglycemia), adrenal insufficiency (Addison’s disease), tubular failure (shock kidney, hypokalemia, hydronephrosis, peripheral diabetes insipidus)
  - Third space losses – intestinal obstruction = Ileus, Edema, Ascites
  - bleeding

!!!It is important to differentiate isotonic and hypertonic dehydration!!!

Signs and symptoms
- severe extracellular deficit: 5% of ECF or more
- in unconscious patients the best information about level of hydration = monitoring of central venous pressure
- thirst - increased plasma osmolarity, increased hematocrit (tendency to thrombogenesis)
- increased urine osmolarity, low production of urine (low glomerular filtration and increased reabsorption of urine via ADH secretion)
- tachycardia (to keep MO in low volume of circulating blood activated via sympathetic system)
- cold and white periphery, decreased tonus (turgor) of skin
- postural hypotension, decreased vein filling
- hypotension, hypovolemic circulatory shock
- increased body temperature due to failure of thermoregulation (hypoperfusion of periphery - centralization of circulation)
- decreased ECF - sunken eyes, soft eyeballs, depressed fontanelle in infants
- increased hematocrit - viscosity of blood leads to thrombogenesis (mainly in combination with immobilization and in old people)
- decreased ICF - dry skin and mucous membranes, cracked tongue
- decreased salivation and lacrimation
- neuromuscular weakness, fatigue, exicosis of cells - in CNS → coma

**Hyperhydration – fluid volume excess**

**Causes**

- **Excessive intake**
  - increased dietary intake (does not develop in normal kidney and heart function – fluid is eliminated via increased glomerular filtration)
  - excessive administration of parenteral solutions (monitoring of central venous pressure is necessary)

- **Inadequate water losses**
  - renal disease (oliguria, anuria)
  - increased mineralocorticoids and/or glucocorticoids (Conn's sy, Cushing's sy)
  - congestive heart failure (decreases glomerular filtration, increases aldosterone)
  - cirrhosis of the liver (secondary hyperaldosteronism due to lower degradation)

**Signs and symptoms**

- clinically significant excess over 5% of ECF
- increased blood pressure (in kidney failure) with all consequences
- pitting edema, puffy eyelids
- pulmonary edema (shortness of breath, rales, dyspnea, cough, venous distension)
- in extreme beer drinkers with normal kidney function only dilated heart ("beer heart" = "Bavarian heart") is present
7. Disorders of osmolarity, etiology and pathogenesis of edema

- ca 90% of plasma osmolarity is ensured by sodium, the remaining osmolarity is ensured mainly by glucose and urea
- thus any change of sodium causes significant change of osmolarity
- regulation of osmolarity is mainly dependent on antidiuretic hormone - ADH
- ADH is released from the posterior pituitary when osmoreceptors in the hypothalamus are activated by increasing osmolarity
- reabsorption of water in the distal tubule and collecting duct in the kidney causes decrease of osmolarity and increase of volume of circulating blood, ECF and also ICF, because decreased osmolarity in the ECF causes shift of water to the ICF (to the compartment with higher osmolarity)
- any hormonal regulation has some delay in feed-back loops influencing appropriate release of hormone and hence the regulated parameter (osmolarity in the case of ADH) cannot be immediately set to the required value, but undergoes some damped oscillations with several overshoots to both sides (Note that in the case of osmolarity regulation this is even more marked with the interference of typical human behavior: When you are very thirsty, you do not drink slowly only small of fluid (it is not important whether it is water, cola or beer – all are hypotonic) of just sufficient volume necessary for osmolarity compensation, but you drink a large volume all at once (usually min. 0.5 l). This leads to a quick decrease of osmolarity to subnormal level and it stops release of ADH. Subsequently the kidney can release more water into the urine than you have drunk. Thus you can come to an even higher osmolarity than before the first drink (and beer drinkers say that ”surprisingly after the first beer they only have that real thirst”).

Hyperosmolarity
- the most frequent type of dehydration is via sweating - loss of hypotonic sweat causes hyperosmolarity, but replacement of volume by standard drinks leads to hypoosmolality because losses of sodium are not replaced (with the exception of special drinks used by sportsmen) - it is important to ensure intake of some salt
- extreme examples of long-lasting thirst:
  - "man lost in a desert" – this leads not only to hypertonic dehydration but also to depletion of sodium (despite relative hypernatremia in the ECF there is !!!absolute hyponatremia!!! (= sodium depletion) because of sodium loss through highly concentrated urine due to action of ADH); when such a person is found, it is risky to attempt rehydration with pure water (hypotonic) without checking osmolarity or without simultaneous intake of sodium – a rapid decrease of osmolarity could cause generalized intracellular edemas (shift of water according to osmotic pressure to intracellular space)
  - including brain edema leading to intracranial hypertension and possible death due to herniation of the brain into the Foramen occipitale magnum - this is named as "poisoning by water"
  - "lost man on a sea" - leads to the same dehydration as mentioned above, but here there is tendency for people to drink hypertonic sea water (because of enormous thirst) - it still increases hyperosmolarity of plasma and ECF and leads to shift of water from ICF to ECF = exicosis - intracellular dehydration including brain cells → coma, death
- diabetic hyperglycemia (with itself partially increases osmolarity) → osmotic polyuria → increases osmolarity up to hyperosmolar coma (exicosis of brain cells)
- diabetes insipidus (deficiency of ADH) - enormous polyuria
- hyperaldosteronism, Cushing's sy
- administration of hypertonic infusions

Manifestations
- thirst, polydipsia, decreased urine output, fever, intracellular dehydration, shrinkage of brain cells, cerebral hemorrhage, confusion, coma

- Near drowning in sea water (hypertonic) is worse because of expansion of the aspired volume by fluid from alveolar capillaries (according to the osmotic gradient)

**Hypoosmolarity**

**Etiology**
- excessive pure water (hypotonic fluid) intake (in low kidney function or too quick - parenteral)
- SIADH sy (↑ ADH)
- hyponatremia (also after excessive diuretic therapy)

**Manifestations**
- intracellular edema, nausea, diarrhea
- depression, seizures, coma

**Edema**
- intracellular - due to the above specified changes in osmolarity
- extracellular (interstitial) - mechanisms:
  - increased filtration pressure
    - venostasis (generalized - right heart failure, local - thrombosis, thrombophlebitis, vein valves insufficiency)
    - hyperhydration (hyperaldosteronism)
    - prolonged standing (especially without motion)
  - decreased oncotic pressure (hypoproteinemia, hypoalbuminemia)
    - malnutrition, quashiorkor, malabsorption
    - proteinuria (nephrotic sy)
    - liver cirrhosis
    - loss of plasma
  - increased permeability of vessels
    - allergic reaction, inflammation, burns
    - acidosis!!!
    - heat stress
  - decreased lymphatic drainage
    - lymphadenitis
    - tumor infiltration of lymphatic nodes
    - loss of lymphatic vessels - postsurgical
  - female sexual hormones proportion → sodium retention
    - premenstrual edema, edemas in pregnancy
    - edemas in contraceptives (not so frequent in new variants)

Tendency to edema formation is dependent on quality of subdermal connective tissues - more frequent in old people.

Generalized massive edema = anasarca.

Ascites formation in liver cirrhosis precedes formation of generalized edemas because there is contributing increased hydrostatic pressure in the portal system.

**Differential diagnostics of edemas**
- right heart failure - about symmetric edemas in lower limbs in vertical position (toward evening), usually accompanied with dyspnea, gastrointestinal problems (nausea, loss of appetite)
renal edemas - mainly periorbital in the morning (lower GF during night), usually simultaneously hypertension
by liver cirrhosis or intra-abdominal tumors - after development of ascites

**Ascites**

**Etiology**
- liver cirrhosis
- right heart failure
- carcinomatosis, TBC, peritonitis
- acute pancreatitis, pancreatic tumors
- renal failure, nephrotic sy
- hypothyroidism - myxedema
- lymphatic obstructions

**Pathogenesis**
- increased hydrostatic pressure in the portal system
- decreased oncotic pressure and changed oncotic gradient (ascitic fluid is relatively rich for proteins)
- secondary hyperaldosteronism (activated RAAS due to loss of fluid to abdominal cavity and decreased metabolism of aldosterone in failing liver)
- after evacuation of ascites - new-formation!!! (repeated loss of fluid and proteins)
8. Hyponatremia, hypernatremia

- it is important to differentiate whether the change is relative (due to hyperhydration/dehydration) or absolute

**Hyponatremia** < 135 mmol/l

**Etiology**

- Excessive sodium losses
  - sweating (necessary to replace sodium not only water)
  - gastrointestinal losses (vomiting, diarrhea)
  - diuresis (with intensive diuretics or in deficiency of aldosterone)
- Sodium dilution
  - excessive administration of sodium-free parenteral solution
  - psychogenic polydypsia
  - ingestion of tap water during periods of sodium deficit
  - kidney failure (decreased glomerular filtration, without intake of salt)
  - increased ADH - trauma, stress, SIADH (syndrome of inappropriate ADH secretion)

**Signs and symptoms**

- decreased osmolarity (intracellular "fingerprint" edema)
- anorexia, nausea, vomiting, abdominal cramps, diarrhea
- hypovolemia, hypotension
- muscular jerks
- headache, mental depression, personality changes, seizures, lethargy, stupor, coma

**Hypernatremia** > 145 mmol/l

**Etiology**

- excessive sodium intake
  - rapid excessive administration (infusions) of sodium chloride
  - excessive oral intake
  - near-drowning in salt water
- decreased extracellular water
  - diuretic therapy
  - diabetes insipidus
  - osmotic diuresis (DM)
  - watery diarrhea
  - inability to drink, withholding of water for therapeutic reasons

Absolute hypernatremia with about normal osmolarity - aldosterone excess (e.g. in liver cirrhosis, left heart failure) → hyperhydration with edemas

**Signs and symptoms**

- thirst (in hyperosmolarity)
- shift of water from ICF → ECF - excisosis of cells → maniacal behaviour, coma, death
- signs as in intracellular dehydration due to hyperosmolarity of ECF (see above)
- accumulation of water in the body → edema
9. Hypokalemia, hyperkalemia

- potassium is mainly a weakly-hydrated intracellular ion - it prevents intracellular edema
- normal plasmatic concentration 3.8 - 5.1 mmol/l (ICF ca 160 mmol/l)
- regulated via aldosteron (↑ aldosteron eliminates K via urine)
- because there is exchange of K\(^+\) and H\(^+\) between ECF and ICF according to pH, acidosis increases kalemia
- anabolism increases influx of K\(^+\) into ICF (dependent on energy available for the Na\(^+\)/K\(^+\) pump)

**Hypokalemia**

**Etiology**
- inability to eat
- vomiting, diarrhea
- excessive renal losses - diuretic phase of renal failure, diuretic therapy (with exception of aldosterone antagonists)
- increased mineralocorticoids (also in Cushing's sy)
- intracellular shift of K\(^+\) in alkalosis or by infusions of glucose with insulin

**Signs and symptoms**
- muscle weakness, paralysis
- decreased tendon reflexes
- hypoventilation, respiratory distress
- postural hypotension
- low voltage T waves in ECG
- arrhythmias - up to cardiac arrest !!!
- anorexia, vomiting, abdominal distension, constipation up to paralytic ileus!!!
- shortness of breath - shallow breathing
- polyuria (due to hypokalemic tubular dysfunction), nocturia
- metabolic alkalosis
- decreased production of insulin and lower sensitivity to insulin
- confusion, depression, hallucinations
- Cushingoid appearance (eg. edema)

**Hyperkalemia**

**Etiology**
- excessive parenteral administration
- massive tissue trauma (crush sy), burns - release of intracellular K
- treatment with cytostatics (massive lysis of cells)
- acute renal failure (hyperkalemia is one of most important indicators for hemodialysis)
- adrenal insufficiency Addison's disease
- potassium sparing diuretics
- acidosis (distributive hyperkalemia - shift from ICF)

**Signs and symptoms**
- paresthesias, muscle cramps
- neurologic examination may reveal diminished deep tendon reflexes or decreased motor strength
- nausea, diarrhea, intestinal colic and GIT distress
- enlarged peaked T waves in ECG, cardiac arrhythmias up to CARDIAC ARREST!!!
- cardiac examination may reveal extrasystoles, pauses, or bradycardia.
10. Deficiency of trace elements – body dysfunctions

**Iron**
- content in the body - ca 5 g
- 70% in hemoglobin, 5% in myoglobin, 15-20% deposited in ferritin, hemosiderin, 0. 1% - in transferrin = transport form

**Etiology of deficiency**
- low intake (< 6 mg/day)
- decreased absorption - mainly due to defective reduction from Fe$^{3+}$ to Fe$^{2+}$ in abdominal hypoacidity (e.g. in chronic atrophic gastritis)
- higher losses - in women due to intensive menstrual bleeding, chronic occult bleeding to GIT

**Manifestations**
- hypochromic (sideropenic) microcytic anemia
- atrophy of mucous membranes in GIT
- gastritis
- trophic changes in skin and nails
- fatigue not only from anemia but also CNS induced, paresthesias

**Increased iron**
- due to increased intake and disorder of deposition mechanism - hemosiderosis (deposits in organs - see hemosiderosis of liver)

**Iodine**
- recommended daily intake ca 200 μg
- normal source - sea food, water
- in mountains - deficiency leading to "endemic goiter" (compensatory hypertrophy of the thyroid gland in decreased hormonal production due to iodine deficiency) - more details about hypothyroidism in "Thyroid gland disorders"
- supplementation of population with iodine in salt or water

**Copper**
- a component of a number of enzymes (oxidase cytochrome, amino oxidase, tyrosinase)
- high content in standard nutrition - deficiency does not exist
- 98% bound in ceruloplasmin - deficit of ceruloplasmin leads do deposits in tissues = Wilson's disease

**Zinc**
- present in enzymes (carbonic anhydrase, carboxypeptidase A and B, alcohol dehydrogenase)
- important for normal conformation of ribosomes, necessary for proteosynthesis

**Deficit**
- bound to non resorbable parts of nutrients
- losses during sweating
- in liver cirrhosis
- in chronic (repeated) infections

**Consequences**
- slowing of growth
- hypogonadism
- rough skin, disorders of nails and hair
- lethargy
**Chromium**
- forms complexes with -SH groups of the cell membrane and A chain of insulin
- increases function of insulin

**Selenium**
- endemic deficiencies - prevention via artificial supplementation of soil with selenium (in Scandinavia, as a part of carcinogenesis prevention)
- deficiency causes chronic fatigue syndrome
- increased supply recommended to sportsmen and people with increased psychic load

**Cobalt**
- component of some enzymes and vit. B12

**Fluorine**
- necessary for a normal quality of hard mineralized tissues
11. Disorders of Calcium, Phosphorus and Magnesium metabolism

Calcium
- total Calcium in plasma 2.25 - 2.75 mmol/l
- free ionized Calcium - ca 50% = 1.25 - 1.5 mmol/l - only free ionized calcium = unbound calcium ions have physiological functions!!!

- ionization depends on:
  - binding of calcium to albumins - hypoproteinemia can mask deficit of calcium, and after normalization of proteins there may be manifestation of hypocalcemia
  - pH of blood - alkalosis increases binding to albumins → ↓ ionized calcium with clinical manifestations (tetany)
  - quick compensation of acidosis → ↓ ionized calcium (must be checked and prevented in intensive care)
- concentration of intracellular calcium is 10,000 times lower (regulated by calmodulin) - increase is harmful - indicates aging of cells, leads to spasm in smooth muscle cells (arterioles - hypertension, bronchi - bronchospasm)
- intracellular Ca$^{2+}$ activates calcium sensitive proteases and NO synthase → formation of free oxygen radicals → oxidative stress - death of cells or genetic mutation

- NMDA receptors (N-methyl-D-aspartate) - their activation leads to increase of intracellular Ca$^{2+}$
  - activated by hypoxia - can be responsible for some hypoxic changes
  - probable role in some neurodegenerative diseases

Physiological role of Ca$^{2+}$
- in basic cellular mechanisms
  - influences permeability of membranes - changes membrane potential
  - increase of extracellular Ca$^{2+}$ decreases excitability = stabilization of membranes
  - decrease of Ca$^{2+}$ increases excitability of postsynaptic membrane - at neuro-muscular junction it leads to tetany (even at normal level of acetylcholine) - in the case of too low Ca$^{2+}$ there is no tetany but a decrease of contractility due to missing intracellular mechanism for interaction of the actin-myosin complex
- in heart function
  - increases contractility (besides Ca$^{2+}$ channels there is also output of Ca$^{2+}$ - in exchange for Na$^{+}$, dependent on the Na/K pump - cardiotonics increase intracellular Ca$^{2+}$ via blocking of this exchange
  - effect on automatic impulse formation and heart transmission system
  - influences endocrine and exocrine functions
  - enzymatic reactions - as co-factor, catalyst
  - increases concentration capacity of kidney
  - important role in hemocoagulation cascade
  - morphogenesis of bones and teeth

Regulation of extracellular Ca$^{2+}$
- recommended daily intake - ca 1 g (only about 30-50% is absorbed)
- elimination via proximal tubule - dependent on Na - diuretics increase loses of Na and Ca
- reabsorption in the distal tubule is dependent on parathormone (PTH)
- PTH increases reabsorption of Ca$^{2+}$ and increases losses of PO$_4^{3-}$
- Ca$^{2+}$ and PO$_4^{3-}$ - their total amount is constant - when one decreases the other increases to prevent precipitation of calcium phosphates - deposits in organs
- Effects of parathormone
  - increases resorption of Ca$^{2+}$ from bones (activates osteoclasts)
  - increases reabsorption of Ca$^{2+}$ from distal tubule
- increases absorption of Ca\(^{2+}\) from intestine - indirect effect (works via calcitriol = 1,25 dihydroxycholecalciferol formed from vitamin D3 - its second hydroxylation takes place in kidney under the influence of PTH)
- facilitates influx of Ca\(^{2+}\) into cells (calcium ionophor)

● **Effects of calcitonin**
- decreases calcemia via inhibition of osteoclasts
- not important in conditions of normal regulation via PTH
- negative influence in hyperproduction (tumors producing calcitonin)

**Hypocalcemia**

**Etiology**

● hypoparathyroidism
  - after goitre surgery
  - Di George sy (congenital aplasia of the parathyroid gland and thymus)
  - autoimmune PTH deficiency

● pseudohypoparathyroidism = Albright disease
  - resistance of bones and kidney (distal tubuli) to PTH

● renal diseases
  - decreased formation (hydroxylation) of calcitriol
  - decreased reabsorption of calcium
  - decreased elimination of phosphates → hypocalcemia

● deficiency of vitamin D3
  - malabsorption of fats and fat - soluble vitamins (biliary problems, chronic pancreatitis)
  - generalized malabsorption - chronic diarrhea, wide-spectrum ATB (dysmicrobia)

● hypomagnesiemia → ↓ PTH → hypocalcemia

● acute pancreatitis - binding of Ca\(^{2+}\) in necrotic lipid tissue - formation of soaps

● osteoblastic metastatic process in bones (incorporation of calcium)

● extreme secretion of calcitonin (medullary carcinoma of thyroid gland)

● substances binding calcium in blood - citrates
  - large transfusion!!!

● binding of calcium in gut - organic acids in vegetables - Phytic acid in spinach or oxalates

● alkalosis - e.g. respiratoriy alkalosis in hyperventilation

● hyperphosphatemia with precipitation of calcium phosphates
  - in renal failure
  - in lysis of cells (cytostatic therapy, crush sy)

● increase of free fatty acids which bind calcium - in stress, alcoholism (in sensitive people), acute pancreatitis

● in babies - after stop of breastfeeding – cow’s milk contains less calcium than mother’s milk

**Clinical manifestations of hypocalcemia**

- increased neuro-muscular irritability - TETANY = tonic spasm - no clonic phase as in epileptic jerks
- slow development of tetany - latent phase:
  - Chvostek's sign – tapping of zygoma activates facial nerve and produces asymmetric motoric activity in face (blinking, oral jerks)
  - Trousseau's sign - tonometer cuff on the arm (100 mm Hg) produces "obstetric's hand" - spasm of the fingers (N. medianus activity)

- hypocalcemia increases irritability of CNS - leads to centrally induced seizures (jerks)
- decreased contractility of myocardium
- disorders of hemocoagulation (only in very low calcemia)
- chronic hypocalcemia causes hypocalcemic cataract, dermatologic disorders, nail and hair changes
Acute treatment - intravenous calcium (!!strictly intravenous!!! -otherwise it causes tissue necrosis)
Chronic treatment - vit. D and causal therapy

**Hypercalcemia**

**Etiology**
- hyperparathyroidism - primary (adenoma of parathyroid glands), secondary (compensatory- e.g in calcitriol deficit = without increase of Ca)
- osteoclastic metastasis or tumors
- intoxication with vitamin D3 (in newborns – mothers overdose)
- milk-alkali sy - enormous intake of milk
- kidney disorders (low degradation of PTH or loss of renal secretion)
- immobolization - release of Ca\(^{2+}\) from bones
- aluminium osteopathy
- familia hypocalciuric hypercalcemia due to low elimination of calcium via kidney

**Clinical manifestations of hypercalcemia**
- increased muscular contractility
  ● heart
    - extrasystoles, arrythmia - over 4 mmol/l - stop of heart in systole
    - increased sensitivity to digitalis
  ● nervous system
    - decreased excitability
    - changes of consciousness
    - psychic changes
  ● GIT
    - nausea, constipation
  ● kidney
    - nephrocalcinosis → kidney failure
    - nephrolithiasis
  ● calcifications
    - cornea, conjunctiva

Therapy of hypercalcemia - diuretics or hemodialysis

**Phosphorus**

**Physiological role**
- \(\text{PO}_4^{3-}\) - intracellular ion (in ECF 0.7 -1.6 mmol/l)
- included in nucleic acids
- macroerogic substances - ATP, creatine phosphate
- in enzymes
- cAMP, cGMP
- intermediary substances - in glycolysis glc-6-P
- phospholipids in CNS
- pH buffer system in blood
- 80% in hydroxy apatite in bones
- daily intake ca 1.4 g

**Regulation of phosphatemia**
- PTH - increases elimination via kidney
- calcitriol increases absorption from gut
Hypophosphatemia  
**Etiology**
- Redistribution of phosphates into ICF during increased metabolic rate - in glucose infusions with insulin
- Losses via kidney
  - In increased secretion of PTH, calcitonin
  - Fanconi sy = "phosphate diabetes" - tubular disorder causing lower reabsorption of glucose, aminoacids, phosphates
  - Glucosuria, diuretics
- Deficiency of vit. D
- Use of antacids containing Al$_2$O$_3$ – Al binds phosphates in the gut, preventing their absorption
- Chronic alcoholism, malabsorption, malnutrition

**Manifestations**
- Muscular dysfunction due to decreased ATP → weakness of respiratory muscles → respiratory insufficiency
- ↓ 2,3-DPG - malfunction of erythrocytes
- Cardiomyopathy

Hyperphosphatemia  
**Etiology**
- Enormous intake in nutrition
- Therapeutic use - in laxative substances (against constipation)
- In GF decrease under ca 25 ml/min
- In hypoparathyroidism
- In massive lysis (damage) of cells (cytostatics, crush sy)

**Manifestations**
- Calcifications
- Possibility of secondary hypocalcemia

Magnesium  
**Physiological role**
- 0.7 mmol/l (plasma), 50% in ICF, 50% in bones
- Competition with calcium in absorption from gut - supplementation in deficiency should be separate from calcium
- Competition in plasma protein binding

Hypomagnesemia  
**Etiology**
- In hypocalcemia reabsorption of magnesium in kidney decreases
- Usually simultaneously with hypocalcemia
- Decreased intake via nutrition, malabsorption
- In diuretic therapy
- Chronic alcoholism
- Intracellular input - in insulin therapy
- Acute pancreatitis (formation of soaps)

**Manifestations**
- CNS and senses
- memory disorders, decreased mental functions
- headache, dizziness
- depression, anxiety
- hallucination, hearing disorders

- cardio-vascular problems
  - stenocardia, anginal pain
  - tachycardia, extrasystoles
  - increased thrombogenesis

- muscular problems - cramps - similar to tetany, paresthesias in limbs

- bronchospasms

- GIT - diffuse abdominal pain, nausea, pylorospasm

**Hypermagnesemia**
- in increased intake of magnesium or in ↓ of GF under 30 ml/min
- cause decrease of neuro-muscular excitability → hyporeflexia, up to stop of breathing
- nausea and constipation
- very individual symptomatology
12. Metabolic osteopathy

**Osteoporosis**
- atrophy of bones without change in proportion of organic/inorganic bone components

**Etiology**
- primary insufficiency of osteoblasts (idiopathic) = Osteogenesis imperfecta
- immobilization, longer state without gravity effect (space - astronauts)
- iatrogenic affect of glucocorticoid therapy (or thyroid gland hormones) - catabolism of proteins
- liver disorders or chronic renal insufficiency (uremia)
- hyperparathyreoidism
- myeloma
- decrease of stimulation effect of sexual hormones - after castration, in menopause (in women increasing incidence because of simultaneous missing effect of physical activity in modern style of life - fitness center twice a week is not sufficient)
- decrease of blood perfusion or loss of innervation
- senile osteoporosis after about 60 years - irrespective of gender
- causes pathological fractures

**Osteomalacia**
- insufficient mineralisation of bones - in children = “rachitis”- deformities of bones (genua vara)
- in calcium and phosphate deficiency
- in increased PTH
- in negative balance of Ca^{2+} (malnutrition, pregnancy, breast feeding etc.)
- important role of vitamin D (routine supplementation in infants - possibility of overdosing - hypervitaminosis D causes calcifications)
- in Fanconi sy ("phosphate diabetes" = "vitamin D resistant rachitis")
- in chronic hemodialytic programme - intoxication with aluminium
- cause fractures, deformities of bones

**Renal osteopathy/osteodystrophy = "uremic bone syndrome"**
- osteomalacia due to decreased formation of calcitriol in disorders of kidney parenchyma
- osteodystrophy due to secondary ↑ PTH - low degradation (metabolism) in kidney and its compensatory increase in hypocalcemia
- PTH causes resorption of bones in the form of small cavities (holes) - later filled by granulomatous tissue (visible in X-ray specific pictures) = "osteosclerosis"
- level of calcemia in chronic renal failure can vary according to prevailing mechanism (hypo-normo-hypercalcemia); hypercalcemia is also possible in chronic hemodialytic program with “hard water” used for dialysate preparation
- pathological fractures
13. Tetany, pathophysiology of cramps

Tetany = tonic cramps - spasm without a relaxing (clonic) phase
Clonic cramps - rhythmic jerks
Tonic-clonic cramps in epileptic seizures

Cramps - causes:
- muscular fatigue - after long lasting physical activity - typically combined with mineral
dysbalance
- venous thrombosis, varicose sy
- changes of membrane potential due to mineral disorders - hyperkalemia
- eclampsia (gestosis in pregnancy)
  ● central (CNS induced) cramps
    - in CNS hypoxia
    - in meningitis, encephalitis
    - tetanus - Clostridium tetani - (typical cramps - opisthotonus, risus sardonicus, trismus) -
      hyperpyrexia, respiratory insufficiency, fractures of bones
    - Rabies (madness, hydrophobia) - cramps of respiratory muscles, laryngospasm → death
    - in phenylketonuria
    - hypertensive encephalopathy
    - febrile cramps - mainly in small children over 39°C, more frequent in boys
    - hypoglycemia below 2.2 mmol/l
    - intoxication -Pb, CO, alcohol, chloroform)
    - idiopathic neurogenic - in emotions, psychic stress
    - Epilepsy

Hypocalcemic tetany
- most quick development in respiratory alkalosis due to hyperventilation (in emotions,
hysteria)
- important to recognize latent phase without developed manifestations - according to positive
  Chvostek's and Trousseau's signs
- treatment - 10% Calcium chloratum

Hypomagnesiemic tetany
- similar development like in hypocalcemic tetany

Neurogenic tetany
- subarachnoidal bleeding (opisthotonus)
- intracranial hypertension - central spastic paresis (tetany is not appropriate term)
14. Acidosis

Acid base balance
= homeostasis of H+ ions in body fluids

Acids: Volatile acids - can change to gas - CO2 - excretion by lungs
Non-volatile acids - all other - metabolic elimination or excretion by kidneys
Daily production - 15,000 mmol of volatile acids + 3,700 mmol of non-volatile acids

The response to an acid-base challenge has three components:
1) Buffering:
ECF - predominantly HCO3-/CO2 buffer system
ICF - the major buffers are proteins and PO4
Buffering reactions are instantaneous and extremely effective.
2) Compensation: Respiratory disorders evoke a compensatory renal response which will tend to correct the pH back towards normal; metabolic disorders are compensated by respiratory mechanisms.
3) Correction: In metabolic acidosis or alkalosis the kidney can increase net acid or base excretion to correct the primary abnormality. Respiratory disorders have to be corrected by normalizing lung function and ventilation.

Timing of ECF pH regulation
- Plasmatic buffers - immediate transient effect (sec)
- Lungs - respiration (min)
- Kidney - urine (24 hours - days)

Role of lungs in acid-base regulation
- high PaCO2 causes hyperventilation
- low PaCO2 causes hypoventilation

Role of kidney in acid-base balance
- reabsorption of HCO3- - proximal tubulus
- „new“ HCO3- formation – collecting tubulus
- secretion of H+ - collecting tubulus
- excretion of H+ - free (very little, but causes pH up to 4) - buffered by „titrable“ acids or ammonium

Diagnosis of acid-base disorders
1) Measurement of pH4 and PaCO2
   Interpretation - Acid–base diagram (nomogram) = dependence of pH on PaCO2
2) Measurement of blood HCO3-
   estimation of Standard base, Base excess
   Standard bicarbonate = plasmatic HCO3- when the blood has normal PaCO2 of 40 mmHg
   Base deficit = amount of alkali in mmol required to restore the pH of 1 L of blood in vitro to normal at PaCO2 of 40 mmHg
   Base excess = amount of acids in mmol required to restore the pH of 1 L of blood in vitro to normal at PaCO2 of 40 mmHg
3) Blood concentration of Na+, K+, Cl- and subsequent counting of anion gap
   Sum of cations (Na+ + K+) normally exceeds that of anions by about 14 mmol/L (10 to 18 mmol/L) = „anion gap (AG)“, AG = [Na+ + K+] - [Cl- + HCO3-]
   reflects difference between unmeasured cations (Mg++, Ca++) and unmeasured anions (proteins, organic acids, phosphate, sulphate)
Acidosis
- metabolic
- respiratory

Metabolic acidosis
= Deficit of HCO₃⁻
HCO₃⁻ < 22 mmol/L, pH < 7.35

Basic causes:
• loss of bicarbonates
• gain of fixed (non-carbonic) acids
• failure of kidneys to excrete the daily acid load

1) Metabolic acidosis with normal anion gap
results from direct loss of HCO₃⁻:
- through the intestines (e.g. diarrhea, pancreatic fistulae)
- through the kidney - e.g. Proximal renal tubular acidosis, Acetazolamide therapy (= carbonic anhydrase inhibitor)
- loss of HCO₃⁻ → more Cl⁻ is retained (in renal tubules, to keep electroneutrality) → low plasma HCO₃⁻ is accompanied by hyperchloraemia, AG = unaltered

2) Metabolic acidosis with high anion gap
arises from ingestion or endogenous generation of acids (usually organic), whose anions are not routinely measured

Etiology:
- ketoacidosis (diabetes mellitus, starvation)
- lactic acidosis (e.g. severe hypoxia, circulatory shock)
- uremic acidosis
- poisoning by salicylates

Plasma HCO₃⁻ is titrated, AG = widened by unmeasured anions

Compensatory response in metabolic acidosis:
• Buffering
- plasma HCO₃⁻
  - excess H⁺ also enters cells - buffering by proteins + phosphates
  H⁺ entry to IC means K⁺ efflux from IC → hyperkalemia
• Respiratory response - min
  - H⁺ stimulates central chemoreceptors → hyperventilation → ↓ pCO₂
• Renal compensation - slow, but final solution
  - H⁺ is secreted to tubuli and excreted as NH₄ or titratable acid - H₃PO₄
  - increased secretion of NH₄ → ↑ HCO₃⁻ reabsorption
  - H₃PO₄ excretion → new HCO₃⁻ formation
• Bone buffering – mainly in chronic kidney disorders
  - breakdown of hydroxyapatite crystals – release of calcium carbonate
  - → release of Ca from bones – osteomalacia (non-dependent on parathormone)

Clinical features
- Vague signs up to level of serum HCO₃⁻ below 15 mmol/L
- Hyperventilation - Kussmaul's breathing - direct effect of H+ on respiratory center in oblongate medulla
- cardiovascular dysfunction - negative effect on inotropic function
  + decreased sensitivity to catecholamines
  + peripheral vasodilation (due to lactacidosis)
- Neurologic - less pronounced than in respiratory acidosis (lipid-soluble CO₂ enters via blood brain barrier more rapidly than water soluble HCO₃⁻), depression of CNS - lethargy up to coma
- Metabolic - glycolysis is inhibited by acidosis (↓ phosphofructokinase, a rate-limiting enzyme of glycolysis), hepatic gluconeogenesis from lactate is inhibited = responsible for perpetuating and worsening lactic acidosis
- DECOMPENSATED SEVERE ACIDOSIS CAUSES VASODILATION OF PERIPHERAL VESSELS AND THEIR INCREASED PERMEABILITY → HYPOTENSION AND EDEMA FORMATION = COMBINED DISTRIBUTIVE AND HYPOVOLEMIC CIRCULATORY SHOCK
- THE SAME MECHANISM CAUSES BRAIN EDEMA → INTRACRANIAL HYPERTENSION → "CONUS OCCIPITALIS" → DEATH

**Respiratory Acidosis**
Primary rise in pCO₂ (hypercapnia) results in pH decrease
PaCO₂ > 45 mmHg, pH < 7.35, HCO₃⁻ slightly rises (but this can not be used for buffering) primary cause = alveolar hypoventilation: causes first hypoxaemia (low pO₂ - because of lower diffusion coeff. of O₂) → anaerobic metabolism ⇒ lactic acid - metabolic acidosis!!!, only later retention of CO₂ = respiratory acidosis
- acute - before visible effect of renal compensation
- chronic - with renal compensation

**Etiology**
- Acute upper airway obstruction
  - aspiration of foreign body or vomiting
  - laryngospasm or laryngeal edema
- Inhibition of the brain stem respiratory center
  - drugs: opiate, sedatives
  - oxygen therapy in chronic hypercapnia
  - sleep apnea
- Disorders of respiratory muscles + chest wall
  - neuromuscular disease – e.g. myasthenia gravis
  - chest wall injury
- Disorders of gas exchange
  - pulmonary diseases when causing hypercapnia

**Compensatory mechanisms**
Acute respiratory acidosis: - only cellular buffering! - not sufficient!
(ECF buffering is not active because increased H₂CO₃ is a member of the main buffer system)
Chronic respiratory acidosis - well compensated - nearly normal pH
  kidneys increase excretion of H⁺ + resorption of HCO₃⁻

**Clinical features**
clinical signs are more attributable to hypoxemia
chronic state is better tolerated than the acute one
similar to metabolic acidosis
- high pCO₂ - brain vessel dilatation, vascular congestion → intracranial hypertension
- chronic CO₂ retention - direct depression of respiratory center
  - respiratory response to pCO₂ increments becomes progressively lost
  - ventilation is dependent upon hypoxic drive

**Treatment**
- restoration of effective ventilation
- oxygenotherapy - safe in acute acidosis patients, dangerous in chronic (removal of hypoxic drive for ventilation)
- treatment of underlying course
15. Alkalosis

- metabolic
- respiratory

**Metabolic alkalosis**

= HCO₃⁻ excess
ECF HCO₃⁻ > 26 mmol/L, pH > 7.45
Rare, since renal bicarbonate excretion is normally very efficient

Factors stimulating HCO₃⁻ reabsorption despite of presence of alkalosis:
- EC volume depletion
- K⁺ deficiency
- mineralocorticoid excess
- thiazide and loop diuretics

**Causes:**
• Loss of net H⁺
  - Gastrointestinal: vomiting
  - Renal loss
    - Mineral corticoid excess (Cushing’s, Conn’s sy)
    - Diuretic therapy (not K⁺ sparing)
  - H⁺ movement into cells in hypokalaemia
• Retention of HCO₃⁻
  - Administration of alkali - Milk-alkali sy (antacids, milk), high intake of bicarbonate

**Hypochloremic metabolic alkalosis** — e.g. vomiting
Cl⁻ and HCO₃⁻ - reciprocal relationship (for maintenance of electroneutrality)
HCl is secreted into stomach ⇒ HCO₃⁻ is secreted into ECF
metabolic alkalosis - loss of HCl + water ⇒ increase of HCO₃⁻

**Compensation**
1) IC buffering – H⁺ exits cells, K⁺ moves in ⇒ hypokalemia
2) Respiratory
   increased pH is detected by chemoreceptors ⇒ hypoventilation (limited by oxygen need)
3) Renal - excretion of base excess (difficult in hypochloremic alkalosis!!! - because the primary regulation is electrical balance, not pH)

**Difficulties with alkalosis compensation**
Chloride depletion disables HCO₃⁻ excretion (again because of electric balance) - maintains alkalosis!!!
Volume depletion (due to vomiting) stimulates renin-angiotensin-aldosterone system (ECF volume protection is prior to pH protection!!!) ⇒ Na⁺ + water reabsorption
⇒ HCO₃⁻ reabsorption (HCO₃⁻ follows Na⁺) ⇒ further ↑ base excess
⇒ H⁺ secretion into urine (stimulated by aldosterone!!!) ⇒ acidotic urine!, contributes to pH increase in ECF
+ K⁺ is excreted ⇒ hypokalaemia

**Clinical features**
- cardiac dysrrhythmias – in severe alkalosis > 7.6 (due to hypokalemia)
- hyperexcitability of nervous system – tetany (directly ↑ neuromuscular irritability), + less Ca⁺ is ionized - it binds to albumins

**Treatment**
- Chloride responsive metabolic alkalosis - usually connected with ECF volume contraction (Vomiting, Nasogastric suction, Diuretics) - supply of Cl⁻ enables HCO₃⁻ excretion, solved by replacement of volume deficit + KCl
- Chloride-resistant metabolic alkalosis - usually not connected with volume contraction - mineralocorticoid excess (leading to losses of H⁺)- e.g. in edematous states (congestive heart failure, nephrotic sy, cirrhosis) - treatment is based on causal therapy of the primary disorder!!!

**Respiratory alkalosis**
= HCO₃⁻ deficit due to decrease of pCO₂ (hypokapnia) results in pH increase
\[
pCO₂ < 35 \text{ mmHg, } pH > 7.45
\]

**Etiology:**
- Central stimulation of respiration
  - Psychogenic hyperventilation caused by emotional stress
  - Hypermetabolic states – thyreotoxicosis, fever – eg. Gram-negative sepsis
  - Head trauma, brain tu
- Hypoxia = stimulus for hyperventilation ⇒ hypokapnia
  - High altitude
  - Pulmonary diseases at the stage of hypoxia but not hypercapnia (partial respiratory insufficiency - see below)
- Excessive mechanical ventilation

**Compensation:**
**Acute phase**
- ICF buffering - H⁺ is released from tissue cells
- little ECF buffering
**Chronic phase**
- Renal tubular reabsorption and production of HCO₃⁻ is inhibited - this develops in about 24 hours after onset

**Clinical features**
- dizziness
- circumoral paresthesia
- tetany in severe alkalosis
- inability to concentrate, tiredness, palpitations, anxiety

**Treatment**
- the only possibility - treatment of underlying cause
- in artificial ventilation - adequate settings are necessary
- in emotional attack - plastic bag

**Mixed pH dysbalances**
Two or more primary disorders can coexist, they occur in complex medical problems

A) With additive effect on pH
- metabolic acidosis + respiratory acidosis
- metabolic alkalosis + respiratory alkalosis
B) Without additive effect on pH (resulting pH can be about normal)
metabolic acidosis + respiratory alkalosis
metabolic alkalosis + respiratory acidosis

Examples of mixed pH disorders
• global respiratory failure and heart failure
  \[\text{→ respiratory + metabolic acidosis}\]
• septic shock
  \[\text{→ respiratory alkalosis (due to hyperventilation in extreme fever) + metabolic acidosis (due to hypoperfusion in periphery)}\]
• chronic obstructive lung disease + vomiting
  \[\text{→ respiratory acidosis + metabolic alkalosis}\]
• hysteria + vomiting
  \[\text{→ respiratory + metabolic alkalosis}\]
16. Disorders of peripheral circulation

- blood flow depends (according to Poiseuille's law) on the fourth power of the vessel radius - any change of radius has significant effect on the blood flow and blood pressure
- main factors influencing peripheral blood flow: tonus of the sympathetic system (level of catecholamines) together with α and β-adrenergic receptor distribution, intracellular (smooth muscle cell) concentration of Ca\(^{2+}\) ions, endothelial NO and endothelin formation (see separate chapter), effects of vasoactive substances (e.g. inflammatory mediators)
- effect of blood viscosity
- "critical closing pressure" = pressure at which blood vessels collapse and the blood flow in a particular organ stops

Peripheral blood flow alterations
- increase of blood flow = hyperemia
- decrease of blood flow = hypoperfusion, ischemia
  - systemic - decrease of circulating volume, pressure
  - local - vessel obstruction (structural changes – atherosclerosis, inflammation, thrombus, embolus), vasospasm

Hyperemia
- active hyperemia - ↑ blood influx - effect of vasodilators (histamine, bradykinin, PGE, NO, CO\(_2\))
  - reactive – after transient vessel occlusion
  - functional – necessary for increased function (thermoregulation – hypothalamus, muscles in exertion - beta2 effect of epinephrine)
- passive hyperemia – blood stagnation – congestion (e.g. venous insufficiency (legs), generalized – right heart failure)

Vasospasm
- Raynaud phenomenon (syndrome) – 4-times more frequent in women
  - attacks of vasospasm (mainly in fingers of hands)
  - usually reaction to cold, high-frequency vibrations - vibrating tools (↑ tonus of sympathetic nervous system, ↑ number of α receptors) → whitening of fingers (nose), pain (later reactive hyperemia - blush)
  - frequently accompanies autoimmune diseases – SLE, scleroderma

Diseases of peripheral arteries
Acute obturation of artery ⇒ ischemia, infarction (thrombus or embolus usually from heart)
Chronic obturation of arteries
- Arteriosclerosis
- Diabetic macro- and microangiopathy
  - acceleration of AS, ↑ protein glycation
- Thrombangitis obliterans (Buerger’s disease) – mainly in 20-40 years of age
  - not clear etiology but exposure to tobacco is essential for both initiation and progression of the disease
  - in some cases inflammation of the arterial wall + event. thrombi (possible reaction to circulating immune complexes)
  - vasospasm due to increased sympathetic tonus

Clinical manifestations:
- smaller arteries – esp. plantar and leg (calf)
- early phase – intermittent claudicatio (limp) because of ischemic muscle pain, weakness, ↑ sensitivity to cold
- later ulceration, gangrene

● Thrombosis - arterial or venous occlusion, coronary arteries
- Virchow's triad
  1) stasis or turbulence of blood
  2) increased blood coagulability (see thrombogenesis)
  3) endothelial injury
- Venous thrombosis – phlebothrombosis
  superficial system – does not result in pulmonary emboli
  deep system – (deep vein thrombosis) - can result in pulmonary emboli!!!

Embolism
- 99% - thrombi = thrombemboli
- systemic or pulmonary circulation
- rare – fat (mechanical + biochemical consequences)
- bubbles of air or nitrogen
- atherosclerotic debris (cholesterol emboli)
- tu fragments
- amniotic fluid

Factors that influence development of infarction
development of infarction depends on:
- duration of occlusion
- velocity of obturation
- properties of vessel system - existence of collaterals, double vessel system – functional and nutritive (lungs, liver), terminal artery → infarction
- sensitivity of the tissue to hypoxia (neurons -3 – 4 min, cardiomyocyte - 20 min)
- oxygen content of blood

Infarction
anaerobic glycolysis – lactic acid - acidosis
shortage of ATP → disorder of active ion transmission → intracellular edema, activation of enzymes – damage to cells

Systemic hypotension – decreases local perfusion according to characteristics of the capillary net
- acute or chronic
- low heart output or low peripheral resistance
- dominant is usually shortage of O₂ in the brain
17. Circulatory Collapse, Syncope

= transitory loss of consciousness
- cessation of cerebral perfusion lasting only 3-5 seconds results in severe brain dysfunction

Note that European pathophysiology differentiates "collapse" (peripheral syncope), caused by decreased preload, and "syncope" (central syncope), caused by transient decrease of the heart MV. In contrast, English/American textbooks use the term “syncope” to denote any short unconsciousness due to hypoperfusion of the brain in decreased blood pressure.

Syncope – central
- cardiac – e.g. bradykardia, exertion in subjects with aortic stenosis
- hyperactivity of parasympathetic system – e.g. sy of carotid sinus, emotional activation via limbic system - influences hypothalamus
- agents that affect cardiac output (eg, beta-blockers, digitalis, antiarrhythmics)
- patients with a history of myocardial infarction (MI), arrhythmia, structural cardiac defects, cardiomyopathies, or chronic heart failure

Collapse – peripheral
- transient decrease of venous blood return (decreased preload) due to peripheral vasodilation or increased intrathoracic pressure → decreased cardiac output, hypotension
- predisposed are old people, dehydrated subjects, patients treated with antihypertensives

Causes:
- hot environment - thermoregulatory reaction lead to vasodilation
- orthostatic (postural) collapse - more frequent in old people due to delayed (decreased) orthostatic reflex keeping roughly constant blood pressure at the level of the brain during changes of body position (senile degeneration of the vegetative nervous system, decreased baroreceptor responsiveness) and in diabetic people (due to peripheral neuropathy involving also the sympathetic system)
- ↑ intrathoracic or intra-abdominal pressure - Valsalva maneuver, coughing, difficult defecation (in constipation), miction (hypertrophy of prostate)
- hypoactivity of the sympathetic nervous system in peripheral polyneuropathies – e.g. diabetes mellitus
- agents that reduce blood pressure (eg, antihypertensive drugs, diuretics, nitrates)

Causes of any short unconsciousness should be verified. It can indicate severe heart or circulatory problems. However it can happen also in young and completely healthy subjects (dehydration, heat stress, emotions etc.)
18. Circulatory shock

Circulatory shock is a failure of the circulatory system (longer than syncope or collapse) with decreased peripheral perfusion and inadequate oxygenation of organs and tissues (usually not spontaneously recovering). It can occur in the course of many life-threatening, traumatic or disease states.

Types:

**Hypovolemic shock**
- ↓ volume - low venous blood return - low „preload“
- bleeding - loss of more than 20 – 30% of blood
- burns, loss of isotonic fluid
- dehydration = hemoconcentration (↑ Ht) - ↑ viscosity – worsens

**Cardiogenic shock**
- Due to any critical decrease of MV
  - infarction (in case of large involvement > 40% of LV myocardium), cardiomyopathy
  - rhythm changes – blocs, severe bradycardia, tachycardia
  - mechanical – papillary muscle defects, ventricular aneurysm, ventricular septal defect
  - obstructive shock - pneumothorax, heart tamponade

**Distributive shock**
- normal volume, severe generalized vasodilation
  - Anaphylactic shock
    - Antigen antibody complex - activation of complement, kinins, histamine
    - vasodilation
    - increased permeability
    - bronchoconstriction
  - Neurogenic shock
    - e.g. transversal lesion of spinal cord – loss of sympathetic inervation (severity dependent on the level of transsection)
  - Septic shock
    - endotoxin (released from Gram- bacteria by macrophages, complement) → activation of interleukins, TNFα - pyrogen effect + activation of complement, prostaglandins, leukotrienes - ↑ permeability – capillary leakage sy, platelet activation f. → DIC, ARDS
    - NO → vasodilation

Pathogenesis - phases of shock
- development of severe hypotension due to a specific condition
  1) compensated (non-progressive) phase
  2) decompensated (progressive) phase
  3) irreversible (refractory) phase

1) compensated (non-progressive phase) – leads to activation of the following compensatory mechanisms
- hypotension activates baroreceptors, chemoreceptors → activation of sympatho-adrenal axis (endogenous stress reaction) → positive effect on heart activity + vasoconstriction in periphery and splanchnic area (centralization of circulation) + respiratory effect (bronchodilation) – this tries to improve oxygenation of vital organs
- activation of RAAS due to renal hypoperfusion + increased ADH tries to increase circulating volume
These mechanisms can be effective in hypovolemic and distributive shock (via compensation of volume or blood pressure) but they are disadvantageous in cardiogenic shock where increased afterload (blood pressure) and preload (circulating volume) lead to earlier heart failure (because of ↑ demands on myocardium) – thus it is necessary to block these compensatory systems!!!

2) decompensated (progressive) phase
- prolonged centralization of circulation → hypoperfusion of peripheral tissues and splanchnic area → hypoxia → anaerobic metabolism → lactic acidosis (+ accumulated CO₂) → forced vasodilation (now prevailing over the former tendency to vasoconstriction) → blood pressure decrease and generalized edema formation (further decrease of circulating volume)
- ischemic damage of cells e.g.:
  - proximal tubulus → acute tubular necrosis (can lead to severe polyuria after eventual recovery from shock)
  - necrosis of the wall of intestines → escape of bacteria → peritonitis
  - pancreas – production of myocardium inhibiting factor (MIF)
  - release of substances from necrotic cells - proteolytic enzymes, myocardium inhibiting factor, tissue thromboplastin → disseminated intravascular coagulation (microthrombi)
- reperfusion tissue damage – oxygen free- radical production (in the case of at least partial reperfusion) → damage to endothelium → leak of fluid + proteins – contributes to general edema formation (including brain edema) = TOTAL FAILURE OF CIRCULATION = IRREVERSIBLE SHOCK

Possible prevention of irreversible shock changes = early volume replacement with volume-expanders:
- hypertonic solutions (3-7.5% NaCl) → shift of water from ICF to ECF, increases ADH production – relatively short term effect
- colloid solutions (albumin, artificial albumins, dextran, hydroxyethyl starch) – danger – decrease of GF
- advantageous combination of both (7% NaCl + 6% dextran)

Impairment of cellular metabolism by shock
- decreased ATP production → decreased activity of Na/K pump → intracellular Na + water = cellular edema + release of lysosomal enzymes

DEVELOPMENT OF MULTIPLE ORGAN DYSFUNCTION SYNDROME (MODS) – e.g. KIDNEY, LUNGS
19. Pathophysiology of inflammation, sepsis

Inflammation is a reaction of living tissues to all kinds of injury. Despite undesirable effects (pain, edema, crippling effects) it is a beneficial reaction trying to eliminate causes (e.g. infection, exposure to poison) with local processes avoiding a spread of the harmful agents. The failure of a local anti-infectious inflammatory reaction (due to low immunity or very virulent infection) generalized sepsis develops.

Agents causing inflammation
- exogenous - e.g. trauma, surgery, infection, chemicals, extremes of heat and cold, irradiation
- endogenous - e.g. ischemia, immune responses

Manifestations (according to Celsus and Galen)
Local:
- rubor (redness) - caused by active hyperemia after momentary vasoconstriction due to stress reaction (catecholamines) related e.g to pain (injury) - dependent on vasoactive inflammatory mediators, in the developed (end stage) inflammation hypoperfusion of the inflamed area can appear due to micro-thrombosis of vessels
- hyperemia increases delivery (supply) of cells (leukocytes) to the place of inflammation
- calor (heat) - ↑ temperature of the inflamed area due to hyperemia and increased metabolism
- tumor (edema) - develops because of increased hydrostatic pressure and increased permeability of vessels (caused by inflammatory mediators -see below); besides transudation into the interstitium, active exudative (secretion) processes also take place (peritoneal cavity, pericardium, pleural cavity)
edema decreases the concentration of toxins, which can prevent necrosis of cells, edema helps also to local leucocyte reactions
- dolor - caused by:
  - irritation of free neural endings by inflam. mediators - mainly prostaglandins, substance P, bradykinin
  - compression of nerves by edema
  - developing acidosis in the case of thrombosis of vessels (in developed, chronic inflam. process)
  - pain is an important informative factor (especially in the case of hidden inflam.
    processes – such as intra-abdominal inflam . - acute appendicitis etc.), it is recommended to eliminate pain (to give analgesics) only in cases where the cause of pain is well known
  - pain also prevents damage by overloading (using) the inflamed part of the body
- functio laesa (malfuctioning) - caused by pain and edema - disabling mainly motion - prevents overload of the involved parts of the body

General manifestations:
- fever - caused by activation by pyrogens (IL-1, IL-6, TNF ...) of the thermoregulatory center (hypothalamus)
- leukocytosis - increased number of leukocytes released from bone marrow (over 10.000/mm³), enormous increase in some childhood viral infections
- changes in the differential count: bacterial infections - ↑ neutrophils, viral infections - ↑ lymphocytes, allergies and parasites - ↑ eosinophils
- decreased Hynek's number (number of segments in neutrophils) = "shift to the left" in prolonged (large) inflammations, extreme "shift to the left" with appearance of non-mature leukocytes in the peripheral blood = "leukemoid reaction"
- leukocytosis is a very non-specific but important sign (e.g. in suspected appendicitis)
- increased FW (sedimentation of erythrocytes) - non-specific sign pointing to inflammation
- lymphadenitis - enlargement of lymphatic nodes

**Acute inflammation**

- reaction of vessels
  - active hyperemia, tendency to stasis of blood
  - increased permeability for both plasma and cells
- reaction of cells
  - attraction of leukocytes to the place of inflammation - opsonisation (IgG, C3b fragment of complement)
  - margination of leukocytes and emigration (via diapedesis), chemotaxis, phagocytosis (destruction of pathogens - pH, enzymes - e.g. myeloperoxidasis)

**Neutrophils (polymorphonuclears)**
- the first cells at the place of inflammation (within 90 min. after onset) with maximum phagocytic capacity in acute inflammations (60 - 70% of all leukocytes)
- survival - only about 10 hours (must be steadily replaced from bone marrow 1 - 2 days
- dominate in bacterial infections

**Monocytes (macrophages, histiocytes)**
- after several days but dominate in chronic inflammations
- formation of lysosomal enzymes

**Lymphocytes**
- mainly in viral inflammations

**Basophils**
- in stress reactions
- production of heparin, histamine

**Eosinophils**
- allergies, reaction to chemical injury

**Inflammatory mediators**

- Vasoactive (dilating)
  - histamine (increases permeability - causes edemas - mainly in allergic reactions)
  - PGE (can be blocked by inhibition of cyclooxygenasisis by non-steroid anti-inflammatory drugs - e.g. Acetylsalicylic acid; availability of Arachidonic acid (the substrate) is blocked by glucocorticoids)
  - bradykinin
  - leukotrienes
  - platelet activating factor (PAF)
- Pain mediators
  - prostaglandins (PG), substance P, bradykinin
- Edogenous pyrogens
  - IL-1, TNF

**Types of inflammation according to the type of exudate:**

- erythema - no exudate, only redness (exposure to sunshine, light frost-bite)
- serous - watery character of exudate, low content of proteins, catarrhal inflam. with no complications - e.g. "hay fever"
- fibrinous - high content of fibrin - leads to formation of adhesions - prevent spread of inflammation (helpful e.g. in peritoneal cavity) but can cause complications - constrictive pericarditis
- membranous - e.g. on the surface of trachea in Diphtheria or in Membranous enterocolitis - causes obstruction
- purulent - includes pus (tissue debris, necrotic leukocytes)
- abscesses - encapsulated purulent exudate with pyogenic membrane
- sanguineous (hemorrhagic) - including blood (damage of blood vessels, diapedesis of erythrocytes)

Resolution of acute inflammation
1. it can undergo full resolution (healing "ad integrum")
2. it can progress - suppurative process
3. can proceed to the chronic phase

**Chronic inflammation**
- either primary chronic character or transfer to chronicity
- due to long lasting exposure to some pathologic agent (smoking - chronic bronchitis)
- autoimmune diseases (Rheumatoid arthritis)

**Influencing factors**
- early application of cold can limit or postpone development of inflammation (via vasoconstrictive - anti-edematous effect)
- application of warm can accelerate development of inflammation
- application of glucocorticoids - most potent anti-inflammatory effect (detailed description of glucocorticoid effects - see stress - general adaptation sy)

Complications of inflammation
- bacteriemia (can make colonies - e.g. infective endocarditis) - typically asymptomatic - without manifestations of inflammation and activation of the immune system
- pyemia -spread of infected thrombi - formation of abscesses in obstructed small vessels

**Sepsis**
- bacterial growth in blood when immune system was not able to liquidate the infection
- systemic inflammatory response to infection (leukocytosis, fever), release of endo- and exotoxins
- danger of SEPTIC SHOCK (systemic reaction of circulation - vasodilation, increased permeability → hypotension, edemas

**Causes** - peritonitis, criminal abortions, infections of urinary system, phlegmones

**Manifestations**
- intermittent fever, increased metabolism with higher oxygen consumption - hyperventilation (respiratory alkalosis can develop)
- tachycardia - heart overload
- fatigue, lethargy
- leukocytosis - possible "leukemoid reaction", splenomegaly
- catabolic state, proteinuria
- dehydration, hypovolemia, hypotension → centralisation of circulation → failure of thermoregulation
- peripheral hypoxia → anaerobic metabolism → lactic acidosis starts to dominate (over the former respiratory alkalosis) → increased formation of edemas including brain edema → coma, death
- possible DIC (disseminated intravascular coagulation) with subsequent consummational coagulopathy (see Bleeding disorders)
- multiorgan dysfunction (ARDS, shock kidney - proteinuria, CNS failure)
- hyperglycemia in diabetics
20. Pathophysiology of pain

Definitions of pain and its significance:
- Pain = unpleasant sensory and emotional experience connected with real or potential tissue damage, or described in these terms (IASP, 1990)
- Causes reactions directed to removal of pain stimuli (unconscious – reflexes)
- Represents probably the most common symptom of a disease that motivates a person to seek professional help.
- Pain is of great informative value for a doctor, thus it should not be eliminated totally before recognition of its causes (critical especially in hidden processes - e.g. abdominal).
- In some cases pain helps to prevent overloading of parts of the body with pathological processes (e.g. arthralgias, lumbago, inflammatory processes in limbs) and contributes to recovery.

Nociception
- a separate sensory quality - separate nociceptive system
- over-excitation of some other sensory systems (via pressure, cold, heat receptors)

Nociceptors (= nocisensors) = pain receptors
= free nerve endings AΔ and C
= uneven distribution in skin, muscles, joints

The way of nociceptor stimulation
- after initial damage/irritation of tissue (by chemicals, heat/frost, mechanical insults) → release of chemical substances
- direct stimulation of nociceptors (opening of Na/Ca channels or closure of K channels → membrane depolarization) or sensitization of nociceptors

Origin of endogenous chemicals
- cell destruction → H⁺, K⁺, ATP release → direct stimulation of nociceptors
- inflammation – bradykinin, histamine, serotonin → direct stimulation of nociceptors
- non-damaging mechanical + thermal stimuli can cause “neurogenic inflammation”
  (mechanical and thermal information enters spinal cord via dorsal root and this information is mediated backwards to afferent terminals → release of Substance P, neurokins and CGRP (calcitonin gene related peptide) → vasodilation, leukocyt adhesion, release of inflammatory mediators that stimulate nociceptors)

Sensitization of nociceptors
physiologic response to painful stimuli and → hyperalgesia
Peripheral - ↓ of threshold + activation of surrounding nociceptors
Central – in spinal cord

Transmission of pain information
C and AΔ fibers enter the spinal medulla via dorsal root and synapse together with afferent fibers from mechanoreceptors on the second neuron of the pain pathway (neurotransmitter = glutamate, Substance P enhances the transmission). Information brought from chemoreceptors can decrease the pain transmission (according to gate theory)

The second neuron of the pathway relays in the thalamus to continue to
- The primary somesthetic cortex (recognizes location and intensity of the stimulus)
- Association somesthetic cortex
- Limbic cortex (responsible for emotional experience and memory)
- Hypothalamus (responsible for vegetative accompanying symptoms) and vagus mediated vasodilation
- Periaquaeductal gray (endogenous anesthetic center) that sends backward information to dorsal horn neurons to influence the pain transmission (by release of enkephalins, the release of Substance P is decreased)

**Types of pain**

1) Somatic pain
   - Superficial somatic pain - receptors located in skin
     - rapid (first) pain - myelinated A δ fibres
       - very acute, well localized, rapidly diminishing
     - slow (second) pain - appears later, lasts longer, is not precisely localized
   - Deep somatic pain
     - originates in muscles, fascias, joints, periosteum
     - more similar to visceral pain
     - can not be localized
     - often is accompanied by nausea, sweating and other vegetative symptoms

2) Visceral pain - originates in internal organs in chest and abdomen
   - cause = ischemia (lactic acidosis), chemical substances, spasm or overdistension of hollow organs
   = diffuse
   = accompanied by vegetative symptoms, also by reflex spasm of muscles

**Acute pain**

Etiology:
- inflammation (due to compressive effect of edema, release of pain mediators, developing acidosis)
- colicky pain (due to intensive periodic peristalsis in obstructed and distended intestine, cystic duct, ureter)
- acute ischemia - IM
- traumatic pain, burns, post-operative pain
- live birth

The organism reacts with the sympathetic pattern of response (stress response) - tachycardia, ↑ heart volume, blood pressure, hyperventilation + anxiety

**Chronic pain**

No sympathetic pattern of reaction, but vegetative + psychosocial changes (= algogenic psychosyndrome) - sleep disorders, ↓ appetite, ↓ pain tolerance, depression, hostility, hypochondria, abnormal pain behavior

**Projected pain** - originates elsewhere than is produced (e.g. pain in limb caused by compression of spinal nerve)

**Referred pain** - Head zones – some organs have connection to some parts of skin

**Phantom pain** - pain in non-existing limb (after amputation)

**Neurogenic pain (neuralgia)** - persisting nerve stimulation

**Causalgia** - after devastating injury (shooting) accompanied by vessel reactions + trophic changes of skin

**Thalamic pain** - arises in thalamic nuclei

**Hypoalgesia, analgesia** - inborn decrease or total loss of pain sensation - danger!!! leads to injuries, ischemic necrosis etc.

**Alldynia** - normal mechanical and thermal stimuli are perceived as painful

**Migraine**
- headaches with a vascular background, in women 3x more frequent than in men
- inborn „readiness“ of brain
Pathogenesis:
- vascular theory) explains migraine as a reactive hyperemia in response to vasoconstriction-induced ischemia during aura
  „something“ (stress, noise, hormonal changes, traveling, food skipping, sleep deprivation) activates „migraine centers“ in pons
  periaqueductal grey, locus coeruleus (↑ adrenaline), raphe nucleus (serotonin) → vasoconstriction → aura → stimulation of trigeminal nucleus → neurogenic inflammation, release of mediators → pain
- vasodilation of brain and meningeal arteries → pain
- connection between „migraine centers“ and hypothalamus and centers of reflexes in pons → vegetative symptoms – nausea, vomiting, photo- and phonophobia
21. Pathophysiology of thermoregulation, fever, hypothermia

Thermoregulation of the human body
- constant body temperature is maintained throughout a wide range of temperature in the environment, provided there is normal function of body systems
- constant temperature is necessary for normal enzymatic reactions and metabolism

Body temperature
- differs in various locations:
  - axillary: 36.5°C
  - oral: 37.0°C
  - rectal, vaginal (closest to body core temperature - also ear-drum infra-red measurement): 37.5°C

- circadian variations – minimum temp. in the morning, max. in the late afternoon (accord. to metabolism - dependent on the level of glucocorticoids)
- influence of menstrual cycle, physical load
- basal temperature is measured immediately after waking-up
- comfortable temperature of the environment (no sweating, no thermogenesis) - 20 - 21°C in a dressed person, 28-30°C in a naked person

Thermoregulation
- thermoregulatory center (TRC) in hypothalamus reacts to the temperature of perfused blood and to signals from central and peripheral thermoreceptors
- increased activity of TRC causes vasoconstriction in periphery - ↓ release of heat
- sweating - evaporation (insensible perspiration) of water from skin → increased losses of heat - 1g = 0.58 kCal (up to 75% - dependent on air humidity), loss of water - up to 1l/hour (however, all of this volume cannot be evaporated)
- increased peripheral perfusion (via arterio-venous shunt closure) → increased losses of heat via irradiation into environment - in the resting condition this represents the main loss of heat (45%)
- via respiratory system - loss of only 10% of heat
- increased glucocorticoids activate metabolic rate (production of heat in liver)
- thyroid gland hormones increase metabolism and temperature
- muscle shivering, chattering of the teeth (thermogenesis)
- brown fat in newborns - source of metabolic heat
- physical activity leads to high production of heat (mainly in non-effective motions in non-trained people)
- people with low cardio-vascular capacity have low capacity for thermoregulation - during vasodilation in the periphery they cannot sufficiently increase cardiac output and the resulting hypotension leads to syncope (collapse) (short unconsciousness due to hypoperfusion of the brain) - critical especially with simultaneous dehydration - thus old people should not be exposed to hot environment

Fever (in contrast to hyperthermia, this is a defense reaction of the body)
- increase of axillary temperature over 37.2°C, critical over ca 40°C
- non-specific information about either an inflammatory or a stress reaction (when in basal conditions, without physical activity or activation of metabolism)
- it is intentional resetting of TRC in hypothalamus - reaction to pyrogens probably through the action of prostaglandin E
Meaning of fever
- fever is a beneficial reaction because of liquidation of thermo-sensitive bacteria and viruses
- particularly in some viruses, it is the only possible reaction of the body for elimination of the infection (when viruses do not activate immune reaction) - thus it is not good when in any fever antipyretics are immediately applied (should be used only in temperatures over 39°C - mainly in small children at risk of febrile cramps)
- fever increases production of antibodies and phagocytosis

Etiology
- exogenous pyrogens - infectious bodies (bacteria, viruses....), toxins, drugs
- endogenous pyrogens - inflammatory mediators, tumorous cells (released substances), injured tissues, substances from immune reactions (PGE₂, IL-1, IL-6, TNF ...)

Phases of fever
- increase of temperature (incrementi) - characterized by vasoconstriction accompanied by shivering, feeling of cold, increased basal metabolism
- plateau (acme) - achieved temperature set by TRC
- decrease of temperature (decrementi) - elimination of heat from the body - vasodilation, sweating, feeling of heat

Patterns of fever
- intermittent fever - temperature comes to norm at last once in 24 hours
- remittent fever - oscillating increased temperature
- sustained or continuous - without variations
- recurrent (relapsing) - several days lasting periods with one or more days of normal temperature - e.g. in malaria

Differences in max. temperature according to age - highest fever children up to about 6 years, old people - even low fever can poin to a severe process

Consequences (manifestations) of fever
- heart rate increases by about 15 beats/min with temperature increase of 1°C - can be critical in old people with compensated heart failure (high mortality of old people in epidemic influenza)
- very demanding of energy supply (it is necessary to ensure good nutrition in long-lasting febrile diseases to prevent catabolic state, despite low appetite (probably due to TNF release)
- quick development of dehydration - important supply of fluids - mainly in old people without expressed thirst
- constipation
- hyperventilation due to increased basal metabolism
- catabolism of proteins, hyperglycemia
- CNS hyperactivity (hallucinations) up to depression, sy of restless legs

Hyperthermia
- failure of thermoregulation
- heat stroke - core temperature over 40°C - unconsciousness

Etiology
- in sunburn
- prolonged exertion in hot environment
- dehydration, heart failure
- drugs (increasing muscle tone and metabolism or influencing TR)
- peripheral heat dissipation can be impaired by antihistamines, atropine, tricyclic antidepressants, sympathomimetics - producing vasoconstriction
- hypersensitivity reaction to drugs
- neuroleptic malignant sy with tachycardia (30% mortality)
- malignant hyperthermia - autosomal-dominant disorder with uncontrolled skeletal muscle contractions (potentially fatal - temperature up to 43°C with rise of 1°C per 5 minutes) - caused by abnormal release of intracellular Ca from mitochondria and sarcoplasmic reticulum - triggered by stress or general anesthesia

**Manifestations (besides those described in fever)**
- in extreme exogenous temperature danger of heat collapse (syncope) due to vasodilation (in people with low cardiovascular reserve)
- can cause pulmonary edema

**Reactions in exposure to cold**
- sudden exposure to cold causes first vasoconstriction (stress reaction - effect of catecholamines)
- signals from peripheral thermoreceptors relayed via TRC cause peripheral vasodilation to try to maintain the temperature of peripheral tissues → redness represents active hyperemia
- when blood temperature decreases, TRC makes peripheral vasoconstriction - preference of constant body core temperature - hypoperfusion in periphery leads to necrotic changes (in longer exposure to extreme cold, especially mainly in combination with high humidity) - "frost bite" (even in temperatures above zero)
- influence of alcohol - makes peripheral vasodilation → subjective feeling of warm, prevention of frost bite but increased loss of heat leads to hypothermia of body core → death - **drunk people can die earlier in cold environment**

**Hypothermia**
- core temperature below 35°C

**Etiology**
- low external temperature (with high humidity) + physical exhaustion
- sepsis
- intoxication - alcohol, barbiturates
- low basal metabolism (hypothyroidism)
- neurological disorders

**Pathogenesis**
- infectious diseases are more frequent after exposure to cold (tonsillitis, influenza, pneumonia etc.) because of impaired balance between pathogens and local immune reactivity - due to vasoconstriction (reaction to cold), there is lower supply of leukocytes, antibodies
- below 30°C loss of thermogenesis, ↓ HR, ↓ respiration, muscle rigidity, stupor, loss of reflexes, analgesia, hypoglycemia
- below 25°C cessation of breathing, cardiac arrest or ventricular fibrillation

Use in clinical medicine - hypothermia decreases metabolism and consumption of oxygen - thus it is used in surgery for prevention of irreversible tissue changes during ischemia
Stress can be anything that can alter the homeostatic processes. Stress may contribute directly to the development of disease.

Response (set of reactions) to stress was termed as General Adaptation Syndrome – GAS (by Hans Selye in 1946) - enables the organism to resist to the stressor in the best possible way by enhancing the functions of the system.

The events or environmental agents responsible for initiating the stress response are called “stressors”.

- stressors (exogenous, endogenous) can be physical, chemical, psychological or sociologic (extreme temperature, hunger, thirst, fatigue, hypoxia, etc)
- in modern society the most frequent is psychic stress

- the majority of signs and symptoms of the stress reaction are common for all stressors, however, some can be specific

- the ability of the same stressor to produce different responses in various individuals indicates different adaptive capacity influenced by conditioning factors (genetic predisposition, age, sex, dietary factors, sleep-wake-cycles, drugs etc.), and also the dynamics of the stressor are important for possible adaptation

**Stages of General adaptation syndrome (GAS)**

1. The alarm stage - characterized by immediate release of catecholamines and their related effects - ↑ heart MV (via tachycardia, increased contractility), ↑ BP (vasoconstriction in periphery but not in muscles!!! (be aware of adrenergic receptor distribution), ↑ glycemia, ↑ lipoproteinemia (including LDL) etc.

2. The stage of resistance - characterized mainly by release of glucocorticoids after activation of the hypothalamic-pituitary-adrenal gland axis → increased glycemia, and anti-inflammatory effects, and decreased of all immune reactions with the exception of the number of circulating polymorphonuclears (neutrophils) - it is increased (prevents bacteriemia and sepsis when pathogens enter into circulation)

- this phase can be quite long (up to several weeks- dependent on capacity for glucocorticoid production and sources of energy for gluconeogenesis)

3. The stage of exhaustion - the necessary level of glycemia is not ensured, hypotension, shock - it leads to malfunctioning of all systems, breakdown of homeostasis and death

Stress response - General adaptation syndrome has been termed "the fight-or-flight-response" because in animals it represents a preparation for intensive physical activity with possible injuries. From the above specified summary of changes during GAS, it is evident that all are oriented toward better perfusion of muscles, increased supply of oxygen and energy (glucose) for physical activity.

The phylogenetically very old set of reactions has persisted with little change into the modern human society, where the most frequent psychic stress is not accompanied with physical activity (should not be - in civilised population). Thus a lot of changes can have harmful effects leading to development of psychosomatic diseases (hypertension, atherosclerosis, secondary DM, stress peptic ulcers etc. - see next chapter).

**Psychosomatic diseases**

- civilization diseases - after prolonged or repeated stress

**Examples**

● cardiovascular disorders
- hypertension - probably due to resetting of the vasomotor center during increased BP in stress
- atherosclerosis, ischemic heart disease - accelerated by increased lipoproteinemia and BP
- more frequent in personality type A (according to typology by Friedman and Rosenman, 1974) - responsible, ambitious men (not so pronounced in women up to menopause)

● gastrointestinal diseases
  - stress peptic ulcer - mainly duodenal - caused by:
    - increased acidity due to activation of n. vagus and increased level of glucocorticoids
    - low mucus production due to gastric ischemia in splanchnic vasoconstriction
  - Crohn's disease - genetic predisposition, psychic stress
  - irritable colon
  - psychogenic nausea, vomiting

● endocrine and metabolic disorders
  - secondary diabetes mellitus
  - hyper/hypothyroidism
  - obesity
  - fever

● respiratory system
  - bronchial asthma

● immune system
  - combined immunodeficiency - higher incidence of infections, tumors (due to decreased immunological surveillance)
  - interaction between progression/regression of tumorous process and stress (behavioral access to treatment)

● sexual dysfunction and infertility
  - erectile dysfunction, decreased spermatogenesis
  - functional infertility in women due to dysbalance in sexual hormones (hypothalamo-pituitary dysregulation) - usually disappears after adoption of a child (eliminates stress from infertility)

● lumbago, stiffness of neck - increased tonus of paravertebral muscles (increased level of gamma innervation)

● dermatological problems - psycho-dermatosis

● psychogenic disorders in nutrition
  - bulimia nervosa
  - mental anorexia
23. Etiology and pathogenesis of anemias

Etiology

Decreased/defective production of erythrocytes
- Altered hemoglobin synthesis
  - iron deficiency (hypochromic microcytic anemia) - either low intake or problems with absorption (gastric hypoacidity)
  - Thalassemia - β-thalassemia most common in Mediterranean populations (Greece, Italy)
  - anemia of chronic inflammation (chronic diseases) - deficiency of erythropoietin, catabolic state, decrease of Fe
- Altered DNA synthesis (deficit of substrate)
  - Pernicious anemia (megaloblastic) - decreased B₁₂, folate or gastric "intrinsic factor"
- Stem cell dysfunction
  - Aplastic anemia
  - Myeloproliferative leukemia
  - Pure red cell aplasia
  - hypothyroidism
- Bone marrow infiltration
  - Carcinoma
  - Lymphoma

Increased erythrocyte loss/destruction
- Blood loss
  - acute hemorrhage, trauma (volume of plasma is replaced much quicker than erythrocytes - 3-4 weeks)
  - chronic bleeding - GIT (occult = hidden), menorrhagia
- Hemolysis (intracorporeal defect)
  - membrane - Hereditary spherocytosis
  - Hemoglobin - Sickle sell trait/disease
  - Glycolysis - pyruvate kinase
  - Oxidation - G6PD deficiency
- Hemolysis (extracorporal defect)
  - immune mechanisms - warm/cold antibodies, transfusion reaction, fetal erythroblastosis
  - infection - Malaria (so far causes death of millions of people in Africa), Clostridia
  - trauma to erythrocytes - artificial heart valves, hemolytic-uremic sy, DIC, hemodialysis, venoms,
  - splenic sequestration - hypersplenism (capture of erythrocytes)

Pathogenesis
- impaired oxygen transport - in slow development up to 50% loss of erythrocytes need not have clinical manifestation (in resting conditions)
- tissue hypoxia → anaerobic metabol. → lactic acidosis → vasodilation, edemas → circulatory shock
- in physical activity - decompensation - brain hypoxia → transient unconsciousness
- hyperventilation, dyspnea
- fatigue, weakness, night cramps, loss of concentration, sleepiness
- angina pectoris (relative insufficiency of coronary arteries)
- tachycardia, palpitations - activation of sympathetic system by hypoxia → high-output heart failure (high but insufficient MV)
- systolic murmur - from decreased blood viscosity and increased MV
- increased 2,3-DPG - decreases hemoglobin affinity to oxygen → better oxygenation of tissues in low partial pressure of O₂
- increased permeability of glomeruli - proteinuria
- GIT - dyspepsia (loss of appetite)
- jaundice in hemolytic anemias
- pallor of the skin, mucous membranes, conjunctiva, nail beds
- increased levels of erythropoetin (when it is not primary deficiency)
24. Blood transfusion, complications, fetal erythroblastosis

Since there are relatively frequent complications (mainly transmission of infections such as Hepatitis C or HIV - despite careful screening of donors), indications for transfusions are quite restricted. Family members or friends can be used for a "directed donation" or in planned surgery autologous (own blood) transfusion is performed. Strict refusal of transfusion in some religions - 7th day Adventists.

- If Hb > 100 g/1l transfusion is rarely indicated
- If Hb < 70 g/1l transfusion is usually necessary

- many laboratory tests are performed to exclude transmission of health problems
- two cross-matching tests are used (both reaction against donor's erythrocytes and against recipient's erythrocytes) to verify compatibility (in AB0 and Rh systems)
- universal donorship - group 0+ is used only in extreme emergency (or large catastrophes)
- "biologic test" - after about 10 ml (and later still 20 ml) doses, the recipient is observed in, order to detect any signs of incompatibility which may become apparent within about 15 minutes (see below)
- normal velocity - ca 80 drops/min
- massive transfusion - replacement of a patient's total blood volume in less than 24 hours

Complications
- pyretic reaction (pyrogens in the blood conserve)
- hemolytic reaction (in cases of incompatibility of blood, inadequate temperature of the conserve, sepsis etc.) - causes pain in the lumbal area, oliguria or anuria (due to microthrombosis/embolisation in glomeruli), tachycardia, hypotension, dyspnea, development of icterus, hives and itching, nausea → stop of transfusion and hemodialysis
- circulatory reaction - due to overload of left ventricle in old people by too rapid transfusion - hypotension, increased central venous pressure
- allergic reaction - urticaria, itching, edemas, dyspnea - up to asthma and anaphylactic shock
- septic reaction - infected conserve - high fever
- toxic reaction - too massive transfusion (or low metabolic/detoxification function of the liver), citrates bind Ca → tetany, hypotension
- embolism - air - in pulmonary circulation, microthrombi - mainly in glomeruli
- hemosiderosis - in repeated transfusions
- rarely ARDS or dilutional thrombocytopenia (thrombocytes survive in blood conserve only for a few days)

Transmitted infections:
- Hepatitis C (ca 1 in 10,000 transfusions), HIV, CMV, bacterial infections, malaria

Fetal erythroblastosis
- hemolytic disease of newborns
- manifestation of Rh incompatibility between Rh- mother and Rh+ fetus
- it develops only after prior immunization of the mother:
  - after Rh+ blood transfusion
  - after previous baby deliveries, abortions (input of fetal blood into circulation)
  - after amniocentesis
- even during pregnancy - transmission of fetal erythrocytes via placental barrier is possible e.g. in transplacental fetal bleeding
- the severity of the disorder increases in repeated pregnancies (1st one usually without problems)
prevention - to all Rh⁻ mothers are given anti-D (RHEGA) antibodies immediately after baby delivery (within 72 hours) - it eliminates Rh⁺ erythrocytes in circulation of mother - prevents immunization

- in the case of immunization anti-D antibodies transmit via placenta to the fetal circulation and cause hemolysis → release of immature erythroblasts from bone marrow of the fetus - cause deficiency of foetal liver (hepatosplenomegaly) → hypoproteinemia → edemas = "hydrops fetalis" → death

- the increased level of bilirubin from hemolysis can give rise to deposits in the basal ganglia = "kernicterus" - causes CNS dysfunction

- normal jaundice of newborns - bilirubin up to 12mg/100 ml

- immature newborns > 15 mg/100 ml - starts to be risky - phototherapy is used - illumination with blue light (wavelengths 420-470 nm) - in subepidermal capillaries the non-conjugated bilirubin is transformed to an isoform that is better water-soluble (better eliminated from blood by immature liver) and less toxic

- exchange transfusion of blood in the worst cases (deposits to basal ganglia start at concentrations of 25 mg/100 ml)

- in critical situations even intrauterine transfusion is used

- severe Erythroblastosis fetalis causes death, mental retardation, athetosis

- in simultaneous AB0 incompatibility anti-A or anti-B antibodies can liquidate fetal erythrocytes before Rh immunization and Erythroblastosis foetalis need not develop

- individual differences in Rh immunization
25. Leukemias - etiology and pathogenesis, lymphoma, myeloma

**Leukemias** - malignant neoplasms of the hematopoietic stem cells, diffuse replacement of bone marrow with immature neoplastic cells distributed usually also in blood
- leading cause of death in children aged 3 to 14
- classified according to the predominant cell type - lymphocytic or myelocytic and whether the condition is acute or chronic

**Etiology**
- not known in all cases
- high incidence after irradiation (Hiroshima, Nagasaki - atomic blasts, Tchernobyl - nuclear power-station catastrophe)
- exposure to benzene and some other chemicals and drugs - e.g. ATB chloramphenicol
- after chemotherapy (cytostatics) of some other primary tumor
- in association with some chromosomal abnormalities - Down's sy, Klinefelter's sy etc.
- very frequent in chromosomal aberrations - usually translocations - e.g. Philadelphia chromosome (translocation from chromosome 22 to 9) - in 90% of people with chronic myeloid leukemia (CML)
- viral etiology - suspected e.g. EBV, CMV

**Pathogenesis and clinical manifestations**
- some characteristics are quite specific for particular type of leukemia, but the majority of them are non-specific - such as anemia and thrombocytopenia due to bone marrow depression (infiltration)

**Acute leukemias** - more frequent in children and adolescents
- sudden onset with critical decrease of immunity and bone marrow depression
- pancytopenia, lymphadenopathy, splenomegaly, hepatomegaly
- fatigue, pallor, weight loss, repeated infections, bleeding disorders, bone tenderness and pain, bone fractures
- CNS involvement - headache, nausea, vomiting, cranial nerve palsies
- leukostasis - number of blasts in peripheral blood over 100,000/ml - circulatory problems - leukapheresis (removal of blasts from blood) is necessary
- in chemotherapy "tumor lysis syndrome" appears = hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, hypomagnesiemia and acidosis develops

**Chronic leukemias** - mainly in adults
- because of insidious onset may only be discovered during a routine medical examination
- bleeding disorders, anemia
- in CML blast crisis is critical
- in CLL "Hairy cell leukemia" represents rare malignant variant

**Lymphomas**
- malignant neoplasms of cells native to lymphoid tissue (lymphocytes, histiocytes)

**Hodgkin lymphoma**
- belongs among the most curable neoplasms
- high probability of viral etiology
- lymph distribution → painless lymphadenopathy (adenomegaly)
- cell-mediated immunodeficiency
- fatigue, loss of weight
- "febris undulans", night sweating
Non-Hodgkin lymphomas
- highly malignant
- unknown etiology - EBV?? Burkitt lymphoma, in acquired immunodeficiencies
- hypogammaglobulinemia - infections
- hematological spread
- infiltration of organs with malfunctioning

Multiple myeloma
- plasma cell cancer of the osseous tissue
- abnormal clone of plasma cells - mainly IgG and IgA type
- proliferation of plasma cells erode the hard bone → pathologic fractures, hypercalcemia
- production of paraproteins - can cause hyperviscosity and form amyloid (heart failure, neuropathy)
- Bence Jones proteins of low molecular weight can be filtered into urine - can be toxic for tubular system and can cause tubular failure
- some malignant cells can form plasmacytomas making spinal cord compressions
- back bone pain is one of first symptoms

In the end stage of leukemias and lymphomas as well as in the end stage of any malignant tumorous processes patients suffer from the following complications (leading to death):
- catabolic state with hypoproteinemia and edemas
- cachexia caused by extreme metabolic rate of tumours, by low appetite (due to nausea- chemotherapy, intrabdominal expansions - adenomegaly), by malabsorption (GIT dysfunction)
- pains - compressions, expansion of GIT organs - increased capsule tension, acidosis, pain mediated substances,
- anemia, bleeding disorders
- immunodeficiencies with severe infections
Polycythemia

= erythrocytosis, polyglobulia

**Polycythemia vera** = primary polycythemia
- recognized as benign hemoblastosis
- chronic increase of erythrocytes due to proliferation of erythroblasts - up to 10.10^{12}/l, Ht = ca 60%
- decreased Erythropoietin!!!
- normal character of erythrocytes
- possible shift to Acute myeloid leukemia

**Secondary polycythemia**
- due to increased Erythropoietin - compensatory mechanism in hypoxia (in high altitude, in some heart defects - mainly cyanotic, in chronic pulmonary disorders, chronic CO poisoning, kidney disorders with increased production of Erythropoietin (e.g. in 10% of Grawitz tumors)
- modern kind of doping in sportsmen (instead of long-lasting intensive training in high altitude) - either autologous transfusions (before the important race) or chronic use of Erythropoietin synthetic derivates
- increase of Ery is not so high as in primary polycythemia

**Pathogenesis (consequences)**
- increases viscosity of blood = increased load for heart → hypertrophy → failure
- hypertension (increased peripheral resistance)
- stasis of blood in periphery - thrombogenesis, embolism, infarctions
- decreased perfusion of fine capillary nets - e.g. in hypothalamo-pituitary portal system → endocrinopathies, in Basal ganglia - Parkinsonism, in kidney - decreased GF, low perfusion of coronary arteries
- hepatomegaly, splenomegaly
- plethoric color - up to cyanosis in periphery (slow blood flow, reduced Hb over 50 g/l of blood
- osteoporosis
- critical in combination of intensive physical activity - in sportsmen causes acute heart failure
- there is tendency to stop participation in endurance sports with Ht over 50%

Relative polycythemia (increased hematocrit with normal absolute number of Ery - in severe dehydration) - risk of thrombogenesis not only due to increased viscosity but also supported by simultaneous low heart MV

Principles of therapy - repeated venipuncture, radioactive phosphorus, cytostatics
27. Bone marrow depression

**Etiology**
- in 50% idiopathic (causes not known)
- primary aplasia of bone marrow - genetic predisposition - distinct chromosomal aberrations
- secondary:
  - chemical substances - carcinogens (derivatives of benzene, aniline dyes...)
  - drugs - cytostatics, ATB (chloramphenicol)
  - endogenous - urea (kidney failure uremia), ammonium (liver failure)
  - biological factors- viruses (oncorna-viruses, CMV, EBV - high asymptomatic incidence in population)
  - infiltration of bone marrow by tumorous, metastatic processes
  - low activity of bone marrow in chronic inflammatory processes (chronic diseases) due to catabolic state, hypoproteinemia (low supply of substrate -aminoacids to bone marrow)
  - similarly decreased activity of bone marrow in malnutrition, general malabsorption (and especially malabsorption of proteins), liver failure, loss of proteins (Nephrotic sy, plasma losses), Cushing's sy, hypothyroidism

**Pathogenesis**
- anemia, immunodeficiency, bleeding disorders - details in the particular chapters to these topics

**Principles of therapy**
- treatment of primary diseases
- realimentation, stimulation of bone marrow, transplantation
28. Disorders of hemostasis

4 phases of hemostasis:
1. reaction of the vessel wall to injury - vasoconstriction
2. reaction of thrombocytes - primary thrombus formation
3. hemocoagulation - fibrin fiber formation - fixation of the thrombus
4. fibrinolysis - dissolution of the thrombus

Some physiological notes
1. phase - Vasoconstriction
   - in the first instance reflexive (short duration), then humoral (serotonin, thromboxane A2 - from thrombocytes)
   - can stop bleeding from small vessels

2. phase - Primary thrombus formation
   - adhesion of thrombocytes to injured endothelium (normal intact endothelium, due to its high negative charge, presents non-wettable surface which resists adhesion) – subendothelial collagen
   - reversible aggregation of platelets

3. phase - Hemocoagulation
   - via intrinsic system activated by contact with wettable surface (subendothelial collagen fibres) fXII → XIIa → Xla → IXa → VIIIa + Platelet lipoprotein+Ca²⁺ → Xa
   - via extrinsic system activated by release of "tissue thromboplastin" (from injured tissues) → VII+ Platelet lipoprotein+Ca²⁺ → Xa
   - joint part of hemocoagulation cascade: Xa+Platelet phospholipid + V → Prothrombin/Thrombin → Fibrinogen/Fibrin monomer - XIII → Fibrin monomer/Fibrin polymer - stabilizes primary thrombus
   - retraction of coagulum under the influence of thrombosthenin (from platelets) decreases size of the thrombus (release of serum = plasma minus proteins) - enables at least partial blood flow in the injured vessel
   - vitamin K dependent coagulation factors formed in liver: II, VII, IX, X
   - inhibitors of coagulation: antithrombin III - supported by heparin; protein C - supported by protein S

4. phase - Fibrinolysis (after reparation of the vessel wall - ca 5-7 days)
   - XII a + activators derived from tissue or bacteria → plasminogen/plasmin → fibrin in clot/fibrin degradation products

Vasculopathies - abnormalities of the vessel wall (disorders in the 1. phase)
• primary - congenital (very rare)
  - m. Rendü-Osler - (autosomal dominant) = "teleangiectasia hereditaria hemorrhagica" = anomaly of muscle and connective tissue layers of the vessel wall
  - m. Ehler-Danlos (autosom. dom.) - abnormal fragility due to abnormality of elastin fibers
• acquired
  - m. Henoch Schönlein - "chronic anaphylactoid purpura" = toxic capilaritis - allergic reaction to infections, drugs (ATB) - ↑ permeability (purpura = reddish colour of the skin because of multiple petechias (small - point-like haemorrhages)
  - thrombotic microangiopathies
  - hemolytic-uremic sy
  - Goodpasture sy (antibodies against basal membrane - pulmonary bleeding, glomerulonephritis)
- Purpura fulminans - effect of bacterial endo- and exotoxins (typhus)
- avitaminosis C - low mechanical resistance of vessels (abnormal synthesis of collagen fibers) - in adults - scurvy (gingival bleeding), in children - scorbut → bleeding under periost (m. Möller-Barlow)
- Purpura senilis - senile atrophy of vessels - formation of hematomas - snake venom

**Abnormalities of thrombocytes** (disorders of the 2nd phase of hemostasis)

- quantitative - thrombocytopenia
  - central - amegakaryocytic
    - disorders of maturation in irradiation, drugs, tumor infiltration of bone marrow
  - peripheral - increased damage - non-immune origin (DIC), autoimmune- Idiopathic
    - thrombocytopenic purpura - m. maculosus Werlhoffi, therapeutical - ATB, antiepileptics, analgesics, diuretics
    - avitaminosis C - low mechanical resistance of vessels (abnormal synthesis of collagen fibers)
    - in adults - scurvy (gingival bleeding), in children - scorbut → bleeding under periost
- hypersplenism (m. Gaucher, m. Banti)
- hyperutilisation - artificial valves, massive transfusions

- qualitative - thrombocytopenia - thrombasthenia
  - Thrombasthenia Glanzmann-Naegeli (autosomal. recessive) - abnormal aggregation and retraction of the coagulum
  - Wiskott-Aldrich sy - abnormal aggregation
  - acquired - decrease of platelet f.3 and aggregation abnormality - in therapy of
    - Acetylsalicylic acid, Dipiridamol + other non-steroid antiinflam. drugs (*used therapeutically as prevention of spontaneous thrombogenesis - after IM, prevention of ictus*)

**Disorders of coagulation factors - hemocoagulation**

- inborn
  - Hemophilia A (most frequent and severe - deficiency of f. VIII - gonosomal recessive), B (f. IX), C (f. XI)
  - Hemophilia A - transmitted via women, clinical manifestation only in man (homozygous women are aborted), severe bleeding - typically to joints - hemarthros - immobilization
  - difficult treatment - only direct transfusions (f. VIII is very thermosensitive)
  - possible but rare deficiencies of some other factors
  - von Willebrand disease - f. VIII abnormality (missing one part - vonWillebrand f.) - does not cause significant problems in hemocoagulation but is a distinct disorder of platelet adhesion = insufficiency of the 2nd stage of hemostasis (recognizable via prolonged Duke's test of bleeding (primary thrombus formation - normal in Hemophilia)

- acquired
  - anticoagulation activities in Rheumatoid arthritis, after baby delivery, Multiple myeloma
  - vit. K. deficiency - in malabsorption of fats, chronic use of broad-spectrum ATB (↓ intestinal flora)
  - liver failure
  - severe hypocalcemia
  - after DIC (disseminated intravascular coagulation - see thrombosis) = phase of "consumptional coagulopathy" - missing consumed factors - decreased coagulation (formerly quite a frequent problem during baby delivery - abruption of placenta, embolisation by amniotic fluid → DIC → disorder of coagulation → disorder of coagulation → severe bleeding of mother → death (nowadays solved through supply of missing factors = mainly fibrinogen)

**Basic tests for examination of hemostatic functions** *(Not all these test are so far clinically used but their demonstration is useful for educational purposes.)*
- Rumpel-Leede's test: max. 10 petechias on 16 cm²
- Bleeding time (Duke): 2-5 min.
- Thrombocytes: 150-300 x 10⁹/l
- Prothrombin time (Quick's test) – norm = 12 - 16 s, 70-110 % from the calibration curve, INR (International Normalized Ratio) was created by the World Health Organization because Prothrombin time results vary depending on the thromboplastin reagent used. Via extrinsic pathway the prothrombin activator is created - velocity of fibrin formation depends on the concentration of factors V, VII, X, prothrombin and fibrinogen.

Therapeutic ranges for Warfarin therapy

<table>
<thead>
<tr>
<th>Indication</th>
<th>INR value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of venous thrombosis</td>
<td>2.0 – 3.0</td>
</tr>
<tr>
<td>Treatment of venous thrombosis</td>
<td>2.0 – 3.0</td>
</tr>
<tr>
<td>Treatment of pulmonary embolism</td>
<td>2.0 – 3.0</td>
</tr>
<tr>
<td>Prevention of systemic embolism</td>
<td>2.0 – 3.0</td>
</tr>
<tr>
<td>Mechanical prosthetic heart valves</td>
<td>2.5 – 3.5</td>
</tr>
<tr>
<td>Prevention of recurrent myocardial infarction</td>
<td>2.5 – 3.5</td>
</tr>
</tbody>
</table>

- Clot retraction test: prolonged in thrombocytopenia and thrombasthenia
- Prothrombin consumption test (assessment of the prothrombin 2 hours after blood clotting): norm. over 45 sec. (pathol. in case of delayed prothrombin activator formation (= "blood thromboplastin" - according to the clinical terminology)
- Blood clotting - Lee-White: 5 - 10 min. (testing of the intrinsic coagulation pathway - activated by contact of blood with subendothelial tissue (e.g. collagen)
- Thromboplastin generation test (Partial thromboplastin time - PTT): tests the formation of prothrombin activator via intrinsic pathway - the most sensitive test for detection of hemophilias and their discrimination

**Differentiation of bleeding disorders with the use of basic tests**

<table>
<thead>
<tr>
<th>Labor. tests</th>
<th>Vasculo-pathy</th>
<th>Thrombocytopenia</th>
<th>Thrombasthenia</th>
<th>Hemophil. A,B</th>
<th>Defic.f. II,V,VII,X</th>
<th>Will. dis.</th>
<th>DIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rumpel-Leede</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>N</td>
<td>N</td>
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<td>N</td>
</tr>
<tr>
<td>Bleeding time (Duke)</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
<td>N</td>
<td>↑</td>
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<tr>
<td>Thrombocount</td>
<td>N</td>
<td>↓</td>
<td>N or ↓</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>↓</td>
</tr>
<tr>
<td>Prothr.time (Quick. INR)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>↑</td>
<td>N</td>
<td>↑</td>
</tr>
<tr>
<td>Clot retr. test</td>
<td>N</td>
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<td>↓</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>-</td>
</tr>
<tr>
<td>Prothromb. consumption</td>
<td>N</td>
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</tr>
<tr>
<td>Clotting time (Lee-White)</td>
<td>N</td>
<td>N</td>
<td>N or ↑</td>
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<td>↑</td>
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<tr>
<td>PTT</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>A</td>
<td>A</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

N - normal result; A – abnormal; ↑ - increased; ↓ - decreased
29. Thrombosis, DIC

Spontaneous primary thrombogenesis represents dysbalance between the system of hemocoagulation and fibrinolytic system that develops when some factors from these systems are missing (important is e.g. proportion of fibrinogen and plasminogen). Secondary thrombosis can be a result of changed rheologic parameters (parameters of the blood flow) in the peripheral circulation causing stasis of blood and predominance of some pro-coagulation factors.

**Thrombophilia - primary increase of blood coagulability**
- deficiency of antithrombin, protein C and protein S
- all these deficiencies are responsible only for 10% of inherited thrombophilic states
- only in 1993 did Dahlbäck et al. describe resistance to the anticoagulation effect of activated protein C (APC) (inactivates Va and VIIIa)
- resistance to APC has high prevalence in population - responsible for up to 64% of venous thrombosis - it is of autosomal dominant heredity
- the changed gene for f. V which is responsible for resistance to APC was named as factor V Leiden (place of detection)
- in heterozygous subjects with resistance to APC the probability of thrombosis increases 5-10 times, in homozygous individuals up to 80 times
- resistance to APC can be induced by oral contraceptives - the probability of thrombosis is increased about 4 times and in women with factor V Leiden 35 times
- over 50% of pregnant women with resistance to APC had some thrombotic complication (e.g. thrombotisation of placenta), presenting an increased risk of abortion
- in ca 30% of thrombophilies the causative factors remain unknown

**Etiology of secondary thrombogenesis**
- polycythemia - increased viscosity → slowing of the blood flow
- dehydration - increased viscosity (sy of "economic class" - dehydration + immobilization during lon-haul flights)
- immobilization (confined to bed due to some disease or working in a fixed standing position
  - stasis of blood in lower limbs
- varices
- elderly - usually with heart failure - low MV and slow blood flow in periphery
- use of contraceptives (development of resistance to APC)
- combination of these factors increases risk (old woman immobilized in hospital, dehydrated, with varices, chronic respiratory insufficiency (compensatory polycythemia) and heart failure = almost sure thrombogenesis - necessary daily ultrasound exam., lower limb bandage, chronic use of anticoagulation therapy - warfarin)
- the concept was described by Virchow (additional factors):
  - injured t. intima (endothelium) - atherosclerosis, inflammation (phlebitis), ischemic injury
  - access to subendothelial collagen activates adhesion and aggregation of platelets
  - effect of slow or turbulent blood flow - in atrial fibrillation, aneurysmas
  - thrombogenic factors- carcinomas, postsurgical status, smoking, large burns

**Development of thrombi**
- embolisation
- dissolution of thrombus (fibrinolysis) - spontaneous or therapeutical - streptokinasis, cabikinasis (mainly in coronary and brain arteries)
- organization of thrombus - fibrotisation → definite obstruction
- recanalisation
- arterial thrombi → infarctions
- venous thrombi → venostasis → thrombophlebitis, phlebothrombosis → embolisation to lungs

**Disseminated intravascular coagulation (DIC)**
- formation of microthrombi in peripheral circulation

**Etiology**
- endothelial damage
  - sepsis (gram-negative)
  - hypoxia
  - cardiac/pulmonary arrest
  - shock - hemorrhagic, septic, cardiogenic, traumatic
  - ARDS
  - aortic aneurysms
- release of tissue thromboplastin
  - trauma (surgery, burns, fat emboli)
  - myocardial infarction
  - malignancies (acute leukemia, carcinomas, sarcomas, pheochromocytoma)
  - obstetric conditions - amniotic fluid embolism, abruptio placentae, eclampsia, retained placenta, septic abortion
- factor X activation
  - acute pancreatitis
  - snake venom
  - liver disease
- miscellaneous
  - massive blood transfusion, hemolytic anemia
  - anaphylaxis
  - near-drowning
  - hypothermia, malignant hyperthermia
  - pulmonary embolism
  - aspirin poisoning
  - extracorporeal membrane oxygenation

**Pathogenesis of DIC (manifestations)**
- widespread hemorrhage - as a consequence of "consumptional coagulopathy"
- acrocyanosis, gangrene
- subarachnoid hemorrhage
- altered consciousness
- hematuria, oliguria, renal failure
- pulmonary infarctions
- ARDS (cyanosis, tachypnea, hypoxemia)
-endocrine disorders - hypothalamo-pituitary dysfunction
30. Atherosclerosis, hyperlipoproteinemia

Atherosclerosis is a type of arteriosclerosis or hardening of the arteries. It represents degenerative (inflammatory) disease of arteries with formation of fibrofatty lesions (plaques) in the intimal lining that change physical parameters of the large and medium-sized arteries and predispose them to aggregation of platelets - thrombus formation. Atherosclerotic lesions can be characterized by:
1. accumulation of intracellular and extracellular lipids
2. proliferation of vascular smooth muscle cells
3. formation of large amounts of scar tissue and connective tissue proteins

**Historical hypotheses of atherogenesis:**

1852 - Thrombogenic hypothesis by Rokitansky: Repeated depositions of blood elements (fibrin, platelets, etc.) on the endothelium results in formation of microthrombi; old deposits degenerate as new material continues to accumulate and platelets release a factor that stimulates smooth muscle proliferation.

1862 - Lipid infiltration by Virchow: Circulating lipids enter arterial endothelium and accumulate around the smooth muscle; endothelial permeability is adversely affected, allowing continued lipid filtration.

These historical opinions fit well to the much newer theories:

Response to injury: Arterial endothelium is injured by altered hemodynamic forces (hypertension), harmful chemicals (nicotine, catecholamines), bacterial infection, hyperlipidemia, or mechanical trauma; endothelial membrane is disrupted, permeability is altered and platelets, lipids and smooth muscle aggregate on the intimal layer.

Lipogenic hypothesis: Elevated levels of low density lipoproteins (LDLs), decreased levels of high density lipoproteins (HDLs) result in migration and accumulation of LDLs and cholesterol in the tunica intima and tunica media.

**Predisposing/contributing factors:**
- endocrine and metabolic - hyperlipoproteinemia/dyslipoproteinemia (see below)
- diabetes mellitus
- obesity
- stress
- personality type A (see chapter - Stress)
- mechanical factors - hypertension, turbulent flow (in bifurcation of arteries)
- toxic (nicotine)
- genetic (familial hypercholesterolemia, hyperhomocysteinemia - not proved sufficiently so far, mechanism is not well known - hypotheses about facilitation of thrombogenesis, toxicity to endothelium, increased oxidation of LDL)
- infectious (Chlamydia)
- endothelial dysfunction (see below)
- inflammation - influx of lipids
- sedentary lifestyle
- increasing age

**Development**
- predisposing factors lead to endothelial dysfunction (lower mechanical resistance, increased permeability)
- development of chronic aseptic inflammation
- influx of lipids - accumulated in macrophages → "foamy cells"
- macrophages produce cytokines → proliferation of smooth muscle cells of tunica media - shift to subendothelial space - inflammatory process makes fibrotisation - growth of plate

Accelerated atherosclerotic process in men
Women are protected by estrogens (until menopause, then they also have acceleration):
- increased formation of NO- increased secretion of prostacyclins - lower number of angiotensin receptors - lower production of endothelin (see below - Endothelial dysfunction) = predominance of vasodilating agents

Consequences
● hemodynamic
  - stenosis (predominance of vasoconstrictive agents)
  - lower perfusion, ischemia, atrophy
● thrombogenic
  - rupture of plates, internal bleeding → stenosis
  - infarctions, aneurysmas

Predilection places
- coronary arteries
- carotids
- visceral branches, aorta ascendens
- iliac arteries

Possible influencing
- elimination of risk factors
- pharmacotherapy - fibrates, statins (↓ LDL), supplementation by estrogens in menopause
- diet rich for L arginine → increased availability of NO, vit. B6, B12, folic acid
  →↓ homocysteine (?? - not sufficiently proved)

Hyperlipoproteinemia
- according to recent theories of the pathogenesis of atherosclerosis it is one of the main etiological factors
- among all possible types of hyperlipoproteinemias, "familial hypercholesterolemia" (type IIA) represents the main risk - is characterized by elevated LDL and normal triglycerides
- more important than absolute level of LDL ("bad cholesterol") is its proportion to HDL (high density lipoproteins - "good cholesterol" - it is posible to increase this with fibrates - e.g. Gemfibrozil)
- it is possible to reduce synthesis of endogenous cholesterol (more significant than decreased intake of exogenous cholesterol in nutrition) in liver by statins (e.g. lovastatin, pravastatin) - tendency to achieve level < 4.5 mmol/l
- fibrates (Fibric Acid derivates – e.g. Clofibrate) can significantly reduce elevated triglyceride through their lipoprotein lipase-mediated effect on lipolysis and by reducing triglyceride production in the liver - adverse effects include cholelithiasis caused by increased cholesterol excretion in the bile and elevated liver transaminases
- cholesterolemia can be decreased also via binding of bile acids in the gut (e.g. with cholestyramine) and their increased elimination (their new formation from cholesterol decreases cholesterolemia)
- there is some evidence that soluble fibre may reduce the absorption of cholesterol from the gut into the bloodstream (Dietary fibre is a collective term for a variety of plant substances
that are resistant to digestion by human gastrointestinal enzymes. They can be classified into two groups depending on their solubility in water. It has been suggested that soluble fibres such as oats, psyllium, pectin and guar gum lower total and low density lipoprotein (LDL) cholesterol.

- in homozygous patients with familial cholesterolemia it is necessary to carry out regular plasmapheresis (removal of cholesterol from plasma) to prevent very early death due to complications of atherosclerosis
- saturated (animal) fats in diet increase cholesterol levels
- intake of non-saturated fatty acids - omega 3 has been recommended (fish oil)
- moderate alcohol intake (up to about 20 g of pure alcohol/day - sex and age dependent - highest tolerance is in older men) increases HDL levels
- suspected beneficial effect of endogenous antioxidants - limit oxidation of LDL cholesterol (vit. E, beta-carotene)
- among all possible exogenous antioxidants particularly vit. C and flavonoids seem to be beneficial (red wine and tea are high in flavonoids and in some studies the low incidence of atherosclerosis in France and Greece is attributed to the high consumption of red wine in these countries - however, other factors such as genetics and style of life can play a role in epidemiological studies of this kind)
- glycation of cholesterol (increased in DM) can also be a contributing factor in acceleration of atherogenesis -
31. Endothelial dysfunction, effects of nitric oxide

Endothelial dysfunction is localized (rarely generalized) involvement of endothelium causing increased permeability of the wall and dysbalance between vasoactive and hemocoagulation factors. It leads to atherogenic, vasoconstrictive and thrombogenic effects. Endothelial dysfunction = first significant stage of atherosclerosis.

- normal endothelium produces and degrades a lot of vasoactive substances
- the most important vasodilating agent is NO (nitric oxide) formerly named as "endothelium derived relaxing factor" - synthesized from L-arginine through activity of NO synthase
- also prostacyclin PGI\textsubscript{2} and prostaglandin E\textsubscript{2} represent potent vasodilators
- the most potent vasoconstrictive substance from endothelium is endothelin 1 (ET-1)

Nitric oxide - NO (released from normal endothelium)
When NO, the signaling molecule, enters a cell, it activates the enzyme guanylate cyclase, which produces cyclic GMP, the second messenger. !!! It is actually cyclic GMP which brings about the relaxation and dilatation of the blood vessels!!! Understanding of the function of NO led also to development of Viagra \textit{(Sildenafil citrate)} influencing a special form of guanylate cyclase that is specific for vessels in the penis. Sildenafil mediates its effects by inhibiting phosphodiesterase 5, thereby increasing cyclic GMP production. The increased levels of cyclic GMP cause relaxation of smooth muscles in penile vessels and this leads to an erection.

NO helps to prevent atherosclerosis by preventing platelets and leukocytes from sticking to the vessel wall. It suppresses abnormal growth of smooth muscle cells which causes thickening of the vessels. NO also reduces the production of free radicals that contribute to the aging of vessels.

Endothelin (increased levels in endothelial dysfunction)
ET-1 release is stimulated by angiotensin II (AII), antidiuretic hormone (ADH), thrombin, cytokines, reactive oxygen species, and shearing forces acting on the vascular endothelium. ET-1 release is inhibited by nitric oxide as well as by prostacyclin and atrial natriuretic peptide.

ET-1 has a number of other actions besides vasoconstriction. ET-1: stimulates aldosterone secretion, produces positive inotropy and chronotropy in the heart, decreases renal blood flow and GF, and releases atrial natriuretic peptide (ANP). ET-1 has been implicated in the pathogenesis of hypertension, vasoconstriction, atherosclerosis and heart failure. In the latter condition, ET-1 is released by the failing myocardium where it can contribute to calcium overload and hypertrophy. Endothelin receptor antagonists have been shown to decrease mortality and improve hemodynamics in experimental models of heart failure. Non-selective ET-1 receptor antagonists are currently used in the treatment of pulmonary hypertension.

Factors inducing endothelial dysfunction
- oxidative stress
  - prevention by enzymes - superoxide dismutase (SOD), catalase (CAT, glutathione peroxidase)
  - by oxygen free-radicals scavangers - vit. C, E, beta-carotene
- intracellular influx of calcium - prevention - Ca channels blockers
- hemodynamic forces - so called "shear stress" - low shear stress (below 4 dyne/cm\textsuperscript{2}) that is present in turbulent or oscillatory blood flow (e.g. around bifurcation of arteries) causes endothelial dysfunction with release of vasoconstrictive agents - this stimulates atherogenesis (shear stress over 15 dyne/cm\textsuperscript{2} induces an atheroprotective profile)
32. Arterial hypertension

Changes of blood pressure in the systemic circulation can be understood through a “water-pipe analogy for Ohm's Law”: If we have a water pump that exerts pressure (voltage) to push water around a "circuit" (current) through a restriction (resistance), we can model how the three variables interrelate. If the resistance to water flow stays the same and the pump pressure increases, the flow rate must also increase etc.

Decisive factors for systolic blood pressure: force and velocity of left ventricle contraction, ejection volume, elasticity (compliance) of aorta and capacity of large arteries
Decisive factors for diastolic blood pressure: peripheral resistance (given by tonus of smooth muscle in the vessel wall, volume of circulating blood and its viscosity (hematocrit)
Level of perfusion in the periphery depends on the mean blood pressure = diastolic BP + 1/3 of the systolic-diastolic BP difference (systole duration is about 1/3 of diastole duration).
Regulation of blood pressure is both vasomotor (vasomotor center in the brain stem - can be reset to increased BP during stress) and volumic (dependent mainly on GF in kidney and the RAAS, partially influenced by atrial natriuretic peptide).

Former criteria for hypertension - diastolic BP > 90 mm Hg, systolic BP > 140 mm Hg
Criteria recommended by "The 7th report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure" (USA, 2003) - diastolic pressure should not be over 75 mm Hg, nor systolic pressure over 115 mm Hg, irrespective of age!!!! (This does not seem to be appropriate in many older people who suffer from brain hypoperfusion in this low level of BP) - above these values there is increasing risk of cardiovascular disorders
Measurement of BP should be done in the horizontal position of the body, on all limbs and in resting conditions (not stressful - difficult in some patients coming to doctor!!!!).

Etiology of arterial hypertension
● Primary (essential) - in 90 - 95% of patients:
  - without known mechanism, probably due to primary peripheral vasoconstriction of not fully understood non-uniform origin - there are various hypotheses - the majority of them based on some genetic predisposition eg.:
    - change in metabolism of catecholamines (increased production or increased sensitivity of receptors)
    - decreased activity of Na/K ATPases → increased intracellular Na and Ca → increased contractility of vessels
    - alcohol (intensive drinking over 20 g/day)
    - suspected enzymatic defects

● Secondary - 5- 10% (caused by a primary disorder of some other organ or system, which changes the volume, peripheral resistance or elasticity of large arteries):
  - renal failure - decreased glomerular filtration leads to increase of circulating volume, worsened by high intake of salt - inability to eliminate sodium leads to accumulation of water - in critical oliguria (anuria) dialysis is necessary
  - reno-vascular - due to arteriosclerosis of the renal artery (vas afferens) there is decreasing perfusion of the kidney - this is recognized as volume deficit and the juxtaglomerular apparatus activates RAAS → enormous increase of BP - formerly it was necessary to carry out nephrectomy (in cases of a single-sided process), but now - ACE inhibitors or angiotensine receptors (AT1) blockers
  - endocrine:
- hyperaldosteronism - primary (Conn's sy), secondary hyperaldosteronism (increased secretion, decreased degradation in liver failure), Cushing's sy - not only the mineralocorticoid effect but also permissive effect on catecholamines increases BP
- pheochromocytoma (Tu of adrenal medulla - vanillylmandelic acid in urine)
- hemangiopericytoma (Tu from juxtaglomerular cells)
- DM (hyperinsulinemia) - macro- and microangiopathies, retention of Na + water, increased sympathetic tonus
- hyperthyroidism - hyperkinetic circulation
- increased STH → increased ECF
- cardiovascular problems:
  - coarctation of aorta (increased BP only in the upper part of body- necessary to measure BP in lower limbs in young people)
  - aortic sclerosis - selective systolic hypertension named "elasticity hypertension"
  - aortic valvular insufficiency - large systol-diastol. pressure amplitude
- pathology of CNS:
  - intracranial hypertension (of any origin) - brain ischemia activates vasomotor center
  - encephalitis
- in pregnancy - gestosis=eclampsia (hypertension, proteinuria, edemas), in hypoperfusion of placenta or caval compression → activ. of RAAS
- increased peripheral resistance
  - stress (personality type A)
  - increased viscosity of blood (polycythemia)
- side effect of some drugs (activ. RAAS, vasoconstrictive effects, cumulation of Na)- contraceptives, inhibitors of mono-amino-oxidase

Phases of hypertension
1. increased BP without any subjective problems and organ changes
2. presence of some organ changes (due to hypertension) - left ventricular hypertrophy, changes in retinal vessels (in hypertonic patients regular ophthalmoscopy can inform about progression - effect of treatment), glomerular pathology - nephrosclerosis (with proteinuria)
3. organ changes with failures of organs - left ventricular failure, hypertensive encephalopathy, intracerebral bleedings (stroke), retinal hemorrhage, kidney failure, aortic aneurysm

Malignant hypertension = diastolic BP > 140 mm Hg - quick development of fibrinoid necrosis of cerebral, heart and especially kidney vessels
Hypertonic crisis - sudden high increase of BP (intracerebral hemorrhage)

Treatment - should be strictly causal (not symptomatic) - according to the etiology either volume (recommended thiazide diuretics), peripheral resistance, or heart activity (via beta-blockers) should be normalised
- in primary hypertension calcium channel blockers or ACE inhibitors are mostly used
- important!! - in many patients (especially younger men) elevated blood pressure is induced only by stressful life - appropriate psychopharmacs or alpha-sympatholytics should be tried
33. Arterial hypotension

Level of blood pressure that is insufficient for adequate perfusion of organs (especially brain)
- large inter-subject differences - usually it is below 100 mm Hg of systolic pressure, however, more decisive for perfusion is the mean pressure

- the brain has an autoregulatory mechanism for ensuring roughly constant perfusion irrespective of actual blood pressure - in the brain, perfusion remains about normal throughout the range ca 70 - 170 mm Hg of the mean arterial pressure
- however, in many situations mean blood pressure decreases below the critical level and hypoperfused brain displays dysfunctions up to unconsciousness

**Etiology of hypotension**
- acute hypotension
  - syncope, collapse, critical in circulatory shock, light acute dehydration (e.g. in sweating)
- chronic
  - in heart failure
  - decreased sympathetic tonus
  - Addison's disease (hypocorticalism of adrenal gland - dehydration with loss of permissive effect of glucocorticoids on catecholamines)
  - chronic dehydration (Diabetes insipidus, tubular failure)
  - side effect in some drugs, overdosing of antihypertonic drugs
  - in some people there is primary hypotension as a part of their body characteristics - it is mainly in young asthenic women
  - in very old people not only due to heart failure but also as a part of general senile atrophy of the nervous system - loss of sympathetic tonus and vasomotor activity - supported quite commonly by dehydration - frequently causes orthostatic collapse

**Pathogenesis (manifestations)**
- first manifestations are usually from hypoperfusion of brain: fatigue, weakness, sleepiness, dizziness, Parkinsonism in older people
- GIT symptomatology: loss of appetite, nausea, malabsorption - leads to asthenic habitus - still supports hypotonic factors
- low GF → development of periorbital edema during night
- low thermoregulation capacity (in cold - low perfusion of periphery, in heat - vasodilation intensifies hypotension
- hypotensive symptomatology disables these people in many activities, they are very sensitive to factors causing vasodilation → worsening of hypotension up to collapse

**Principles of therapy**
- according to primary causes - supply of fluid volume, increase of heart MV
- main problem - peripheral vasodilation - treatment is difficult because of the significant unpleasant side effects of sympathomimetics (e.g. tachycardia - palpitation, dry mouth, sweating)
34. Disorders of cardiac rhythm and conduction

Etiology
A variety of underlying factors can lead to disorders of cardiac rhythm and conduction:
- cardiac conditions, including coronary artery disease, cardiomyopathy, mitral valve prolapse, etc.
- abnormal levels of electrolytes in the blood (decreased potassium and/or magnesium are the most common associated abnormalities of electrolytes - both may be caused by the use of diuretics among other reasons)
- congenital (familial) causes of ventricular arrhythmias
- changed activity of vegetative nerves
- increased thyroid hormones
- toxins, including alcohol.
- stimulants (e.g. Caffeine, Nicotine, Cocaine)
- infection, inflammation or degeneration of the heart muscle
- they are often worse with lack of sleep or stress.

Consequences (manifestations) of hemodynamically significant arrhythmias:
Chest pain, shortness of breath, lightheadedness, dizziness, fainting (syncope) or near fainting

Disorders of impulse formation
Sinus bradycardia - HR below 60, decreased MV, BP (caused by hyperkalemia, vagal activity)
Sinus tachycardia - HR 100-150, decreased filling time, decreased BP, increased myocardial demands (caused by catecholamines, Ca influx, fever, early failure)
Atrial extrasystoles - P waves of changed morphology and deviant PQ int., influence on filling of ventricles, (hypoxia, elevated preload, cell membrane disorder, hypercalcemia)
Atrial flutter - F waves up to ca 270, decreased ventricular filling, ↓ MV (causes as for trial extrasystoles, aging)
Atrial fibrillation - f waves > 270, decreased ventricular filling (causes as for extrasystoles)
Junctional rhythm - P absent or independent, HR up to 60, regular, decreased MV (sinus bradycardia or standstill or block)
Junctional extrasystoles - premature QRS without P waves, decreased MV (hyperkalemia over 5.4 mmol/l, hypercalcemia, hypoxia, elevated preload)
Idioventricular rhythm - P absent or independent, QRS > 0.11, HR 20 - 40, severe decrease o MV (sinus, atrial and junctional bradycardia, standstill or block)
Ventricular bradycardia - as above, HR 20-60
Ventricular extrasystoles - premature QRS without P, > 0.11 s, decreased MV (aging, anesthesia, hypoxia, hyperkalemia, hypercalcemia)
Ventricular tachycardia - P absent or independent, QRS > 0.11 s, HR > 100, severe decrease of MV (causes as for ventric. extrasystole)
Ventricular fibrillation (VF) - P absent, QRS frequency over 300 - zero MV - as in ventricular standstill
VF occurs in a variety of clinical situations (antiarrhythmic drug administration, hypoxia, atrial fibrillation, very rapid ventricular rates in the preexcitation syndrome, electrical shock administered during cardioversion or caused by accidental contact with improperly grounded equipment, competitive ventricular pacing to terminate ventricular tachycardia) but is most often associated with coronary artery disease and as a terminal event. VF may be due to acute myocardial infarction or ischemia, or it may occur in the setting of chronic infarct scar. Intracellular calcium accumulation, the action of free radicals, metabolic alterations, and autonomic modulation are some important influences on the development
of VF during ischemia. Thrombolytic agents reduce the incidence of ventricular arrhythmias and inducible ventricular tachycardia after myocardial infarction.

**Disorders of impulse conduction**

Sinus block - occasionally absent P and QRS, decrease of MV (local hypoxia, scarring of conduction pathways, electrolyte imbalances, increased atrial preload)

First-degree A-V block - PQ int. > 0.2 s, no functional consequences
(hypokalemia/hypokalemia, endocarditis with abscesses, aging)

Second-degree A-V block - Mobitz I - Wenckebach's periods - progressive prolongation of PQ int. until one QRS is dropped - decrease of MV (hypokalemia, digoxin toxicity, beta-blockade, diabetes)

Second degree A-V block - Mobitz II - constantly prolonged PQ int. with some QRS missing (regular pattern), decreased MV, danger of development of Third-degree block (hypokalemia, faulty cell metabolism below the A-V node, antiarrhythmics, cyclic antidepressants, hypoxia, diabetes)

Third stage A-V block - P waves independent of QRS, MV dependent on the frequency of idioventricular rhythm - can be critically low - in some cases asystolia with immediate requirement for pacemaker (causes as above)

Preexcitation - sy Wolff-Parkinson-White - shorter PQ int. < 0.12, presence of delta wave at the beginning of QRS - depolarization of ventricles before completion of atrial systole - can decrease filling of ventricles and lower MV - not significant in resting conditions (caused by congenital existence of bundle of Kent and fibers of Maheim bypassing the A-V node, thus causing earlier depolarization of ventricles - danger of ventricular tachycardias)

His bundle blocks - in all of them there is no normal co-ordination of ventricle contraction, hemodynamically most significant in LBBB (causes - faulty cell metabolism, scar after infarction)

- RBBB (right branch His bundle block)
- LBBB (left) - less frequent
- LAH - left anterior hemiblock

All cases of dysrhythmias and conduction problems are demonstrated in practical classes.
Ischemic (coronary) heart disease represents insufficient perfusion (oxygenation) of myocardium via coronary arteries. The insufficiency of coronary arteries can be absolute (decreased volume of perfused blood) - most frequently due to atherosclerotic process or it can be relative (normal or even increased but still inadequate volume of perfused blood relative to the myocardium demands for oxygen) - typically in myocardial hypertrophy or anemia. Because of quite characteristic pains from myocardial hypoxia in the majority of patients (behind the sternum, irradiating to neck, arms under scapula), it is named as "Angina pectoris".

**Etiology**

- **Absolute insufficiency of coronary arteries**
  - atherosclerosis (with all predisposing factors described in the chapter concerning atherosclerosis) - coronary arteries represent one of the most frequent localizations of this process
  - vasospasm (predominates in countries with low incidence of atherosclerosis - e.g. Japan) - caused by catecholamines (??- beta2 receptors should cause vasodilation), histamine, serotonin, endothelin, thromboxane A₂ (from platelets), intracellular influx of calcium)
  - embolisation
  - congenital abnormality of coronary arteries (only 1 - 2% in population)
  - systemic causes - hypotension, hypovolemia, aortic valve deficiency
- **Relative insufficiency of coronary arteries**
  - myocardial hypertrophy
  - anemia, hypoxemia of another origin (respiratory insufficiency, low pO₂)
  - polyglobulia (can decrease blood flow due to high viscosity)
  - significant tachycardia (decreasing coronary filling time due to shortening of diastole - the only period of coronary perfusion) - in physical activity, fever, hyperthyroidism, when myocardial demands are increased

**Types of Angina pectoris**

- Stable angina pectoris - classic, exertional angina (related to physical activity or emotional stress), usually predictable, caused by atherosclerotic process, pain is relieved by rest and nitrates - in negative case → infarction
- Unstable angina - (preinfarction, crescendo angina) - advanced ischemia, unpredictable, also at rest, ischemia caused by combination of atherosclerotic changes and vasospasm
- Prinzmetal angina (variant) - transmural ischemia, unpredictable, exclusively at rest caused by vasospasm (even without atherosclerosis), frequently in night - in REM sleep, explained by hyperactivity of sympathetic nervous system (??- beta2 receptors?), influx of calcium, prostaglandin I₂ or thromboxane A₂

**Diagnostics**

- ECG - can be normal in the absence of pain, should be performed during an attack of angina or during exertion (bicycle ergometry) - includes transient ST segment depression and T wave inversions (subendocardial ischemia) or ST elevation can be present in transmural angina (in Prinzmetal's angina)
- radioisotope imaging with Thallium-201 - ischemic area is displayed as a "cold spot" in the scan
- coronary angiography - the most precise examination prior to by-pass surgery, percutaneous transluminal coronary angioplasty (PTCA - balloon dilation catheter is used) or use of stents
Pathogenesis
- hypoxia develops within 10 seconds of decreased perfusion
- cardiac cells remain viable for approx. 20 minutes under ischemic conditions - then → irreversible changes - myocardial infarction
- pain is transient - lasts ca 3-5 minutes, temporary ischemia has only reversible effects
- character of pains is sometimes mistaken for indigestion
- decreased contractility causes ↓ MV, ↓ BP → activation of sympathetic system → tachycardia
- use of nitrates reduces coronary spasm, peripheral vasodilation decreases afterload and preload → decreased oxygen demands
- β-blockers decrease contractility and HR = decrease of oxygen consumption, prolonged diastole helps filling of coronary arteries
- Calcium channel blockers - influence vasospasm and contractility
36. Myocardial infarction and its complications

Myocardial infarction has been the most frequent cause of death in developed countries - nowadays its incidence is decreasing thanks to modern diagnostics of ischemic heart disease and its preventive treatment (surgery).

**Etiology**
- necrosis of myocardium develops after about 20 min. of hypoxia due to obstruction of some larger branch of coronary artery
- obstruction is caused by atherosclerotic process and its complications: hemorrhage into plaque, embolism caused by thrombi or atheromatous material or vasospasm
- thrombus formation seems to be most frequent cause of occlusion
- fissuring and rupturing of atherosclerotic plaques stimulate platelet aggregation and increased vasomotor tone
- serotonin, thromboxane A₂, ADP, ATP, platelet activating factor (PAF) contribute to vasospasm

**Pathogenesis**
- myocardial oxygen reserves are used within about 8 seconds
- anaerobic glycolysis does not provide sufficient energy
- accumulation of H⁺ and lactic acid, low pH buffering capacity and high sensitivity of myocardium to low pH
- suppressed conduction, contractility → heart failure
- lysosomal enzyme activation - damaging effects
- electrolyte disturbances - loss of K, Ca and Mg from cells
- release of catecholamines - dysrhythmia, hyperlipidemia, hyperglycemia
- after 20 min. tissue necrosis develops - however, these changes are recognizable (e.g. in ECG) only after 6 - 12 hours after onset of the infarction
- for early diagnostics myoglobin (non-specific) or enzymes released by myocardial cells are detected in plasma - creatine kinase (CK), lactic dehydrogenase (LDH) - most specific for myocardial infarction is isoenzyme CK-MB
- still more specific as a marker of myocardial injury are monoclonal antibodies against troponin I
- attempts for reperfusion should be performed within 20 min. after onset of infarction - later reperfusion causes "reperfusion injury" of the myocardium via generation of oxygen free-radicals (reactive oxygen species - ROS)
- during the ischemic phase high levels of hypoxanthine accumulate in the myocardium - after reperfusion the hypoxanthine is transformed under the increased oxygen supply to uric acid, with simultaneous production of O₂⁻ and OH⁻ causing myocardium injury
- effect of antioxidants in acute myocardial infarction has been intensively studied without convincing results
- "pre-conditioning" - transient episodes of ischemia prior to infarction seem to have a beneficial effect on infarction development - decrease of myocardial injury - it is based not only on the formation of anastomoses (better outcome of infarction in people who suffer from angina pectoris compared to those who have had no apparent coronary insufficiency), but also thanks to induction of enzymes which help to protect myocardium during prolonged ischemia - e.g. protein kinase C (PKC) - its activation seems to be positively influenced by alcohol intake several minutes before ischemia
- ischemic myocardium releases also kinins that seem to have cardioprotective action (resembling effect of ACE inhibitors)
- post-infarct scar (according to it size) can significantly decrease contraction and its coordination - leads to distinct decrease of MV
ECG changes in myocardial infarction
- 12-lead ECG helps to localize the affected area (anterior, inferior-diaphragmatic, basal, lateral, posterior, transmural, subendocardial, epicardial etc.)
- acute infarction- Paarde's wave (elevation of ST segment)
- large scar after transmural infarction produces pathological Q after 2-3 weeks, small subendocardial infarction is "non-Q wave infarction"
- ST segment and T wave changes are reversible, pathological Q as a sign of a scar persist

Principals of treatment
- dissolution of thrombi by thrombolytic agents- e.g. streptokinase or plasminogen or PTCA application, acetylsalicylic acid
- oxygen supply
- pain relief - morphine
- prevention of arrhythmias (atropine or β-blockers)
- β-blockers are recommended to reduce infarction size (decreased consumption of oxygen)
- attempts to use stem cells for replacement of the infarction area

Complications of myocardial infarction
- Dysrhythmias - (due to hypoxia, vegetative nervous system dysbalance, lactic acidosis, electrolyte abnormalities, drug toxicity):
  - ventricular fibrillation - frequent cause of death
  - atrial fibrillation - no critical hemodynamic effect
  - bradycardia - can cause critical decrease of MV
  - left ventricular failure with pulmonary edema
  - cardiogenic shock - if 40% or more of the left ventricle myocardium is infarcted - causes death within first minutes
  - pericarditis - after about 2-3 days
  - Dressler's sy - after 1 week - delayed immunologically caused pericarditis - pain, fever, pleural effusion, friction rub, arthralgias
  - rupture of heart structures - wall rupture after aneurysm formation → hemopericardium, cardiac tamponade, septal rupture, rupture of papillary muscles
  - systemic thromboembolism - long prophylactic anticoagulation therapy is necessary
37. Valvular heart disease

Etiology of acquired heart valve disorders

- rheumatic fever - delayed immune response to Streptococcus A (β-hemolytic) - cross autoimmune reaction (both humoral and cell-mediated) primary against Streptococcal membrane antigens, 10% of people after rheumatic fever display involvement of heart valves, prevention - treatment of pharyngeal Streptococcal infections (tonsillitis) with ATB by the 9th day from the onset at latest
- acute form - pancarditis, polyarteritis, involvement of joints, CNS, subfebrilias 7-14 days after Streptococcal infection, most susceptible are children between ages 5-15 years
- chronic form - valvular disorders (even many years after acute attack), almost exclusively in the left heart, fibro-hyaline thickening + commissural adhesions - insufficiency and/or stenosis (quite frequently combined)
- skin infections cannot cause rheumatic fever but can cause glomerulonephritis
- infectious (bacterial) endocarditis - insufficiency of left ventricle valves, predisposition - formerly existing primary involvement of valves, endothelial damage
  - infection - bacteriemia (via hemodialysis, surgery, urinary infections, teeth infection, skin infection, intravenous drug abuse
  - 60% Streptococcal - on formerly involved valves
  - 20% Staphylococcus - also normal valves, very lethal - up to 70%
  - colonization on endocardial surface - growth of vegetation - destruction of valve - acute → death, chronic →adaptation (hypertrophy)
  - release of vegetations = septicemia (central pyemia) → abscesses
- immune reaction - immunocomplexes (Systemic lupus ...)
- mechanical injury - catheterization, turbulent flow in primary disorder
- hypoxia, stress, non-stable angina pectoris, high altitude, exposure to cold
- non-bacterial thrombotic endocarditis
- prolapsus of mitral valve

Pathogenesis - manifestations

- valvular stenosis
  - pressure overload = increased afterload → concentric myocardial hypertrophy (with relative insufficiency of coronary arteries)
  - long-lasting compensation is possible, late decompensation
- valvular insufficiency
  - volume overload = increased preload → excentric hypertrophy
  - short compensation → dilation (insufficient overlapping of myosin and actin disables contraction), decompensation

Mitral stenosis
- stasis of blood in lungs → pulmonary hypertension (post-capillary) with pulmonary edema
- right ventricular failure (with all consequences)

Mitral insufficiency
- volume overload of the left ventricle and atrium - dyspnea, hemoptysis - pulmonary post-capillary hypertension not so frequent, left heart failure - decreased MV → fatigue, weakness

Aortic stenosis
- increased afterload → left ventricular failure, fatigue, dyspnea on exertion (pulmonary edema), angina pectoris (hypertrophy - relative insuff. of coronary arteries, their filling is
worsened due to Venturi effect (increased velocity of blood → suction effect at coronary orifices), syncopes - especially on exertion

Aortic regurgitation
- volume overload of left ventricle → left heart failure, dyspnea, syncope, angina, large pulse amplitude

Tricuspid regurgitation - almost exclusively congenital disorder
- right heart failure, peripheral edema, atrial fibrillation, dyspnea
38. Congenital heart defects

- incidence - in about 1% of newborns (without abortions)
- about 1/3 of them die during the first year of life
- improved intrauterine diagnostics (ultrasound) lead to decrease of deaths

Etiology
environmental and genetic risk factors:
- intrauterine viral infection (mainly rubella)
- diabetes mellitus, phenylketonuria, maternal alcoholism, hypercalcemia
- drugs - thalidomide, lithium, dilantin
- increased maternal age
- antepartum bleeding, prematurity

Genetic:
- Trisomy 18 - 90% of defects: ventricular septal defect, patent ductus arteriosus Botali, patent foramen ovale, bicuspid aorta, dextrocardia
- Trisomy 13 - 15, 80% of defects: ventricular septal defect, atrial septal defect, patent ductus arteriosus, anomalous pulmonary venous connection, bicuspid aorta
- Down sy - trisomy 21, 12 - 44% of defects: endocardial cushion defect, ventricular septal defect, patent ductus arteriosus, atrial septal defect, transposition of great vessels, tetralogy of Fallot, persistent truncus arteriosus, coarctation of aorta
- Turner sy - 20 - 40% of defects: coarctation of aorta, pulmonary stenosis, aortic stenosis, patent ductus arteriosus, septal defects

Incidence of congenital heart defects (in percentage of all cases)
- Ventricular septal defect - 25 - 30% - blood is usually shunted from left to right
- Atrial septal defect - 6 - 8% - blood is shunted from left to right
- Patent ductus arteriosus (Botali) - 6 - 8% - blood from aorta is shunted back to the pulmonary artery
- Coarctation of aorta - 5 - 7% - enormously increased afterload → left ventricular failure
- Tetralogy of Fallot - 5 - 7% - ventricular septal defect + dextroposition of aorta, right ventricular outflow obstruction and right ventricular hypertrophy, blood is shunted from right to left
- Pulmonic valve stenosis - 5 - 7% - decreased pulmonary blood flow + right ventricular hypertrophy
- Aortic valve stenosis - 4 - 7% - increased afterload, left ventricular failure
- transposition of great vessels - 3 - 5% - life-incompatible when simultaneously ventricular septal defect is not present (as in tetralogy of Fallot)

Classification
- Acyanotic - with no shunting or with shunting from left to right
- Cyanotic - with significant shunting from right to left
Shunting can differ according to actual pressure proportion between the left and right heart (dependent on an outflow obstruction)

Normal - Increased - Decreased pulmonary flow
- increased pulmonary flow → pulmonary hypertension and possibility of Eisenmenger sy (change in shunting to right → left in ventricular septal defect = cyanosis)
39. Heart failure

*Heart failure* is the condition in which the heart as a pump is unable to meet the metabolic requirements of the tissues for blood. The failure is defined *relative to the metabolic requirement*, so it is not possible to define a particular critical MV which is insufficient. *Myocardial failure* refers specifically to abnormalities in myocardial function - circulatory compensatory mechanisms can delay progression to failure of the heart as a pump. *Circulatory failure* refers to the inability of the cardiovascular system to perfuse the tissues adequately (includes alteration in blood volume, vascular tone).

- the most frequent disease requiring health care in patients over 65 years, 50% mortality, high cost of treatment

**Etiology**
- Myocardial disease
  - Cardiomyopathies
  - Myocarditis
  - Coronary insufficiency - Myocardial infarction
- Valvular heart disease
  - Stenotic valvular disease
  - Regurgitation valvular disease
- Congenital heart defects
- Pericardial disorders
  - Constrictive pericarditis
  - Cardiac tamponade (hemopericardium)
  - Congenital disorders or neoplastic disease
- Increased pressure work
  - Systemic hypertension
  - Pulmonary hypertension (e.g. emphysema, embolism)
  - Polycythemia
- Increased volume work
  - Arteriovenous shunt
  - Hypervolemia
- Increased perfusion work
  - Thyreotoxicosis
  - Pheochromocytoma
  - Anemia

**Left heart failure - pathogenesis**
- low cardiac output (insufficient for actual body oxygen demands) causes general hypoxia which influences function of all organs
- activation of the sympathetic system causes centralization of the circulation which keeps vital organs better perfused compared to peripheral tissues and the splanchnic area
- due to peripheral hypoxia and anaerobic metabolism, lactic acidosis can develop compensation is difficult despite hyperventilation (low perfusion ),and kidney compensation also fails because of kidney ischemia
- acidosis leads to vasodilation, increased permeability and edemas formation - these mechanisms subsequently cause circulatory failure
- chronic hypoxia increases erythropoiesis with increased viscosity of blood contributing to left heart failure via increased afterload and worse perfusion of coronary arteries
- manifestations are the same as in any other primary disorder causing peripheral hypoxia with lactic acidosis
- stasis of blood in pulmonary veins and capillaries (postcapillary hypertension) increases hydrostatic pressure over 25 mm Hgs (oncotic pressure) and leads to pulmonary edema (= congestive heart failure)
- pulmonary edema causes respiratory insufficiency which contributes to general hypoxia and lactic acidosis
- slowing of blood flow in periphery (with simultaneously increased viscosity) predisposes these patients to thrombogenesis and embolism
- increased overload activates release of natriuretic peptide which should decrease volume of circulating blood - however, its activity is lower compared to effect of RAS system (see below) - attempts to use natriuretic peptide in a higher dose as a pharmac in heart failure

**Principles of treatment of congestive heart failure**
- restriction of physical activity
- instead of bed a chair is preferable - there is lower hydrostatic pressure in pulmonary circulation in vertical position = preventive factor of lung edema
- restriction of sodium intake → lower circulatory volume (preload)
- digitalis glycoside - increased contractility
- inotropic agents - increases MV
- diuretics - decrease of circulatory volume (preload) - prevention of lung edema (instead of formerly used venipuncture
- vasodilators - decrease afterload (block effect of catecholamines and angiotensin)
- important monitoring of the hydrostatic pressure in pulmonary capillaries = "wedge pressure" via Swan-Ganz catheter (should not exceed oncotic pressure - normally up to 20 mm Hgs -
- consider intraaortic baloon pump, left ventricular assist device or heart transplantation
- artificial heart (various prototypes - all have the same problem - to supply adequate energy it must be too heavy - limits mobility

**Right heart failure - pathogenesis**
- function of the right ventricle is mainly dependent on the blood pressure in the pulmonary precapillary circulation
- in the case of right ventricle failure - stasis of blood in the venous system causes:
  - peripheral edema (due to increased hydrostatic pressure and later also due to hypoperfusion and acidosis) worsening towards evening (particularly in the lower limbs in the upright position)
  - hepatic angina with venostatic induration of the liver and subsequent centrilobular cirrhosis with liver failure and ascites
  - splenomegaly causes anemia
  - venostasis in GIT - edema, malfunctioning
  - stasis of blood in the brain - edema
40. Cardiac compensatory mechanisms

Myocardial hypertrophy (concentric)
- in the case of prolonged increased afterload
  - aortic stenosis
  - systemic hypertension (pulmonary hypertension for the right ventricle)
- myocardium cannot increase number of cardiomyocytes - it can only hypertrophy
  (enlargement with increase of myofibrils, mitochondria)
- hypertrophy requires more energy - possible hypoxia
- after exhaustion of sources → dilation → quick decompensation
- in the right ventricle there are very limited possibilities of hypertrophy - quick
decompensation

Dilation of the heart (excentric hypertrophy - according to classification of Pathologists)
- reaction to increased preload = increased filling of ventricles
- e.g regurgitation of blood in aortic valve insufficiency
- according to Starling's law, the higher the filling of ventricles, the better is their contractility,
  however this is not the case for extreme situation where overlapping of actin and myosin
  filaments is insufficient for normal contraction (normal length of sarcomeres is 0.5 - 2.2
  μm - at both extremes contractility decreases)
- quick development of dilation and failure of the heart

Release of natriuretic peptides
The natriuretic peptides are hormones released mainly from the cardiac ventricles in response
 to increased wall tension, and involved in volume homeostasis and cardiovascular
remodeling. So far, Atrial Natriuretic Peptide (ANP), Brain Natriuretic Peptide (BNP)
and C-type Natriuretic Peptide (CNP) have been identified.
The levels of B-type natriuretic peptide are elevated in patients with left ventricular
dysfunction and they correlate with both the severity of symptoms and the prognosis.
Observational studies have suggested that rapid measurement of B-type natriuretic
peptide in the emergency department may be useful in establishing or ruling out the
diagnosis of heart failure in patients with acute dyspnea. Furthermore, plasma peptide
levels predicted the risk of death and cardiovascular events after adjustment for
traditional risk factors.
41. Peripheral compensatory mechanisms in heart failure

Heart failure → decreased MV → :
- activation of sympathetic system → increased HR+ increased contractility + increased peripheral resistance → increased MV + increased BP = compensated heart failure
- activation of RAS (due to hypoperfusion of kidney) → increased circulatory volume + peripheral resistance - up to some level it can help in compensation

!!!However!!!
- activation of sympathetic system:
  - decreases diastolic time → worse coronary perfusion
  - increases afterload → increases pressure work and consumption of oxygen (also increased contractility requires more oxygen)
  - decreased perfusion of kidney (due to hypoperfusion in the splanchnic area) moreover activates RAS
- activation of RAS:
  - increases preload - leads to earlier dilation because of decreased contractility (if not primary then secondary because of hypoxia)
  - contributes to pulmonary edema formation in failing left ventricle

Both mechanisms contribute to (accelerate) heart failure, mainly when primary is some myocardial problem like coronary insufficiency - in such a case the main task in treatment is to decrease heart work - consumption of oxygen via blocking of these compensatory systems
There is production of vasodilating substances in tissues as a response to extreme hypoperfusion - this can partially help
Pulmonary circulation, ventilation/perfusion ratio, effect of hypoxia

Dual circulation - nutritive and functional
- Bronchial circulation - oxygenated blood from systematic circulation for metabolic needs from thoracic aorta
  - larger veins → azygos system → sup vena cava - right heart
  - small veins → pulmonary veins (shunt - 2-3% of cardiac output)
- Pulmonary circulation
  From right ventricle to left atrium - gas exchange

Characteristics of pulmonary circulation
• Low pressure
  - systolic pulmonary arterial pressure at rest <30 mmHg or the mean pressure < 20 mmHg = lower than colloid osmotic pressure (25 mmHg)
• Great distensibility, low resistance
  - relatively low workload for right heart
  - possibility to increase blood flow during exercise without significant increase of pulmonary blood pressure

Regulation of pulmonary flow - differences from the systematic circulation:
• sympathetic nervous system – minimal influence
• ↑ of blood pressure in pulmonary capillaries → precapillary vasoconstriction (= prevention of edema)
• hypoxia (local (e.g. atelectasis), generalized (obstruction, restriction diseases, high attitude)
  → precapillary vasoconstriction !!!(to maintain normal ventilation/perfusion ratio)

Ventilation/perfusion (V/Q) ratio
optimal V/Q relationship = necessary for optimal gas exchange
- average V/Q = 4/5 = 0.8
Ventilation without perfusion = dead space
Perfusion without ventilation = shunt
Local regulation of V/Q dysbalances
1) Reduction of blood flow → broncho-constriction (= air redistribution)
2) Obstructed bronchioles - hypoxia + accumulation of CO₂ → vasoconstriction (= blood redistribution)

general hypoxia (high altitude, pulmonary diseases) - whole lung vasoconstriction (dis disadvantageous)
prolonged vasoconstriction → pulmonary hypertension (PH)

Pulmonary perfusion depends on gravity
- smallest in apical zone
- it is largest in basal zone (blood amount = 8x larger than in apex)
- apex - better ventilation than perfusion
- basal part - - better perfusion than ventilation (pulmonary edema starts at base of lungs)
43. Ventilatory and diffusion lung dysfunction

Gas diffusion depends on:
- partial pressure of gas in alveoli
- pressure gradient
- diffusion coefficient (CO₂ - 20x easier transport)!!!
- extent of alveolo-capillary area
- length of diffusion pathway - thickness of alveolo-capillary membrane

Values of partial pressure of gases

<table>
<thead>
<tr>
<th></th>
<th>pO₂ (mm Hg)</th>
<th>CO₂ (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air in alveoli</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>Arterial blood</td>
<td>95</td>
<td>40</td>
</tr>
<tr>
<td>Venous blood</td>
<td>40</td>
<td>46</td>
</tr>
</tbody>
</table>

Diffusion lung dysfunction results from:

a) Restriction of alveolo-capillary membrane extent
   - atelectasis
   - pneumothorax
   - emphysema (rupture of alveoli)
   - pneumonectomy
b) Restriction of capillary bed
   - successive pulmonary embolism
c) Increased thickness of alveolo-capillary membrane (longer diffusion pathway)
   - atypical pneumonia (inflammatory process in interstitium)
   - increased thickness of membrane by accumulation of fibrous tissue
     - primary idiopathic fibrosis,
     - fibrosis due to pneumoconiosis,
     - irradiation injury,
     - sarcoidosis,
     - noxious inhalation of nitrogen oxides (silo filler), chlorine, sulphur oxides, metal fumes)
     - mucoviscidosis
   - increased thickness of capillary wall
   - intraalveolar edema or exudate (left heart failure, bacterial pneumonia, ARDS)

Signs of inadequate gas exchange

Dyspnea
Cyanosis
= bluish coloration of skin resulting from ↑ in absolute amount of reduced Hb
= detectable when amount of reduced Hb is 5 g/dl or more (normal is 2.5 g/dl)
Central cyanosis - insufficient oxygenation of Hb in lungs, apparent in face, lips, earlobes
44. Obstructive respiratory diseases

main pathological change = ↑ resistance against flow of air
→ difficulties during expiration
→ air trapping
→ ↑ of residual volume → ↓ respiratory excursions → insufficient ventilation
→ change in composition of alveolar air → hypoxemia and event. hypercapnia

Bronchial asthma
Obstruction of medium-sized bronchi and bronchioli down to 1 mm diameter
Allergic asthma (= extrinsic a.) - predominantly in children
- results from sensitization to allergen
IgE AB – bound to mast cells

Idiopathic asthma (intrinsic a.) - after 40
usually after infections

Acute asthma
Exposure to allergen → IgE stimulation → Mast cell degranulation →
Release of histamine + slow reacting substance → Mucus secretion, Inflammation +
Bronchospasm → Airway narrowing

Chronic asthma
- Muscle thickening
- New vessel formation
- Epithelium thickening + deposition of collagen beneath epithelium → further narrowing
  of airways between acute seizures

Although asthma begins as an allergic response, in time attacks can be triggered by
nonspecific factors such as cold air, exercise, and tobacco smoke
Asthma attack lasting for days = “status asthmaticus”

Chronic bronchitis
= clinically characterized by coughing for at least 3 months in a year in at least 2 successive
years
Bronchi wall inflammation
  - inflammatory infiltration of wall, edema
  - inflammatory exudate
small bronchioles ⇒ destruction of walls – ev bronchiectasias
hypertrophy of mucous glands -↑ production of mucus

Smoking, air pollution → ↓ ciliary and phagocytic activity of epithelium → mucus accumlation → cough + expectoration → obstruction
obstruction → expiratory dyspnea → ↑ of residual volume → hypoventilation → hypoxia, hypercapnia

→ precapillary vasoconstriction – pulmonary hypertension, event. cor pulmonale
→ ↑ production of erythropoietin → polycythemia
→ cyanosis (“blue bloaters“)
→ emphysema (obstruction with difficult expiration increases intraalveolar pressure –
  leads to rupture of alveolar membranes → emphysematous bullae)
chronic inflammation – proteolytic enzymes + pressure or trapped air
Emphysema
= dilation of the alveolar spaces and destruction of the alveolar walls
Bullae represent restriction of alveolo-capillary membrane + capillary bed
+ ↑ residual volume (decreased expiratory reserve volume → decrease of VC)
Primary (idiopathic) emphysema
= Panlobular
- less common
- both central and peripheral parts involved
Pathogenesis
Inherited absence of Alpha1-anti protease (homozygotes) decrease protection of lung against proteases (destroy elastin + collagen fibers) produced by bacteria, neutrophils, monocytes, macrophages

Emphysema accompanying chronic bronchitis (most common form)
= Centrilobar emphysema
- smokers, more men
  - low production of antiprotease - heterozygotes (rel. common – cca 10% of population)
  - smoking + chronic bronchitis → inflammation → ↑ production of proteases + oxidants
    → inhibition of Alpha1-anti protease
- affects bronchioles and alveolar ductuli

Senile emphysema
- deterioration of elastic + reticular lung fibers due to aging -usually does not significantly decrease lung function

Pathogenesis of emphysema
Pressure of air trapped in enlarged spaces + proteolytic enzymes → bullae
Obstructive cause (when resulting from chronic bronchitis)
restriction result - bullae ↑ residual volume (decreased vital capacity) = mixed disorder!!!

- Alveolo-capillary septa reduction → pulmonary capillary bed reduction
  → blood flows through remaining capillaries → hypertension (tendency to edema)
  → protective vasoconstriction (↓ edema development possibility) → precapillary hypertension → Cor pulmonale
- ↑ residual volume → ↓ vital capacity → dyspnea, especially on exertion
  → barrel shape thorax in inspiratory position
- cyanosis is relatively rare (dyspnea is usually only on exertion) - „pink puffers“
- superficial bullae may rupture to pleural cavity → pneumothorax
45. Restrictive pulmonary diseases

= reduction of all lung volumes including vital capacity
Causes:
1) non-pulmonary deficits (chest injuries, respiratory muscle weakness, paralysis)
2) pleural disorders (inflammations, pain, pneumothorax)
3) pulmonary deficit
   - atelectasis
   - pneumonias
   - pulmonary fibrosis - abnormally stiff, non-compliant lungs

Atelectasis
Alveoli are collapsed, out of ventilation - ↓ of VC and of residual V
- Absorption atelectasis - distal to an obstruction (intrinsic - bronchial) or extrinsic - tumor, nodus, aneurysm
- Compression atelectasis - compression of a larger part of lung causing its collapse

Pneumonia
= Acute inflammation of lung parenchyma

Bacterial pneumonias
- Streptococcus pneumoniae (75%)
- intra-alveolar suppurative exudate with consolidation
- lobar
- lobular = bronchopneumonia - infectious areas (3-4 cm) surround and involve bronchus

Atypical pneumonia
Alveolar spaces are free, inflammation is in interstitial space
Bacteria Mycoplasma pneumoniae - most common
   Legionella sp. (Legionnaire's disease)
   Francisella tularensis (tularemia)
   Bacillus anthracis (anthrax)
   Chlamydia psittaci (psittacosis)
   Coxiella burnetii (Q fever)
Viruses: Influenza, Parainfluenza, Adenovirus
Fungi

Non-infectious pneumonias
Chemical - aspiration pneumonia
- aspiration of acidic stomach content (anesthesia), very fast onset
  massive - death from obstruction
  less massive - dyspnea, tachypnea, fever
- aspiration of non-acidic matter (food) - obstruction

Pneumoconioses
= diseases caused by the inhalation of certain inorganic or organic dusts
some of the dusts, when inhaled, produce a fibrous tissue reaction
the dust inhalation is usually related to certain occupations

Inorganic dusts:
   Silica – silicosis (grinders, sandblasters)
Silica particles destroy macrophages by which they are phagocyted, which results in the formation of fibrotic nodules
Coal - black lung – coal miner's pneumoconiosis
Iron - siderosis
Asbestos - asbestosis
Organic dusts
Sugar cane - bagassosis
cotton - byssinosis
moldy hay - farmer's lung
maple bark
Organic material can have unusual antigenic effect → allergic reaction

Symptoms
No symptoms (early stages) to progressive dyspnea on exertion

Pathogenesis
- extensive fibrosis means lung stiffening - loss of lung elasticity → restriction of lung volumes
- dyspnea reflects the poor compliance and results in a concomitant ↑ of the work of breathing
- in the case of the event. destruction of septa hypoxemia, pulmonary hypertension and cor pulmonale may develop

Pneumothorax
Presence of air in pleural space → partial or complete collapse of the lungs
break in parietal pleura (trauma) or in visceral pleura (subpleural air pocket or necrosis rupture)

Types of pneumothorax
1) Open pneumothorax
2) Tension pneumothorax - one-way valve
   most dangerous
   intrapleural pressure gradually increases
   - compression of the other lung
   - compression of venous return → blood pooling in capacitance veins
   → cardiovascular collapse and shock
46. Pulmonary arterial hypertension, pulmonary edema

= systolic pulmonary arterial pressure at rest > 30 mmHg
    or the mean pressure > 20 mmHg

Primary pulmonary hypertension (PH)
Caused by problem in pulmonary vasculature itself - likely deficient release of vasodilator mediators from endothelium

Secondary pulmonary hypertension
General causes:
- chronic hypoxia from lung disease
- high blood flow through lung - cardiac shunt
- obstacle to blood flow – mitral stenosis, left heart failure, emboli

Classification of secondary PH (related to the possibility of pulmonary edema development)
1) Precapillary pulmonary hypertension - results from:
- shunts - ↑ flow through pulmonary vascular bed → precapillary HT
- long-term hypoxia (e.g. chronic obstructive pulmonary disease)
- emphysema – alveolar wall destruction - bullae
  ⇒ vascular bed reduction ⇒ ↑ pressure in remaining capillary bed + hypoxia (if on basis of chronic bronchitis) + direct compression of capillary bed by bullae + ↑ RV
- emboli (frequently from deep lower limb veins - phlebothrombosis)
  small emboli - only local inflammation, pain, dyspnea (↓ of alveolo-capillary membrane extent)
  massive embolisation - large embolus
    → dyspnea, tachypnea, tachycardia
    → larger vessel closure → reflexive bronchoconstriction (to maintain normal V/Q ratio)
    → hypoxia → (reflexively + endothelin) → vasoconstriction also of non-obturated vascular bed → precapillary PH (primary it is mechanism for keeping of constant ventilation/perfusion ratio)

Pulmonary infarction is rare because of existence of dual circulation - necrosis, hemoptysis

Precapillary PH consequences
*This type of PH does not lead to edema!!! In the case of increasing pressure, vasoconstriction at the of arteriole level keeps roughly normal perfusion and hydrostatic pressure at the capillary level!!*
However, represents ↑ resistance – *increased afterload for the right ventricle!!!*
→ blood accumulates in front of pulmonary artery → pulmonary valve dilatation – insufficiency → COR PULMONALE (= right ventricle hypertrophy and dilatation) → right heart failure

2) postcapillary pulmonary hypertension
= pulmonary venous hypertension
- results from left heart failure, mitral stenosis, mitral insufficiency
- stasis of blood in pulmonary veins → ↑ pressure in capillaries → PULMONARY EDEMA!!! (there is no protective mechanism against edema formation here – no available vasoconstriction in the venous system)

Cor pulmonale
= hypertrophy and dilation of right ventricle resulting from lung disorder
Causes:
- Pulmonary obstructive disorders (most common - chronic bronchitis)
- Pulmonary restrictive disorders
- Primary vascular disorders (primary pulmonary hypertension)

Cor pulmonale consequences
Right ventricle dilatation → right atrium dilatation → ↑ amount of blood in neck veins
→ blood accumulation in systematic vessels → ↓ venous return to heart → ↓ MV
→ peripheral vasoconstriction with peripheral cyanosis
right heart failure signs = lower limb edemas, hepato-splenomegaly with consequences

**Pulmonary edema**
= excessive accumulation of fluid in interstitial spaces and in alveoli - decreases diffusion of gases → hypoxemia

Causes
- hydrostatic pressure in pulmonary capillaries
  - mitral stenosis
  - mitral insufficiency
  - left heart failure
  starts in lung bases (highest hydrostatic pressure)
- ↓ oncotic pressure in capillaries
  - nephrotic sy - loss of proteins
- damage to capillary wall - ↑ permeability – circulatory shock, ARDS

Signs of pulmonary edema
Interstitial edema: tachypnea, dyspnea, orthopnea, cyanosis
Intralveolar edema: + bubble sounds, cough, pink sputum
47. Adult respiratory distress syndrome - ARDS

= different from RDS – respiratory distress syndrome in premature newborns – shortage of surfactant
ARDS = pulmonary edema leading to acute respiratory failure
mortality = 50% within 48 hours of onset if not promptly diagnosed and treated

Causes of ARDS
- injury to the lung from trauma (most common cause)
- trauma-related factors - fat emboli, sepsis,
- anaphylaxis
- aspiration of gastric contents
- diffuse pneumonia, especially viral pneumonia
- drug overdose - heroin, aspirin
- inhalation of noxious gases - nitrogen dioxide, ammonia, chlorine

Pathogenesis
- causative agents induce release of histamine, serotonin, and bradykinin → damage of alveolo-capillary membrane → filling of alveoli by fluid from circulating blood with high content of proteins!!! (compared to normal pulmonary edema - in heart failure)
- ↑ capillary permeability → proteins and fluids leak out, increasing interstitial osmotic pressure and causing also interstitial pulmonary edema
- first oxygenation is impaired, but CO₂ still crosses alveolar capillary membrane = partial respiratory insufficiency (see below)
- later fluids in the alveoli damage surfactant and impair the cell's ability to produce more surfactant → collapse of alveoli - impairment of also CO₂ exchange - global respiratory failure
- event. recovery – organization of edema - pulmonary fibrosis
48. Respiratory Failure

Acute x chronic

**Chronic respiratory failure**
= long lasting impairment of respiratory functions
= combination of disease + compensatory mechanisms
blood gases - mildly abnormal at rest,
but markedly abnormal during exertion

**Acute respiratory failure**

Arterial blood gases definition:
pO$_2$ of 50 - 60 mmHg or less
with or without pCO$_2$ of 50 mmHg or more

**Causes:**
1) extrinsic - normal lung, but ↓ minute ventilation
   - depression of respiratory centre
   - neuromuscular diseases (myasthenia gravis, multiple sclerosis)
   - chest disorders + injuries
2) intrinsic
   - COPD - acute-on-chronic failure
   - massive pulmonary oedema
   - extensive pneumonia
   - ARDS

**Classification of respiratory failure**
1) Hypoxemic respiratory failure = Hypoxemia + normo/hypocapnia
2) Ventilatory (hypercapnic) failure = Hypercapnia + hypoxemia

**Partial (hypoxicemic) respiratory failure**
1) low ventilation (V), normal perfusion (Q) (= low V/Q), alveolo-capillary restriction
   - pneumonia
   - atelectasis
   - pulmonary edema
   - ARDS (earlier phase)

low V/Q $\Rightarrow$ ↓ PaO$_2$ and $\uparrow$ PaCO$_2$ in blood from affected regions
   $\Rightarrow$ hyperventilation in remaining alveoli
   - sufficient for CO$_2$ elimination but not for adequate O$_2$ income (Hb saturation limit)
   $\Rightarrow$ hypoxia + normocapnia

2) venous-to-arterial (or right-to-left) blood shunting
   alveoli collapsed or filled with exudate - pneumonia, edema
   $\Rightarrow$ severe hypoxemia, but CO$_2$ might be normal (comp. hyperventilation)
   - or even decreased $\Rightarrow$ hypocapnia, respiratory alkalosis

3) normal V + ↓ Q (high V/Q)
   - acute decrease of heart output
   - acute decrease of pulmonary blood flow - pulmonary embolisation
     (very massive = “dead space” diseases – no perfusion)

4) “dead space” diseases - normal V, but no Q
   - acute pulmonary immobilization

5) thickening of alveolo-capillary membrane
   - interstitial pneumonia

**Global (hypercapnic) respiratory failure**
= characterized by hypoxemia + hypercapnia

1) Extrinsic causes = “pure” hypoventilation e.g. chest injury, respiratory center depression
2) very severe respiratory disease
   • obstruction d
   • restriction d. – massive pneumonia, ARDS
3) very massive pulmonary embolisation (= “dead space” diseases – no perfusion)

Clinical symptoms of respiratory failure
Combination of underlying cause + hypoxemia + event. hypercapnia

Hypoxia:
• CNS – agitation, restlessness, headache, confusion
• tachycardia
• vasoconstriction in pulmonary vessel bed
• tissues - anaerobic metabolism – lactacidosis (with consequences to peripheral circulation)

Hypercapnia
• always accompanies hypoxia ⇒ mixture of symptoms
• Stimulation of respiratory center up to level of 70 mmHg
  further ↑ ⇒ respiratory center depression
  adaptation to hypercapnia (central chemoreceptors adapt to long-termed hypercapnia)
• Depression of CNS - confusion to coma, severe condition = “CO₂ narcosis”
• Respiratory acidosis (contributes to generalized edema formation – possibility of brain edema with intracranial hypertension!!! – see below)
• Severe hypercapnia - systematic vasodilation - hypotension - circulatory shock!!!
49. Hypoxia

= shortage of O₂ in peripheral tissues
(Hypoxemia = decrease of O₂ in arterial blood, Asphyxia = shortage of O₂ and accumulation of CO₂)

1) hypoxic hypoxia
- ↓ atmospheric partial pressure of O₂ - ↓ pO₂ in arterial blood
  acute – hyperventilation (stimulation of ventilatory center), activation of cardio-vascular system - ↑ heart frequency + blood pressure, chronic hypoxia leads to compensatory polycythemia (in about 14 days – can even worsen peripheral oxygenation due to decreased perfusion - increased viscosity of blood)

2) anemic hypoxia
  ↓ capacity of oxygen transporters
  (CO, anemia…)
  normal pO₂, but low absolute amount of oxygen
  respiratory center does not react
  (= no hyperventilation)

3) stagnation hypoxia
  distinct A-V difference = all oxygen is consumed
  heart failure, emboli, thrombosis
  blood pO₂ = normal

4) histotoxic hypoxia
  inability of tissues to use oxygen
  deficit/inhibition of tissue respiratory mechanisms
  high oxygen content in venous blood
  causes: poisoning (H₂S…), radiation,

Compensatory mechanisms in hypoxia
- hyperventilation (due to reaction of peripheral chemoreceptors)
- accumulation of 2,3-DPG in red blood cells and ↓ of blood affinity to O₂
- ↑ of red blood cells number (erythropoietin)

Clinical signs of hypoxia
- ↑ of heart output (tachycardia) – via activation of sympathetic system (endogenous stress)
- ↑ of pulmonary ventilation (hyperventilation, dyspnea)
- paleness of skin and mucous membranes (in anemia or ischemia)
- cyanosis (in case of ↑ deoxygenated Hb)
- ↓ of skin temperature (in peripheral ischemia due to sympathetic activation)
- ↑ fatigue
- ↓ physical performance
- ↓ mental performance
- pain (acidosis)
50. Hyperoxia, hyperbaria, decompression

• Normobaric oxygenotherapy = breathing of 100% O₂
  = effective in disorders accompanied by ↓ pO₂ (high attitude) but not in those related to shunts (inborn right to left heart shunt)
• Hyperbaric oxygenotherapy (in hyperbaric chamber)
  - ↑ PaO₂ and amount of free O₂ dissolved in blood
  - effective in CO poisoning + in injuries infected by anaerobic microorganisms
  - only short-term therapy is possible because of toxicity of O₂

Toxicity of O₂
Depends on pO₂ and on duration of exposure
- depression of breathing (in cases where the shortage of O₂ is the only stimulus for breathing
  – e.g. in chronic bronchitis, when the central chemoreceptors are adapted to hypercapnia)
- lungs – change of capillary permeability and ↓ surfactant production
  pulmonary edema, atelectasis
- tissues – vasoconstriction, ↑ production of free oxygen radicals
- premature newborns – retina neovascularisation, induction of fibrotic process that leads to detachment of the retina

Diving - ↑ pressure = hyperbaric condition
  40 m → loss of judgment, drowsiness
  80 m → nitrogen narcosis

Caisson disease = decompression disease
rapid loom
(every 10 m = +100 kPa – N dissolves esp. in fat)
loom – N bubbles (other gases metabolize more quickly)
  → joint pains
  → neurologic signs
  → embolization
51. Nephritic syndrome

Nephritic syndrome is a group of glomerular disorders with inflammatory origin (glomerulonephritis - GN).

Clinical aspect:
- acute GN - typically benign
- rapidly progressive GN - rapidly advancing to complete damage
- chronic GN - slow, often late recognized

Pathological aspect:
- diffuse GN- most or all glomeruli are affected
- focal GN - only some glomeruli are affected
- segmental GN - only some capillary loops of given glomerulus are damaged

Histological aspect: minimal change, membranous, proliferative

Immune aspect:
- immune complex GN
- pauci-immune – idiopathic rapidly progressive GN

Clinical characteristics:
- hematuria with red cell casts
- mild proteinuria
- ↓ GFR
- oliguria
- azotemia
- hypertension

Pathogenesis:
- often immune etiology
- proliferative inflammatory response following immune complex depositions or glomerular infiltration by immune cells
- antigens - endogenous - systematic lupus, tumors (pulmonary carcinoma)
  - exogenous - β hemolytic Streptococcus, hepatitis B, treponema

1) Damage of glomerulus by complexes arising in plasma (these are trapped in glomeruli during filtration)
   forms predominantly sub-endothelial depositions
   antibodies – usually of IgA type (IgA nephropathy, Henoch-Schönlein purpura, lupus erythematoses)

2) Damage of glomerulus by complexes arising directly in renal structures
   - immunocomplexes originate from exogenous antigen adhering to glomerular structures and corresponding antibodies
   - immunocomplexes originate from interaction of renal antigen and antibodies
     - Cross reaction – β hemolytic Streptococcus + glomerular basal membrane
       (the other hypothesis is that streptococcal neuraminidase alters Ig and this reacts with basal membrane antibodies
     - Autoimmune defect – antibodies against glomerular basal membrane
       - Anti GBM nephritis
       - Goodpasture sy (+ antibodies against basal membrane in pulmonary capillaries)

3) Cell mediated injury – T lymphocytes – these are activated when macrophages phagocytose antigens, but are not able to destroy them. T lymphocytes destroy the glomerular structures directly or through cytokines

Immunocomplex deposition (trapped during filtration or arising in situ)
→ complement activation + chemotaxis → enzymes (or presence of activated T-lymphocytes)
→ capillary wall damage → ↑ permeability → hematuria, mild proteinuria – dark (cola-like) urine
→ mechanical effect of immune complex deposition, platelet aggregation, glomerular thrombosis, release of vasoactive amines, mesangial proliferation and proliferation of extracellular matrix (sclerosis) → ↓ GF, oliguria
→ Fluid retention, Edema
→ Azotemia
→ Hypertension

Causes
- Post-streptococcal glomerulonephritis (most frequent)
- Viral diseases such as mononucleosis, measles, mumps
- IgA nephropathy (Berger's disease)
- Henoch-Schönlein purpura
- Goodpasture's syndrome
- Rapidly progressive (crescent) glomerulonephritis
- Systematic lupus erythematoses
- Infective endocarditis

Acute glomerulonephritis
= postinfectious glomerulonephritis, usually children, usually caused by β hemolytic Streptococcus A
less common – other infections (bacterial endocarditis, pneumonia, hepatitis B, C, varicella, mumps, toxoplasmosis, malaria) = diffuse proliferative GN
clinical picture - nephritic sy

Rapidly progressive glomerulonephritis (crescent)
= less often - most glomeruli are partly destroyed
progresses rapidly (in months) to severe kidney failure
urine - protein, blood, and red blood cell clumps (casts) = nephritic sy
Causes:
Goodpasture sy
complication of any acute GN event. idiopathic

Chronic glomerulonephritis
= slowly progressive - years
cause not fully known
50% of people have underlying glomerulopathy, although usually asymptomatic
(some glomeruli are affected, some not – these take over the function of those damaged - therefore can be unnoticed in most people)
event. can proceed to chronic renal failure

Alport's syndrome (hereditary nephritis)
= hereditary glomerulopathy
- genetic mutations in type IV collagen (main constituent of GBM)
- X-linked dominant disease (event. + deafness and eye abnormalities)

IgA nephropathy - Berger’s disease
= massive hematuria + mild proteinuria following a respiratory infection, GIT symptoms or flu like disease
In USA - most common cause of acute GN
Deposition of IgA (rarely IgG) in glomerular mesangium → mesangial proliferative nephritis
Relatively good prognosis - some patients have only one hematuric episode, some others exhibit slow progression with recurrent hematuria

Glomerulonephritis can cause acute and chronic renal (glomerular) failure or nephrotic syndrome (see below).
52. Pyelonephritis

**Tubulo-interstitial nephritis**
Affects tubuli and/or interstitium
- Pyelonephritis – infection - tubuli
- Interstitial nephritis – interstitium – other origin than infection

Early stages - fluid + electrolyte imbalances
- diminished tubular reabsorption of Na

**Pyelonephritis**
= most common renal disease
= bacterial infection of one or both kidneys - 90% - Escherichia coli
usually ascendant origin (more frequent in women) but can be also blood born (esp. in case of obstruction)
more frequent during pregnancy, in patients with diabetes mellitus, or vesico-ureteral reflux
Diagnostics:
- microscopic analysis of urine - leuco casts in upper renal infection and bacterial culture
- can lead to interstitial suppurative inflammation + tubular necrosis

**Acute pyelonephritis**
sudden onset with chills, fever, pain in the lower part of the back
- nausea, and vomiting
In 1/3 of patients + symptoms of lower urinary tract infection (frequent + painful urination), pyuria
are acute form is usually mild, but can lead to medullary necrosis and renal (tubular) failure

**Chronic pyelonephritis**
Slow, longtime deterioration of renal function - can be asymptomatic for a long time
Infection gradually destroys tubulo-interstitium → scars - loss of functional parenchyma
Affects tubuli (glomeruli usually are not affected!)
- loss of tubular functions and concentration ability
- polyuria, nocturia, event. mild proteinuria

**Interstitial nephritis**
inflammation of the spaces between tubules and event. of tubules
- allergic reaction to drugs
- side-effect of medicaments
  - ATB – penicillin, ampicillin
  - NSAID
  - furosemide, thiazide antidiuretics
- causes reduction in kidney function, ranging from mild dysfunction to acute (tubular) kidney failure

Clinical picture:
- inability to concentrate urine → polyuria, nocturia
- inability to acidify urine sufficiently → metabolic acidosis
About one-half of patients - ↓ urine output with signs of acute kidney (glomerular) failure
(due to decreased glomerular filtration - because of tubular blockage from cellular debris or in the case of severe dehydration)
53. Nephrotic syndrome

= sy caused by processes leading to ↑ glomerular permeability for plasma proteins

Etiology
primary - minimal change disease (lipoid nephrosis)
  - focal segmental glomerulosclerosis
  - membranous glomerulonephritis
secondary - diabetes mellitus, amyloidosis, SLE, Henoch-Schönlein purpura

Pathogenesis
severe proteinuria (daily loss ≥ 3.5 g) - mainly albuminuria
  - loss of proteins > daily production by liver
  → hypoproteinemia (< 3 g/100ml) → ↓ plasma oncotic pressure
    → generalized edema
    → loss of plasmatic binding proteins → hypocalcemia
    → loss of immunoglobulins → ↓ resistance to infections
    → loss of anti-coagulation factors → hypercoagulability - thrombosis
    → compensatory synthesis of proteins + lipoproteins by liver
      → hyperlipidemia (cholesterol > 300 mg/dl, ↑ triglycerides) → ↑ risk of atherosclerosis

Clinical picture
Early:
- loss of appetite, a generally sick feeling, puffy eyelids, abdominal pain, wasting of muscles,
- edemas (in hypoalbuminemia - albumin less than 3g/100ml) - first peri-orbital, then
  generalized - event. swollen abdomen, shortness of breath (fluid in pleural space), swelling of knees, scrotum
- typically - moving edemas - eyelids in the morning, ankles after walking
- blood pressure - children - low blood pressure, orthostatic hypotension, adults - no specific
  blood pressure status, can be even hypertension
- urine output may be increased (polyuria) or decreased

Treatment – diet
- normal amounts of protein and K (but too much protein raises protein levels in the urine)
- low saturated fat and Na

Minimal change disease (lipoid nephrosis)
most frequent in children, often connected to respiratory infection or routine immunization
in adults – connected with Hodgkin disease, leukemias
relatively benign, well responding to corticoids
mechanism not completely known - ? some immune dysfunction?
loss of foot processes of epithelial cells – defect in charge barrier
+ detachment of epithelial cells → albumin loss

Focal segmental sclerosis
- only some glomeruli (= focal), only their tufts (=segmental)
- ↑ collagen depositions + hyaline mass (“sclerosis”)
- secondary in HIV, heroin abuse, sickle cell disease, extreme obesity
- as inherited disorder or idiopathic
Clinical picture:
- proteinuria (often non-selective)
- event. hematuria + hypertension
- pure response to corticosteroids
- often progresses to chronic GN and 50% to end-stage disease during 10 years

**Membranous nephropathy**
adults - clinical picture of severe nephrotic sy
2/3 idiopathic
1/3 – SLE, hepatitis B, penicillamin, bronchial and colorectal Ca
diffuse thickening of GBM + subepithelially located immunocomplexes
membrane is damaged by complement

**Diabetic glomerulosclerosis**
main complication of diabetes mellitus (appears in 30% patients with DM I)
3 glomerular sy
1. non-nephrotic proteinuria
2. nephrotic sy (↑ GF – hyperfiltration, ↑ of pores – proteinuria → nephrotic sy)
3. renal failure (glomerular)
   - deposition of glucose to extracellular space → thickening of BM + diffuse
     proliferation of mesangial cells + event. nodular deposition of hyaline to mesangium
     (= Kimmelstiel-Wilson - glomerulosclerosis)
   - mesangial cells gradually infringe on capillary lumen (→↓ GF) up to event. complete
     obliteration → renal insufficiency

**Hypertensive glomerular disease**
Hypertension can be viewed as both a cause and an effect of kidney disease
Hypertension
→ hyperperfusion and hyperfiltration + glomerular changes → proteinuria
→ sclerosis + thickening of arterioles - ↓ blood perfusion of kidney → tubular ischemia →
  loss of concentration ability – nocturia
54. Hydronephrosis

= distention of kidney with urine caused by backward pressure when the flow of urine is obstructed.

Causes
- primary (inborn) - e.g. compression of ureter by fibrous bands, an abnormally located artery or vein, too high insertion of ureter into renal pelvis
- secondary - stones in the renal pelvis or ureter, tumor
- vesicoureteral reflux - in either primary or secondary insufficiency of vesical valves (retrograde increase of urine pressure up to the kidney pelvis, calyces and tubular system)

Pathogenesis
- urine stasis
  → infection - pyelonephritis
  → calculi formation
  → backward pressure – urine formation disorders
- first – polyuria - danger of hypovolemia
- results from retrograde pressure damage to tubuli + mechanical compression of renal medulla (ischemia) – Henle loop disorder → loss of concentration ability (obstruction to urine flow is not complete)
- later - retrograde pressure damage to cortex + compression of cortex = ischemia - loss of functional area + ↑ pressure in B space, ↓ GF → kidney failure

Clinical picture
- acute obstruction (urinary stones) - leads to renal colic (in repeated problems - surgical treatment or ultrasound lithotripsy)
- inborn hydronephrosis (in majority of cases only unilateral) can be latent for a long time (if no ultrasound intrauterine or perinatal examination is not performed) with either no symptoms or attacks of dull, aching discomfort in flank and repeated urinary tract infections (mainly in vesicoureteral reflux)
- after some time (usually several years) severe polyuria (due to the above specified tubular failure) can develop - requires unilateral nephrectomy (to prevent chronic critical dehydration) or it can cause atrophy of the renal cortex with glomerular kidney failure
55. Acute and chronic renal failure

Although it is not usually explicitly specified, it should be differentiated whether the failure concerns glomerular or tubular functions (or both). Commonly it is understood to be loss of the kidney's ability to clear blood of toxic substances leading to accumulation of nitrogenous wastes in blood (due to decreased GF).

Both glomerular and tubular functions can be involved due to primary renal, pre-renal or post-renal diseases (pathological processes).

Acute
- loss of glomerular functions with preserved tubular functions = oliguric/anuric
- loss of tubular functions – acute tubular necrosis (ATN) = non-oliguric (polyuric)

Chronic
loss of entire nephrons - enlargement + hyperfunction of remaining nephrons → gradual insufficiency up to the end-stage disease

Oliguric/anuric acute renal failure
General features:
↓ GF → Oliguria (<500 ml/day) - Anuria (<150 ml/day)
- azotemia - progressive ↑ in blood concentration of creatinine + urea (= BUN = blood urea nitrogen) + uric acid
- metabolic imbalances: metabolic acidosis, hyperkalemia, hyponatremia (relative) – danger of CNS edema

Etiology
● prerenal
- hypovolemia - hemorrhage, dehydration, excessive loss of gastrointestinal tract fluids, excessive loss of fluid due to burn injury
- circulatory shocks
- heart failure
- decreased renal perfusion due to vasoactive mediators (e.g. hepatorenal sy = complication of advanced liver disease - progressive oliguria + acute renal failure, pathogenesis is not completely clear - may be related to renal cortical arterial vasoconstriction caused by catecholamines after primary vasodilation caused by non degraded vasoactive substances)
- drugs, diagnostic agents

Essential = reduction of blood flow to kidneys (failure of renal autoregulation) → inadequate GF → oliguria + azotemia

Pathogenesis
- ↓ kidney perfusion → ↓ GF → oliguria first with normal tubular function → reabsorption of water, Na + urea → in blood more urea than creatinine (↑ urea/creatinine ratio)
- when kidney perfusion ↓ to ca 20% of norm or in case of prolonged hypoperfusion → ischemia of tubular epithelial cells (most vulnerable) → acute tubular necrosis (ATN see below)

● intrarenal
- acute renal disease - glomerular disorder (acute glomerulonephritis, acute vasculitis) → ↓ permeability of glomerular membrane → ↓ GF
- intratubular obstruction - hemoglobinuria, myoglobinuria, myeloma light chains, or uric acid casts → ↑ of tubular pressure → ↑ pressure in B space → ↓ GF
- **Acute tubular necrosis (ATN)** = kidney disorder involving damage to the renal tubule cells resulting in acute kidney failure

**Etiology**
- ischemia of the kidneys (lack of oxygen to tissues)
- shock or severe hypotension (longer than 30 minutes)
- exposure to nephrotoxic agents
- aminoglycoside ATB,
- antifungal agents - amphotericin
- medications against rejection of transplanted organs (cyclosporine)
- poisoning by mercury, lead …

**Pathogenesis of ATN**
- shock, hypotension → vasoconstriction of renal artery → ↓GF + ischemia of proximal tubular cells → tubular necrosis
- toxic ATN → tubular cell necrosis
- tubular cell necrosis → loss of concentration + acidification ability → polyuria, isostenuria + acidosis
- decrease of Na reabsorption → more Na comes to macula densa → vas afferens vasoconstriction → ↓GF
- tubular obturation (detached epithelial cells) → ↑ of tubular pressure → ↑ pressure in B space → ↓GF

**Postrenal** - essential problem = urine flow obstruction
- bilateral ureteral obstruction
- bladder outlet obstruction - stones, compressions by tumor or swollen tissues
- back pressure causes urine accumulation →↑ intratubular pressure → ↑Pressure in Bowmans capsule → ↓GF → (later) compression of renal tissue → ischemia → loss of tubular concentration ability
- after removal of obstruction  GF returns to normal, but tubuli do not concentrate properly → polyuria (= post-obstructive diuresis) - danger of dehydration

**Acute renal failure - pathogenesis**
1) acute phase – oliguric/anuric either dialysis necessary or recovery of glomerular function - but tubuli still do not function properly → polyuria - (about 2 weeks)
2) either complete recovery or change to progressive disease with gradual loss of nephrons leading to gradual oliguria

**Treatment of acute kidney failure**
- restriction of water intake to the volume actually lost from the body - person's weight is measured every day to monitor fluid intake
- restriction of all substances that are eliminated through the kidneys (e.g. digoxin and some antibiotics must be strictly limited)
- prevention of blood phosphorus level from rising too high antacids that contain Al bind Ph in intestines
- treatment for high blood level of K

**Dialysis**
Indications for dialysis
- oliguria or anuria longer than 3 days
- manifest uremia
- plasmatic BUN > 30 mmol/L
- creatinine > 700 µmol/L
- hyperkalemia > 6.5 mmol/L (danger of cardiac arrest)
- non-manageable hyperhydration (manifested via severe systemic hypertension)
Types of dialysis

Hemodialysis – most frequently used
- Blood is removed from the body and circulated through a machine called a dialyzer that filters the blood. Inside the dialyzer, an artificial membrane separates the blood from a fluid (the dialysate) that's similar to normal body fluids. Fluid, waste products, and toxic substances in the blood filter through the membrane into the dialysate. The purified blood is returned to the person's body.

Possible complications of hemodialysis
- Life-threatening allergic reaction (anaphylaxis) - allergy to a substance in the machine
- Fever, possibility of hepatitis B transmission
- Low blood pressure - removal of too much fluid
- Air embolus - air entering blood in the machine
- Bleeding in the intestine, brain, eyes, or abdomen - Heparin being used to prevent clotting in the machine
- "Disequilibrium syndrome" – too fast changes in plasma ion concentrations can lead to brain edema
- Aluminium intoxication - encephalopathy (in cases of high aluminium content in dialysate)

Peritoneal dialysis, the peritoneum is used as the filter - a catheter is inserted through a small incision in the abdominal wall into the peritoneal space. The dialysate drains by gravity or is pumped through the catheter and left in the space long enough to allow waste products from the bloodstream to filter through the peritoneum into the dialysate. Then the dialysate is drained out, discarded, and replaced.

Automated cycler intermittent peritoneal dialysis can be performed at home, eliminating the need for constant nursing attention. A timed device automatically pumps fluid into and drains it from the peritoneal cavity. Usually, people set the cycler at bedtime so the dialysis takes place while they're sleeping. These treatments need to be performed 6 or 7 nights a week.

Chronic renal failure (CHRI)
= slowly progressive decline in kidney function leading to azotemia
= often progressive, event. resulting in end-stage renal failure
(homeostatic mechanisms are insufficient to preserve life)

Etiology
- Arterial hypertension
- Urinary tract obstruction
- Glomerulonephritis
- Kidney abnormalities, such as polycystic kidney disease
- Diabetes mellitus
- Autoimmune disorders, such as SLE

Pathogenesis = different from acute renal failure
- Irreversible loss of some nephrons → greater functional burden for remaining nephrons → ↑ filtration pressure → hyperfiltration in individual nephrons → Polyuria, isostenuria → hypovolemia
- For unknown reason → fibrosis and scarring (= glomerular sclerosis) → nephron destruction → greater functional burden for remaining nephrons……
- Diminished renal reserve - GF = about 50% of normal
  Usually asymptomatic (latent) - but with little functional reserve any additional problem (infection, obstruction) may → manifest uremia
- Clinically manifest renal insufficiency when GF < ca 30 ml/min = azotemia
adaptive changes in remaining nephrons

Renal failure - GF < ca 15 ml/min
- fluid retention, edema, metabolic acidosis, hypercalcemia, uremia
- necessity of dialysis, transplantation

Clinical manifestations of CHRI - clinical picture of uremic syndrome

Uremia
- characterized by accumulation of toxic metabolic wastes in blood (urea, uric acid, creatine, creatinine, phenols etc.) and by water and mineral dysbalance (dependent on nutrition and drinking - important coordinated behavior of patients)
- loss of appetite, nausea, vomiting
- skin – yellow-brown, event. with „uremic frost“ (urea), pruritus (= itching)
- water retention
- metabolic acidosis (lost acidification of urine)
- hyperkalemia → cardiac arrhythmias (cardiac arrest)
- hypocalcemia (due to low calcitriol formation) → hyperparathyroidism → renal osteodystrophy → renal osteosclerosis
- bone marrow depression (due to toxicity of metabolites) → anemia, thrombocytopenia, leukopenia
- peripheral nervous system – peripheral polyneuropathy → paresthesias, motoric disorders, vegetative dysfunctions (e.g. orthostatic hypotension, collapses)
- central nervous system - uremic encephalopathy - direct toxicity of accumulated metabolites (event. with dysequilibrium sy - brain edema) - confusion, apathy, convulsions, event. coma (diagnostics of encephalopathy - see hepatic/portosystemic encephalopathy)
- endocrine dysfunctions
- anemia - ↓ erythropoietin (+ bone marrow depression)
- GIT - anorexia, nausea, vomiting - due to accumulation of toxic waste products
- cardiovascular system
  - systematic hypertension (kidney is unable to excrete water + salt)
  - coronary ischemia (effect of hypertension + hyperlipidemia)
  - pericarditis - relatively often - indication to start with dialysis

Renal adaptations in CHRI
When some nephrons are destroyed - those remaining adapt to improve kidney function

1) Glomerular adaptations
- Glomerular hyperfiltration = markedly ↓ afferent arteriole tone (→ vasodilation)
  + little ↓ efferent arteriole tone → ↑GF
  with high number of destroyed glomeruli kidney become insufficient

2) Tubular adaptations
- Isostenuria - urine of relatively invariant osmolarity (300 mOsm/kg or 1,010 specific gravity = isotonic with plasma)
- decreased ability to dilute or concentrate (decreased solute excretion from affected nephrons combines with higher solute excretion from surviving nephrons)

Ion changes:
- Sodium – plasma concentration
  - may be relatively normal - ↑ Na excretion in remaining nephrons
  - may be ↑ - insufficient excretion – edemas…
  - may be ↓ = salt losing nephropathy - usually in CHRI after hydronephrosis, pyelonephritis ⇒ danger of dehydration esp. in salt restriction diet
Potassium - despite general tendency to hyperkalemia, due to ↑ secretory capacity of surviving nephrons (↑ number of K pump) in some patients the K balance is maintained till the end-stage

Phosphate
- mild CHRI - plasma P ↓ or normal - due ↑ PTH (due to ↓ D vit)
- severe CHRI - P exceeds renal excretory capacity → ↑ of plasma P

Calcium
- ↑ PTH (due to ↓ D vit - ↓ intestinal Ca absorption) → ↑ of plasma Ca
- severe CHRI - ↓ Ca - hyperphosphatemia → ↓ Ca (PxCa in plasma = constant) + development of skeletal resistance to PTH

Acid base balance
- mild CHRI - ↓ ammonia production → ↓ H⁺ excretion → ↑ H⁺ in ECF → ECF HCO₃⁻ consumption
- severe CHRI - metabolic acidosis worsens:
  HCO₃⁻ in ECF falls
  H⁺ is buffered by hydroxyapatite of bone – this helps to keep HCO₃⁻ but at expense of dissolution of bone minerals - contributes to osteomalacia
56. Pathophysiology of Hypothalamo-Pituitary system

Principles of hormonal action
- endocrine - produced substances (hormones) are distributed via blood to the target cells
- paracrine - hormones influence directly surrounding cells
- autocrine - hormones regulate directly the cells which produced them

Endocrine regulation
- center for endocrine regulations - Hypothalamus - its activity is dependent on signals form the periphery (feedback loops) and from CNS (psychic state can cause dysbalance - psychosomatic disorders)
- liberins and statins regulate anterior pituitary - trophic hormones influence peripheral glands
- Endocrine glands are regulated via feedback loops - ultra-short (to its own production level - e.g. trophic hormones to pituitary), short (over two levels - e.g trophic hormones from pituitary influence hypothalamus), long (e.g. hormone from the peripheral endocrine gland act up to hypothalamus)

Endocrine disorders
- hypo/hyperproduction of a hormone
- disorder at the level of receptors on the target organs (tissues) - deficient, insensitive (= pseudoendocrinopathy), blocked or activated by specific antibodies
- disorder at the level of intracellular "second messenger" (mostly cAMP, in some endocrine actions not known - e.g. for insulin, growth hormone)
- disorder at the level of intracellular receptor protein
- paraneoplastic disorders- hormone production outside endocrine gland - e.g. by tumours
- Hypothalomo- pituitary portal system - fine capillary nets sensitive to changes of blood pressure and viscosity of blood → hypoperfusion → endocrine disorders - e.g Sheehan sy (postpartum severe hypotension with irreversible severe endocrine changes)
- precocious puberty - idiopathic or in case of hypothalamic, adrenal or gonadal tumours
57. Decrease of Anterior Pituitary hormones

Hypopituitarism - etiology
- non-secreting adenoma
  - compression of hypothalamus → diabetes insipidus (↓ ADH)
  - expansion of Sella turcica, suprasellar extension → compression of optic chiasm or optic nerves - typical visual field defects - bitemporal hemianopsia (loss of lateral vertical half- fields in the visual field) = compression of the central crossing fibres of visual nerves, binasal hemianopsia = compression of the lateral (non- crossing) fibers
  - hydrocephalus - blocked outflow from the third ventricle
  - compression of ventricles - headache
  - cerebrospinal fluid rhinorrhea
  - may invade into paranasal sinuses, cavernous sinus
- craniopharyngeoma - suprasellar expansion
- suprasellar chordoma
- histiocytosis X (Hand-Schüller-Christian disease)
- ischemic necrosis - within Sheehan sy - stop of lactation and amenorrhea
- chronic inflammatory lesions - tuberculosis, syphilis, sarcoidosis
- infiltrative processes - amyloidosis, hemochromatosis, mucopolysaccharidoses
- congenital pituitary dwarfism - Laron type (normal proportions and intelligence but delayed sexual development), Fröhlich type (obese with stunted growth, mental retardation and abnormal sexual development)
- hypothalamic etiology for pituitary deficiency - with simultaneous decrease of ADH diabetes insipidus)

Growth hormone (GH) deficiency → short stature
- Growth hormone influences bone growth indirectly - via activation of IGF production in liver (IGF = insulin-like growth factors = "somatomedins"; two kinds - IGF-I (more important) and IGF-II - similar to proinsulin - explains partial cross effects of insulin and GH)
- regulation via somatoliberin and somatostatin from hypothalamus
- somatostatin released also in delta cells of Langerhans islets
- 70% of GH is produced during the night (sleep stages 3,4) - mainly in children
- secretion stimulation: hypoglycemia, fasting, ↑ aminoacids (mainly arginine), stress condition, heavy exercise
- secretion inhibition: ↑ glycemia, free fatty acids, cortisol, obesity, severe emotional deprivation in children

Causes of short stature:
Variants of norm
- genetic short stature
- constitutional short stature
Endocrine disorders
- deficit of somatoliberin
- growth hormone deficiency - primary, secondary (hypothalamic-pituitary tumors, radiation, head injuries, brain infections, hydrocephalus, production of biologically inactive growth hormone)
- Laron type dwarfism - normal (elevated) GH but missing IGF receptors
- Hypothyroidism
- Diabetes mellitus (not treated)
- Glucocorticoid excess (Cushing's sy, exogenous glucocorticoids)
- chronic illness malnutrition
- malabsorption sy
- Turner's sy

**Pathogenesis**
- congenital deficiency of GH - normal parameters of body at birth but decreased growth rate, obvious by the end of the second year - normal intelligence, obesity, immature facial features, delayed puberty, microcephalus in males, hypoglycemia
- acquired GH deficiency appears in later childhood (most frequently due to hypothalamo-pituitary tumors or irradiation for therapeutical reasons)
- prevention of short stature - replacement therapy- formerly GH from cadavers, now prepared via recombinant DNA (rDNA) technology

**Other hormone deficiency**
- either panhypopituitarism (more frequent) or single hormone deficiency
  - ↓ TSH - hypothyroidism
  - ↓ FSH, LH - hypo-gonadism, amenorrhea, infertility
  - ↓ ACTH - Addison's disease - central type without hyperpigmentation (different from the peripheral - adrenal cortex insufficiency)
  - ↓ prolactin - disorder in milk production
  - ↓ MSH - hypo-pigmentation
58. Hyperfunction of anterior pituitary gland

- primary hyperpituitarism mainly caused by small adenomas with excessive hormone secretion:
  - 30% produce prolactin → galacmm Hghea, gynecomastia
  - 25% GH → gigantism (children) or acromegaly (adult)
  - 10% ACTH → Cushing's sy (see adrenal cortex disorders)
  - 5% TSH → hyperthyroidism - hyperfunctioning goiter
  - < 5% LH, FSH -amenorrhea, impotence, infertility
  - 30% of adenomas have no excessive hormone secretion
- secondary hyperprolactinemia - dopamine receptor antagonists (chlorpromazine, fluphenazine, haloperidol etc.), exogenous estrogens, some antihypertensives (methyldopa, reserpine, verapamil), primary hypothyroidism, liver cirrhosis, chronic liver failure, stress

Effects of GH excess (in adulthood)
- general - fatigue, increased sweating, heat intolerance, weight gain, glucose intolerance - blockage of the insulin effect up to exhaustion of β-cells of Langerhans islets → secondary diabetes mellitus
- skin and subcutaneous tissue - enlarging hands, feet, coarsening facial structures (acromegaly), oily skin, hypertrichosis
- head - headache, parotid enlargement
- eyes - decreased visual acuity, visual field defects
- ears - enlarged
- throat, face - increased tongue size, voice change, prognathism, obstructive sleep apena due to visceromegaly
- cardiovascular system - hypertension (retention of Na and water), left ventricular hypertrophy
- genitourinary system - urolithiasis, decreased libido, impotence, oligomenorrhea, infertility
- neurologic system - paresthesias, hyporsomnolence, carpal tunnel sy
- muscles - weakness, proximal myopathy
- skeletal system - joint pains, increased calcitriol due to increased hydroxylase - increased bone density

Giantism
- GH excess occurring before puberty - before fusion of the epiphyses of the long bones (GH stimulates differentiation of prechondrocytes into early chondrocytes which then secrete IGF-I. IGF-I stimulates clonal expansion and maturation of chondrocytes.

Tall stature
- constitutional
- genetic or chromosomal disorders - e.g. XYY (Klinefelter's sy) or Marfan's sy
- therapy - use of estrogens (girls) or testosterone (boys) can make early epiphyseal closure (about 3-4 years before expected epiphyseal fusion)

Somatomedins, or insulin-like growth factors (IGFs), comprise a family of peptides that play important roles in mammalian growth and development. IGF1 mediates many of the growth-promoting effects of growth hormone. Early studies showed that growth hormone did not directly stimulate the incorporation of sulfate into cartilage, but rather acted through a serum factor, termed 'sulfation factor,' which later became known as 'somatomedin'. Three main somatomedins have been characterized: somatomedin C (IGF1), somatomedin A (IGF2) and somatomedin B.
59. Alterations of the Posterior Pituitary gland hormones

Antidiuretic hormone (ADH = vasopressin)
- produced in Paraventricular and Supraoptic nuclei of hypothalamus, stored in posterior pituitary

Etiology of central and peripheral-nephrogenic diabetes insipidus
Central (decrease of ADH production):
- hereditary - autosomal dominant
- acquired
  - idiopathic
  - traumatic or postsurgical
  - neoplastic disease (craniopharyngeoma, lymphoma, meningioma, metastatic carcinoma
  - ischemic or hypoxic - Sheehan's sy, aneurysms, cardiopulmonary arrest, circulatory shock, thrombosis, brain death
  - granulomatous disease (sarcoidosis, histiocytosis X)
  - infections (viral encephalitis, bacterial meningitis)
  - autoimmune disorder

Nephrogenic (insensitivity of tubular system to ADH):
- hereditary - familial (X-linked)
- acquired
  - hypokalemia (loss of concentration capacity of the tubular system)
  - hypercalcemia
  - postrenal obstruction (hydronephrosis - mechanical effect on tubuli)
  - drugs - e.g. lithium, methoxyfluran
  - sickle cell trait or disease
  - amyloidosis
  - pregnancy

Pathogenesis of diabetes insipidus
- total inability to concentrate urine - comes from polyuria causing washout of the renal medullary concentration gradient
- polyuria - loss of volume up to 12 l/day - low urine specific gravity - 1.00 - 1.005
- increased osmolarity → thirst
- polydipsia
- treatment via supply of synthetic ADH = desmopressin
- must be distinguished from other polyuric states - diabetes mellitus, osmotic diuresis,
  primary polydipsia - possible differentiation via restriction of water - in diabetes mellitus there is no decrease of urine volume
- psychogenic diabetes insipidus - polydipsia with urine production over 18 l/day

Etiology of SIADH (syndrome of inappropriate (↑) ADH release)
- secreting tumors
  - bronchial carcinoma (small-cell type mainly)
  - other carcinomas (duodenum, pancreas, bladder, ureter, prostate)
  - leukemia, lymphoma
  - thymoma, sarcoma
- CNS disorders
  - infections
  - mass lesions (tumors, abscess, hematoma, trauma)
  - hydrocephalus
  - delirium tremens, acute psychosis
● pulmonary disorders
  - infections - tuberculosis, pneumonia
  - acute respiratory failure
● drugs
  - vasopressine, desmopressin acetate, chlorpromazine, clofibrate, carbamazepine, cytostatics, tricyclic antidepressants
● idiopathic

Pathogenesis - manifestations
- hyperhydration - hypertension, heart failure
- hypotonicity of ECF (consequences - see osmolarity changes)

Oxytocin
● in women:
  - helps ejection of milk (contraction of myofibroepithelial cells in breast)
  - starts contractions of uterus at the beginning of physiological baby delivery - mechanoreceptors in the cervix of uterus react to distension by fetal head (in the case of normal position and normal mature size - does not work normally in the opposite pelvic position or hypotrophic fetus)
● in men:
  - facilitates transport (ejaculation) of sperm
  - supports libido and normal sexual behavior
60. Hyperthyroidism, Hypothyroidism

- iodination of thyroglobulin and formation of physiologically active T₃ (triiodothyronine - much higher physiological effects compared to T₄) and T₄ (tetraiodothyronine) is dependent on normal levels of iodine in blood
- storage in colloid form
- formation of thyreoliberin and TSH via negative feedback loops - dependent on levels of T₃ and T₄ (more important for precise regulation because of shorter "life time" in circulation)

Physiological effects of thyroid hormones
● metabolic
  - general calorigenic effect in all tissues - increase metabolic rate via activation of oxidative processes (exceptions - adult brain, testes, uterus)
  - stimulate lipolysis (adipose tissue)
  - catabolism of proteins - increased protein breakdown (muscles)
  - stimulate formation of LDL receptors → decreased cholesterolemia
● heart
  - positive chronotropic effect - increases number and affinity of beta-adrenergic receptors (acceleration of heart - increased MV for better oxygen supply in the increased metabolic rate)
  - positive inotropic effect - permissive effect on catecholamines - in deficiency causes decrease of MV
● bone - promote normal growth and skeletal development
● CNS - promote normal brain development in childhood -(deficit = cretinism)
● gut - increase of carbohydrate absorption
● bone marrow - activates erythropoiesis - deficiency leads to macrocytic anemia

Hyperthyroidism - etiology and pathogenetic mechanisms
- Grave's (Basedow) disease - overproduction via receptor-stimulating antibodies (TSH-R[stim]) - autoimmune disorder - stimulating antibodies are formed probably due to primary defect in suppressor T lymphocytes (Ts) allowing helper lymphocytes (Th) to stimulate B lymphocytes for antibody formation), there are some other autoimmune processes associated with Grave's disease
- toxic multinodular goiter - autonomous hyperfunction
- follicular adenoma - autonomous hyperfunction
- pituitary adenoma - rare TSH hypersecretion
- pituitary insensitivity - rare resistance to thyroid hormones → dysregulation
- hypothalamic disease with decreased thyreoliberin (TRH) formation (rare)
- germ cell tumours - choriocarcinoma, hydatidiform mole
- struma ovarii - ovarian teratoma
- metastatic follicular thyroid carcinoma
- iatrogenic - overdosing of T₃ therapy or use of thyroid gland hormones in pills against obesity
- thyroid gland destruction with transient release of stored hormones - Hashimoto's thyroiditis, lymphocytic thyroiditis, granulomatous thyroiditis

Consequences - clinical manifestations
Symptoms:
- alertness, emotional lability, irritability
- poor concentration
- muscular weakness (breakdown of proteins), fatigability
- voracious appetite but weight loss
- hyperdefecation - diarrhea due to increased peristalsis of the gut (decreases absorption and enhances catabolic state with weight loss)
- heat intolerance

Signs:
- hyperkinesia, rapid speech
- muscle weakness (proximal - quadriceps), fine tremor
- fine, moist skin; fine, abundant hair; onycholysis
- lid lag, stare, proptosis (exophthalmus), chemosis, periorbital edema
- tachycardia, accentuated first heart sound, atrial fibrillation, increased pressure amplitude, dyspnea

Laboratory findings:
- elevated serum T<sub>3</sub>, T<sub>4</sub>, suppressed serum TSH (in case of peripheral hyperthyroidism), increased radioiodine uptake by thyroid gland (in scan)
- increased basal metabolic rate
- decreased cholesterol level

**Hypothyroidism** - etiology and pathogenetic mechanisms

- **Congenital**
  - aplasia or hypoplasia of thyroid gland
  - defects in hormone biosynthesis or action
- **Acquired**
  - Hashimoto's thyroiditis - autoimmune destruction
  - severe iodine deficiency - diminished hormone synthesis, endemic goiter (compensatory hyperplasia in regions with low availability of iodine - in central continental mountains with low proportion of sea food in nutrition and low content of iodine in superficial sources of potable water), accompanied by low IQ - prevention - iodination of salt or water
  - lymphocytic thyreoiditis - diminished hormone synthesis
  - thyroid ablation - non adequate surgery or radiation treatment of hyperthyroidism
  - external beam radiation therapy of head and neck cancer
- **Drugs**
  - iodine - inorganic, organic (amiodarone)
  - thioamides
  - potassium perchlorate
  - lithium
  - hypofunctional goiter - inducing substances in nutrition - e.g. cabbage
- **hypopituitarism** - deficient TSH secretion
- **hypothalamic disease** - deficient thyreoliberin secretion

**Consequences - clinical manifestations**

**Symptoms**
- slow thinking, lethargy, decreased vigor (dementia -cretinism - in case of childhood deficit)
- loss of appetite, diminished food intake but weight gain
- constipation (due to decreased peristalsis of gut - increases absorption of nutrients - contributes to weight gain)
- cold intolerance
- diminished libido, menorrhagia

**Signs**
- dry skin, thickened hair, hair loss, broken nails
- round puffy face, slow speech, hoarseness
- hypokinesia, generalized muscle weakness, slower tendon reflexes
- periorbital edema, ankle edema, ascites (decreased plasma proteins), pericardial effusion (= myxedema)
- faint cardiac impulse, indistinct heart sounds, cardiac enlargement, bradycardia
- mental clouding, depression

Laboratory findings
- decreased serum $T_3$, $T_4$, increased serum TSH (in case of peripheral disorder)
- decreased radioiodine uptake
- decreased basal metabolic rate
- macrocytic anemia
- elevated cholesterol level - atherosclerosis
- decreased circulation time = hyperkinetic circulation $\rightarrow$ high output heart failure

**Goiter**
- eufunctional = normal thyroid function, compensatory hyperplasia of thyroid gland (e.g. in non-severe iodine deficiency)
- hyperfunctional goiter - e.g. in increased levels of TSH
- hypofunctional goiter - compensatory hyperplasia with insufficient function - e.g. in severe deficiency of iodine = endemic goiter
Adrenal cortex hormones – hypersecretion

- Zona glomerulosa - aldosterone
- Zona fasciculata - cortisol, sex hormones
- Zona reticularis - sex hormones, (cortisol?)

Steroid hormones all have similar structure - formed from cholesterol under the influence of various enzymes - their different activity can cause changes in hormonal production

**Actions of cortisol**

- **Metabolic**
  - increase glycemia via gluconeogenesis, decreases utilization of glucose by the tissues
  - increases breakdown of proteins, increases plasma protein levels
  - increases mobilization of fatty acids, increases utilization of fatty acids

- **Antiinflammatory**
  - stabilizes lysosomal membranes of the inflammatory cells - prevents release of inflammatory mediators
  - decreases capillary permeability and prevents edema
  - suppresses all immune responses with exception of increased number of circulating polymorphonuclears (neutrophils) - prevents bacteriemia (sepsis) via increased phagocytosing capacity
  - reduces fever
  - inhibits fibroblast activity (decreases formation of scars)

- **Psychic effect** - contributes to emotional stability
- **Permissive effect on catecholamines** (contributes to normal vascular tonus and blood pressure)

Distinct circadian rhythm in release of glucocorticoids - with maximum in the afternoon

**Overproduction of glucocorticoids**

- *Cushing’s syndrome* - central cause - increased production of ACTH
- *Cushing’s disease* - peripheral cause - adrenal adenomas, cancer, iatrogenic (therapeutic use of glucocorticoids)

**Clinical manifestations**

- central obesity (80% of patients) - fat trunk and abdomen, thick neck, "moon" face, thin extremities (due to atrophy of muscles - breakdown of proteins)
- striae
- steroi myopathy (muscle wasting and weakness)
- osteoporosis (pathological spontaneous fractures)
- easy bruising, delayed healing
- steroid encephalopathy (psychiatric effects)
- growth retardation (in childhood)
- androgen excess in female - virilism, acne, menstrual irregularity, infertility
- in childhood - adrenogenital sy, pubertas praecox
- increased mineralocorticoid effect (hypertension, hypokalemia)
- steroid (secondary) Diabetes mellitus (exhaustion of the Langerhans islets)

**Mineralocorticoids - Aldosterone**

- retention of sodium and water (hypervolemia, hypertension), increased release of potassium under the influence of aldosterone
Hyperaldosteronism
● primary = Conn's syndrome
  - adenoma, secreting adrenocortical carcinoma
  - bilateral hyperplasia of zona glomerulosa
  - idiopathic
● secondary - increased production
  - renal ischemia (renal artery stenosis)
  - decreased intravascular volume or congestive heart failure (left ventricle)
  - sodium-wasting disorders (chronic renal failure, tubular acidosis)
  - juxtaglomerular cell hyperplasia (Bartter's sy)
  - diuretic ingestion (pseudo-Bartter's sy)
  - oral contraceptives
  - renin-secreting tumors
● secondary - decreased degradation (metabolism) of aldosterone in liver
  - liver failure - cirrhosis (hyperaldosteronism contributes to ascites formation)

Clinical manifestations
- increased volume of circulating fluid → hypertension, edemas (pulmonary edema in failing left ventricle)
- mineral dysbalance - hypernatremia, hypokalemia

Androgens (testosterone, dihydrotestosterone (DHT), androstenedione, dehydroepiandrosterone (DHEA)) - enhance muscle mass, stimulate cell growth, and aid in the development of the secondary sexual characteristics - in hyperfunction it leads to adrenogenital sy, increased muscle mass, virilisation and decreased fertility in women
62. Adrenal cortex hormones - acute and chronic deficiency

Deficiency usually concerns both glucocorticoids and mineralocorticoids and has prevailing manifestations of glucocorticoid deficit = **Addison disease**.

**Etiology**
- **primary**
  - autoimmune (about 80% of primary cases)
  - Tuberculosis
  - adrenal hemorrhage and infarction = Waterhouse-Friedrichsen sy
  - metastatic and lymphomatous replacement
  - AIDS related, CMV adrenalitis
  - amyloidosis, sarcoidosis, hemochromatosis
  - radiation therapy
  - surgical adrenalectomy
  - congenital defects due to enzymatic deficit - Congenital adrenal hyperplasia (CAH) - autosomal recessive diseases resulting from defects in steps of the synthesis of cortisol. All of the forms of CAH involve excessive or defective production of sex steroids and can impair development of primary or secondary sex characteristics in affected children and adults. Many also involve excessive or defective production of mineralocorticoids, which can cause hypertension or salt wasting. The most common type of CAH is due to deficiency of 21-hydroxylase.
  - enzyme inhibitors, various cytostatics (Mitotane)
- **secondary**
  - chronic exogenous glucocorticoid therapy
  - pituitary tumors (hyposecreting)
  - hypothalamic tumors

**Clinical manifestations and pathophysiologic mechanisms of Addison disease**
- includes deficiency of all adrenal gland hormones - destruction of parenchyma
- weakness and easy fatigability worsening towards evening and in stress situations (due to hypoglycemia, decreased perfusion of tissues in hypotension, decreased metabolism of proteins)
- hypotension (ECF decrease, missing permissive effect ont catecholamines) - can lead up to **Addisonian crisis** = circulatory shock (combined hypovolemic and distributive) with severe hypoglycemia, hyperkalemia (cardiac arrest) - develops e.g. in massive bleeding to adrenal cortex
- hypoglycemia - decreased gluconeogenesis, decreased glycogen storage, increased insulin sensitivity - leads to fatigue, mental confusion, apathy, psychosis
- mineral dysbalance - hyponatremia, hyperkalemia
- gastrointestinal disturbances - anorexia, nausea, vomiting, diarrhea, abdominal pain (probably due to decreased perfusion, hypoglycemia and mineral changes)
- hyperpigmentation - only in cases with increased ACTH (primary deficiency of adrenal gland) - increased ACTH is accompanied with increased secretion of beta-lipoprotein and MSH - both induce pigment changes of epithelial cells

Glucocorticoid therapy must only be discontinued by gradual reduction of the dosage - several weeks of gradual decrease of the cortisol doses to prevent deficiency of own production due to its suppression during therapy (negative feedback to the hypothalamus). It could cause even **Addisonian crisis**.
63. Adrenal medulla dysfunction

**Catecholamines** - production is dependent on sympathetic tonus - produced also in paravertebral sympathetic ganglia
- common stimuli for secretion of adrenomedullary hormones include e.g. exercise, hypoglycemia, hemorrhage and emotional distress
- physiologic effects are dependent on distribution of adrenergic receptors in tissues (α, β₁, β₂)

**Major effects** mediated by epinephrine and norepinephrine are:
- increased rate and force of contraction of the heart muscle - predominantly an effect of epinephrine acting through beta receptors
- constriction of peripheral (not muscular) blood vessels - mainly norepinephrine causes widespread peripheral vasoconstriction, resulting in increased resistance and hence arterial blood pressure increase
- dilation of bronchioles - helps in pulmonary ventilation
- stimulation of lipolysis in fat cells - provides fatty acids for energy production in many tissues and aids in conservation of dwindling reserves of blood glucose
- Common stimuli for secretion of adrenomedullary hormones include exercise, hypoglycemia, hemorrhage and emotional distress.
- increased metabolic rate - oxygen consumption and heat production increase in response to epinephrine, breakdown of glycogen in skeletal muscle to provide glucose for energy production
- dilation of the pupils - particularly important in dangerous situations under conditions of low ambient light
- inhibition of certain "non-essential" processes in a stress situation - an example is inhibition of gastrointestinal secretion and motor activity.

**Hypoproduction of catecholamines**
- primary selective hypofunction of the adrenal medulla is virtually unknown
- can accompany Addison's disease in cases of extensive destruction of adrenal parenchyme
- senile atrophy of the adrenal gland can partially decrease capacity for catecholamine production
- consequences - according to the above specified effects

**Hyperproduction of catecholamines - Pheochromocytoma**
- 90% from adrenal medulla, 10% from paravertebral sympathetic ganglia
- constant or paroxysmal hypertension with tachycardia, sweating, headache, chest pain
- abdominal pain, nausea, vomiting (splanchnic hypoperfusion)
- anxiety, exhaustion, tremor
- visual disturbances
- symptoms between paroxysms - increased sweating, cold hands and feet, weight loss, constipation
- important is early adrenalectomy - before fixation of the extreme hypertension

Neuroblastoma - malignant adrenal tumor usually without production of catecholamines
64. Diabetes mellitus, etiology and pathogenesis

Diabetes mellitus (DM) represents a chronic disorder of insulin production or its actions leading to consequences in metabolism of carbohydrates, proteins and lipids and subsequently to changes in water, mineral and pH balance with a lot of secondary complications.

Insulin
- polypeptide formed from two chains linked by two disulphide bridges - created from pro-insulin after separation from connecting peptide
- produced by β-cells of Langerhans islets - exocytosis into ECF → blood
- basal secretion in short intervals (10 min.), release stimulated mainly by increased glycemia (over 4 mmol/l), gastrin, secretin, cholecystokinin - reacts to expected postprandial increase of glycemia, STH (increase of intracellular glucose for growth support), glucocorticoids (via increasing glycemia), prolactin, sulphonylurea derivates (peroral antidiabetics)
- secretion inhibits increased insulinemia via negative feedback loop, somatostatin
- hyposecretion in hypokalemia (in hyperaldosteronism pathological Glucose tolerance curve - see below))

Effects
- increases glucose transport into skeletal muscles and adipose tissues (together with potassium - should be included in glucose infusions) → decreased glycemia
- increases glycogen synthesis
- decreases gluconeogenesis
- increases fatty acid transport into adipose tissues
- increases triglyceride synthesis - blocks lipolysis (inhibition of hormone sensitive lipase) -no ketone formation in DM II
- increases active transport of amino acids into cells - increases protein synthesis
- insulin independent (non-sensitive) tissues - CNS, erythrocytes
- insulin antagonist (counterregulatory) effects - glucagon, catecholamines, growth hormone, glucocorticoids
- degradation of insulin mainly in liver - ca 80% (in one perfusion- decrease to about 50%)

Glycemia
- kept in the range ca 3 - 6.7 mmol/l (fasting value)
- over about 8 mmol/l - glucosuria (interindividually variable) - due to limited capacity of glucose reabsorption from primary urine
- Glucose Tolerance Test - evaluation of glycemia increase after oral intake of glucose - maximum after ca 60 min. - normal value not more than 7.8 mmol/l, impaired tolerance up to 11.1 mmol/l (in capillary whole blood) - over this value = Diabetes mellitus
- fasting and long-lasting exertion influences glycemia according to liver function (glycogen storage), glucocorticoid levels and fat deposits

Hypoglycemia
Etiology
- Endogenous
  - insulinoma (uncommon neoplasm of beta cells of Langerhans islets)
  - hyperplasia of beta cells or nesidioblastosis - rare hypoglycemia in infancy
  - extrapancreatic neoplasms - hepatomas, adrenocortical carcinomas, GIT tumors, lymphomas
  - inborn errors of metabolism - hereditary fructose intolerance, fructose-1,6-diphosphatase deficiency, galactosemia
  - inborn errors in glycogen metabolism (Gierke dis., glycogen storage dis.)
● Exogenous
  - intentional or accidental overdose of insulin
  - exercise combined with fasting
  - alcohol - especially in food deprivation (drinking on an empty stomach)
  - salicylates and some other hypoglycemic agents
● Functional
  - alimentary hypoglycemia - rapid dumping of carbohydrates into the upper intestine
  - postgastrectomy status (= early postprandial sy = Dumping sy) - based on overshooting of insulin release
  - spontaneous hypoglycemia - unknown origin
  - endocrine deficiency states - glucocorticoid deficiency, growth hormone deficiency, catecholamine deficiency
  - liver deficiency (fasting hypoglycemia)
  - profound malnutrition
  - transient neonatal hypoglycemia - in 10% of neonates in first 3 days of life

**Signs and symptoms of hypoglycemia (insulin reaction)**
- blood glucose below ca 2.5 mmol/l
- sudden onset
- impaired cerebral function - vagueness, headache, slurred speech, vision impairment, impaired motor function, emotional changes, seizures, hypoglycemic coma
- autonomic nervous system responses - hunger, anxiety, hypotension, sweating, skin vasoconstriction (pale, cool and sweat skin), tachycardia (due to sympathetic activation)

**Hypoinsulinemia**
- decreased production
- formation of defective insulin structure
- disorder of release into blood-stream
**Consequences:**
- decreased input of glucose into the ICF → hyperglycemia
- glycogenolysis
- lipolysis → ketoacidosis (acetone, β-hydroxybutyrate, acetoacetic acid)
- proteo-catabolism - increased aminoacids, decreased proteosynthesis in muscles
- hyponatremia due to losses of Na via kidney (diabetic polyuria)
- normokalemia - also losses via kidney but low K input into cells

**Insulin resistance**
- decreased effect of insulin on a target organ
- auto-antibodies against receptors
- deficiency of the glucose transport mechanism
- receptor - post-receptor disorders
- can be genetically predisposed but frequently caused probably only by exogenous factors - especially obesity - visceral fat causes insulin-resistance (change in the structure of muscle cell membranes)
- leads to hyperglycemia (even in fasting)
- increased glycemia - toxic effect on beta-cells → decreased production of insulin

**Insulin-like activity**
- proinsulin
- somatomedins (= IGF insulin-like growth factors)
- substances (polypeptides) formed in liver
Diabetes Mellitus (DM)
Etiology (specific etiology for particular DM type - see below)
- not fully understood
- multifactorial
- genetic predisposition
- external factors - style of life - stress, nutritional habits, alcohol, smoking, low physical activity, etc.
- geographic differences (genetic or style of life??) - North American Indians - 10%, Europe ca 5% increasing towards elderly
- increasing number of diabetics due to survival and reproduction (increased genetic endowment)

DM - classification
● Type I - Insulin-dependent diabetes mellitus (IDDM) = Juvenile onset DM - 10-20%
  - total deficit of insulin
  - starts in childhood or early adulthood
  - tendency to ketoacidosis
  Etiology
  - autoantibodies against beta-cells - known responsible genes (HLA DR3 and others)
  - formation of antibodies against insulin (HLA DR4 and others)
  - viral infection, damage of pancreatic tissue (inflammation)
● Type II - Non-insulin-dependent DM (NIDDM) = Adult onset DM - 80%
  1. Nonobese NIDDM
  2. Obese NIDDM (60 - 90%)
  - at least partial production of insulin
  - not ketosis prone (insulin prevents lipolysis)
  Etiology
  - non-autoimmune
  - insulin resistance (missing receptors, non-sensitive receptors, intracellular problem - second messenger??)
  - more important exogenous factors (obesity, stress, low physical activity, smoking, nutrition)
  - autosomal dominant heredity

● MODY diabetes: Maturity Onset Diabetes of the Young (MODY) is a form of diabetes that is genetically inhereted. Whereas most types of diabetes only have genetic inheritance as a "risk factor", MODY is more strongly inherited. MODY is similar to Type II diabetes in its severity, leading to a form of insulin deficiency. Whereas typical Type 2 diabetics are over-forty and over-weight, a MODY patient is typically in teens or twenties and is thin.

● Secondary DM
  - pancreatic disease (chronic pancreatitis), carcinoma, pancreatectomy, hemochromatosis "bronze diabetes"
  - hormonal - "steroid diabetes", STH (growth hormone) -by acromegaly, thyreotoxicosis, glucagon
  - gestational DM - glucose intolerance developed during pregnancy - perinatal complications (large fetus, fetal hyperinsulinemia - danger of hypoglycemia), risk of DM in the mother after 5-10 years or in next pregnancy
  - drug or chemical induced insulin receptor abnormalities
  - certain genetic defects
- Impaired glucose tolerance
  - asymptomatic - normal fasting glycemia, glucose tolerance between normal and diabetic
  - latent DM with slight fatigue and later development into DM

- Metabolic syndrome = syndrome of insulin resistance = Raeven's syndrome
  The metabolic syndrome is characterized by a group of metabolic risk factors in one person.
  They include:
  - Central obesity (excessive fat tissue in and around the abdomen)
  - Atherogenic dyslipidemia (mainly high triglycerides and low HDL cholesterol — that foster plaque buildups in artery walls)
  - Insulin resistance or glucose intolerance
  - Prothrombotic state (e.g., high fibrinogen or plasminogen activator inhibitor in the blood)
  - Raised blood pressure
  - Proinflammatory state (e.g., elevated high-sensitivity C-reactive protein in the blood)
  - The underlying causes of this syndrome are overweight/obesity, physical inactivity and genetic factors. People with the metabolic syndrome are at increased risk of coronary heart disease, other diseases related to plaque buildups in artery walls (e.g., stroke and peripheral vascular disease) and type II diabetes.

DM - pathogenesis, clinical manifestations
- insulin is the only hormone decreasing glycemia
- deficiency of glucose in cells - activates catabolic mechanisms (as in fasting)
- main source of energy are lipids
- ketoacidosis → ketoacidotic coma (see below)
Consequences of hyperglycemia
- osmotic diuresis → hypovolemia, hypotension, hyperosmolar coma (see below)
- increased glycation of proteins (The term "glycation" is the non-enzymatic glycosylation of proteins, nucleotides and lipids by saccharide derivatives. It is thought to contribute to the development of chronic vascular and other complications of diabetes - see below.)
- glycation of Hb - increases affinity of Hb for oxygen (interference with 2,3-DPG) → hypoxia (level of Hb glycation represents a criterion for evaluation of DM compensation)
Clinical signs and symptoms
- polyuria, polydypsia (increased drinking), polyphagia
- glucosuria
- decreased body weight (in DM type I) - catabolic state, loss of glucose via urine
- increased fatigue - loss of muscle glycogen
- acidic Kussmaul's breathing
- decreased immunity
- chronic inflammatory processes, skin infections
- accelerated atherosclerosis
- micro/macrophangiopathies
- polyneuropathies
- orange skin colour due to increased beta-carotene (decreased transformation to vitamin A in insulin deficiency)
- increased level of hemoglobin glycation
65. Diabetic coma (ketoacidotic, hyperosmolar, lactoacidotic)

**Ketoacidotic coma**
- total deficit of insulin leads to lipolysis and ketoacidosis in DM type I
- despite compensatory Kussmaul's breathing it can lead to severe pH decrease (renal compensation can be insufficient because of renal failure due to diabetes)
- decreased pH buffer capacity due to hypoproteinemia
- acidosis can be combined with lactoacidosis (see below)
- pH 7.3 - 7; hyperglycemia 16 - 60 mmol/l
- decompensated acidosis leads to peripheral vasodilation (causes hypotension, circulatory problems still increase lactacidosis in periphery) and increased vessel permeability - formation of generalized edemas including brain edema leading together with brain hypoxia to coma
- compensation of acidosis must be careful - not to switch to respiratory alkalosis due to persisting Kusmaul's hyperventilation

**Hyperglycemic hyperosmolar coma**
- not compensated diabetes (mainly in type II and older patients)
- extreme glycemia causes polyuria (glucose in urine induces osmotic diuresis) with large loss of water → dehydration (hypovolemic circulatory shock), hyperosmolarity of ECF → exicosis (drying) of cells including CNS → coma
- simultaneous depletion of Na and K, however, there is usually no hypokalemia because of a shift of K from ICF to ECF (low input of K into cells due to missing insulin)
- activation of sympathetic system causes tachycardia and decreased perfusion in periphery - cold skin but dry skin (dehydration)
- extreme thirst
- hyperthermia
- neurologic manifestations - positive Babinski's sign, paresis or paralysis, sensory impairment, seizures
- signs and symptoms are masked by diuretic therapy (quite common in old people), decreased expression of thirst and psychic alteration (also frequently seen in old patients)
- hyperglycemia 40 -90 mmol/l
- no signs of ketoacidosis

**Lactoacidotic coma**
- can be a consequence of high doses of biguanide peroral antidiabetics - their induction of anaerobic glycolysis
- contributes peripheral hypoperfusion (diabetic micro/macro-angiopathies) increasing anaerobic metabolism
- low ability to compensate via hyperventilation in old people as well as through decreased kidney function
- lactic acid over 8 mmol/l (can be decreased by hemodialysis)
- mechanism of coma development as in ketoacidosis - via increased vessel permeability and brain edema formation

**Important differentiation of diabetic (hyperglycemic) and hypoglycemic comas** - may not be clear outside hospital (despite some signs like hyperreflexia in severe hypoglycemia - irritation of the CNS) - anyhow, it is recommended to give injection of 40% glucose (improves hypoglycemia, does not increase significantly hyperglycemia)
66. Diabetes mellitus – complications

**Angiopathies**
- 3/4 of diabetic patients die because of some vascular complication - myocardial infarction is 3 times more frequent than in the rest of population

**Macroangiopathies - etiology**
- hypertension due to nephropathy (glomerulosclerosis) and atherosclerosis
- atherosclerosis activated via increased polyol concentration in arterial wall, glycation processes, increased LDL etc.

**Microangiopathies - etiology**
- glycation of proteins in basal membrane (e.g. in glomeruli)

**Manifestations**
- coronary heart disease → myocardial infarction
- diabetic nephropathy - atherosclerosis
- glomerular involvement (microangiopathy), transudation of albumins - mesangial reaction
  → glomerulosclerosis (specific for diabetes = Kimmelstiel-Wilson) → renal failure
- retinopathy - microangiopathy and hypoxia due to glycation of Hb → blindness
- diabetic leg (gangrene due to hypoperfusion)

**Polyneuropathies**
- glycation of proteins
- microangiopathy of vasa nervorum
- peripheral paresthesias, dysesthesias, decreased reflexes
- impaired pain, temperature, light touch sensation
- diabetic amyotrophy
- vegetative disorders - heart arrhythmias, postural hypotension (collapses), gastroparesis, diarrhea, disorders of micturition (paralytic bladder), sexual functions
- oculomotor nerve palsy

**Immunodeficiency**
- glycation of immunoglobulins
- blocked chemotaxis of neutrophils, activity of complement
- infections (e.g. renal - pyelonephritis, skin infections, vulvovaginitis, pruritus vulvae), risk of sepsis

**Worsened healing of wounds**
- hypoperfusion
- infections (hyperglycemia)

- bleeding disorders - due to hypoproteinemia and vessel wall changes
- microaneurysms
- glaucoma (changed oncotic pressure of chamber water)
- tubular disorder - deposits of glycogen into the proximal tubulus - decreased reabsorption
67. Pathophysiology of water-soluble vitamins

- Kazimierz Funk Polish biochemists introduced in 1912 the term "vitamines" = vital amines (no longer valid - not all are amines)
- first isolated vitamin A in 1831

Vitamin C - ascorbic acid
- important in synthesis of collagen (changes proline → hydroxyproline, lysine → hydroxylysine)
- hydroxylation of cholesterol (bile acids)
- formation of norepinephrine
- release of Fe from ferritin
- transformation of folic acid into FH4
- effect on immunoglobulins IgA, IgM, C3 complement
- antioxidative effect - prevents oxidative stress
- prevents scurvy (scorbut) - bleeding disorder because of vasculopathy - due to deficit in collagen maturation (mainly gingival bleedings)
- in childhood - m. Möller Barlow - bleeding under periost
- sources: fruits, vegetables
- recommended dose - 60 mg/day, not cumulated, eliminated via urine, no hypervitaminosis
- hypovitaminosis - frequent in bad quality nutrition

Vitamin B1 - thiamin (aneurin) (isolated 1926)
- important for the function of carboxylases (Kreb's cycle, glycolysis)
- influences metabolism of nerves and muscles (myocardium)
- severe hypovitaminosis causes "Beriberi"
  - dry Beriberi - neuritis - involved are spinal cord, peripheral nerves (distal motoneurones, sensory nerves - symptomatology similar to Multiple Sclerosis)
  - quite frequent neuropathies similar to Beriberi in chronic alcoholism (probably due to malnutrition)
- CNS involvement - Wernicke-Korsakoff sy (encephalopathy)
- wet Beriberi - cardiomypathies (decreased contractility → dilation), vasodilation, edemas
- Beriberi appears in Asian countries with monotonous nutrition - polished rice
- sources: non-polished corn, liver, dark bread
- recommended dose - 1.5 mg/day(in alcoholics 50 mg or more)

Vitamin B2 - riboflavin (isolated 1932)
- influences metabolism (cofactor of enzymes)
- deficiency causes inflammations of mucous membranes - "anguli infectiosi" - quite specific sign, stomatitis,
- sources: milk, yeast, liver
- dose - 1.5 mg/day

Vitamin B6 = pyridoxin
- transmits amine group - NH₂ and carboxyl group - COOH - influences metabolism of amino acids
- deficit causes jerks, irritability, nausea, vomiting, diarrhea, anemia
- sources: corn, liver, yeast

Vitamin B12 - (cyano)cobalamin
- gastric "intrinsic factor" is necessary for its resorption (formed by parietal cells - deficiency e.g. in atrophic gastritis, after gastrectomy))
- important for synthesis of nucleic acids - in erythropoiesis, metabolism of CNS
- deficit - pernicious (macrocytic) anemia, neuropathy - "sy of socks and gloves"
- sources: liver, meat, eggs, milk
- long deposits

**Vitamin PP = niacin = "pellagra preventive" = PP**
- part of NADP, important in metabolism of carbohydrates
- partially synthesized in the body from Tryptophan
- deficit - pellagra = dermatitis, dementia, diarrhea
- sources: meat, liver, yeast

**Vitamin FF (= filtration factor - captured on the filtration paper) = panthothenic acid**
- protects acetylating - metabolism, part of CoA
- supports epithelisation
- deficit - sy of feet burning = neuropathy, dermatitis, alopecia, enteritis
- source: liver, eggs, yeast

**Vitamin H = biotin**
- transmits carboxyl group - COOH
- produced by intestinal bacteria - blocked by avidin from raw egg white matter
- deficit leads to dermatitis, enteritis
- source: liver, vegetables yeast

**Folic acid = folacin**
- transmits methyl groups
- important for erythropoiesis in connection with B12
- deficit - macrocytic anemia, leucopenia
- source- vegetables, formed by intestinal bacteria

**Vitamin P = bioflavonoids**
- e.g. rutin - influences quality of vessel walls

and others - PABA, choline, etc.
68. Pathophysiology of lipid-soluble vitamins

- resorption from the gut is dependent on absorption of fats - deficit in malabsorption of fats (bile disorders, pancreatic disorders, chronic diarrhea etc.)
- compared to water-soluble vitamins, lipid-soluble ones are stored in fatty tissues and hypovitaminosis develops only after longer deficit

**Vitamin A = retinol**
- first known vitamin (discovered in 1831)
- provitamin A = beta-carotenes
- 5-10 month reserve exists in the body
- main functions: 11-cis-retinal isomer is the chromophore of rhodopsin (retinal pigment), important for normal quality of epithelia/mucous membranes, antioxidant activity (oxygen free-radical scavenger)
- seems to prevent lung carcinoma - 20 mg of carotenes recommended daily to smokers
- hypovitaminosis manifestations: nyctalopia - decreased vision in dim conditions, decreased quality of epithelia and skin - inflammations, xerophthalmia, keratomalacia (corneal changes - frequent cause of blindness in undeveloped countries with low quality of nutrition), acne
- Vit. A = potential teratogen!!! in hyperdoses
- recommended dose - retinol 1 mg/day or beta-carotenes 6 mg/day
- hypervitaminosis - toxicity of vit. A, liver steatosis, hepatomegaly
- sources: carrot, liver, milk, eggs, yellow vegetables

**Vitamin D** (D2 - ergocalciferol, D3 - cholecalciferol)
- via two hydroxylations (first one in liver, second one in kidney under the influence of parathormone) is converted to calcitriol (1,25 dihydroxycholecalciferol), essential for absorption of Ca from the gut
- D2 - plant sources
- D3 - fish liver, milk, yeast, formed in skin under UV light
- hypovitaminosis or liver and kidney disorders leads to *rachitis in children* = severe ossification disorder leading to skeletal anomalies
- *osteomalacia in adults* - decreased inorganic components of bones → pathological fractures
- calcemia may not be decreased - parathormone causes resorption of calcium from bones
- hypervitaminosis - in overdoses of D3 in newborns - calcifications - mainly in kidney
- recommended 0.01 mg/day, reserves in the body for 2-4 months

**Vitamin K** (quinones)
- necessary for formation of vit. K dependent coagulation factors in liver - II,VII,IX,X (via carboxylation of glutamic acid)
- deficit, or reversible inhibition via coumarin preparations (Warfarine), leads to bleeding disorders (tested with the use of Prothrombin time = Quick test, INR)
- sources: vegetables
- recommended daily intake - 0.08 mg

**Vitamin E = tocopherol**
- plays role in metabolism of muscles, probably important in pregnancy, may contribute to maturation of sperm
- antioxidation effect - largest among vitamins
- effects not fully clarified yet
- sources: eggs, milk, vegetables
- dose- about 10 mg/day
**Vitamin F - essential fatty acids** (arachidonic acid, linolenic acid, ...)
- formation of prostaglandins
- added to cosmetics
69. Nausea, Vomiting

Nausea is a subjective unpleasant sensation due to stimulation of the medullary (brain stem) vomiting center. Nausea is usually preceded by anorexia (lack of a desire to eat despite physiologic stimuli that would normally produce hunger), and some stimuli (e.g., foods and drugs) that cause anorexia in small doses usually produce nausea or vomiting when given in larger doses. Nausea is frequently accompanied by autonomic responses such as salivation and peripheral vasconstriction with pallor, sweating and tachycardia. Nausea may function as an early warning signal of pathology (not only GIT but also cardiovascular, pulmonary, hepatic, renal and CNS!! - see below).

Vomiting is a basic physiologic protective mechanism that limits the possibility of damage from ingested noxious agents by emptying the contents of the stomach and upper part of small intestine. However, it can also represent a total-body response to a lot of factors influencing either functional state of the stomach or directly affecting vomiting center or chemoreceptor trigger zone in the brain stem (important diagnostic information).

- chemoreceptor trigger zone (area postrema, floor of the fourth ventricle) - reacts to input of emetogenic (emesis = vomiting) substances from blood or cerebrospinal fluid
- vomiting center (dorsal part of of the reticular formation) - integrates emetogenic signals from chemoreceptor zone, vestibular system, hypothalamus, thalamus, cortical structures (psychic stimuli - emotions, stress) and also peripheral signals from GIT (stomach, upper intestine - via n. vagus and splanchnic nerves)
- efferent signals activating vomiting - via cranial nerves VII, IX, X, XII and spinal cord (diaphragm, abdominal wall)
- neuromediators of vomiting - dopamine, serotonin

Etiology

Nausea and/or vomiting is activated either through peripheral stimuli coming from GIT - this kind of "peripheral" vomiting has a protective character or via direct influences on the centers within CNS (chemoreceptor zone, vomiting center) - this kind of "central" vomiting represents usually complication of some other primary pathological process but has warning (signaling) character important for early diagnostics or intervention in case of pathological CNS processes.

Peripheral vomiting

● mechanical stimuli
  - distension (not normal emptying) of the stomach - overeating, upper ileus (see below)
  - distension of the duodenum (upper intestine) - dumping sy (see below), ileus
  - mechanical influence to the solar plexus (strike to the abdomen)
  - 3rd trimester of pregnancy - enlarged uterus compresses stomach
  - renal-gastric reflex - nausea up to vomiting in renal colic (obstruction of the ureter by a stone)

● chemical stimuli
  - prevention of toxin absorption - however, some toxins are not recognized (not emetogenic)
    - e.g. Phalloidin from the toxic mushroom Amanita phalloides (hepatototoxic), in such cases vomiting must be evoked (e.g. by oral intake of hypertonic solution of NaCl) or gastric suction must be used
  - irritation by blood in massive bleeding to esophagus or stomach (esophageal varices in portal hypertension, peptic ulcer) - vomiting of blood = hematemesis

● ischemia/hypoxia of the stomach (digestion is energetically demanding)
  - extreme physical activity (redistribution of blood to muscles)
- stress or circulatory shock, heart failure - centralization of circulation (vasoconstriction in the splanchnic area via sympathetic activity)
- respiratory failure - e.g. pneumonia in children
- drugs causing gastric vasoconstriction (also caffeine)
- signals from inflammations in GIT and urinary system

Central vomiting
- chemical stimuli
  - 1st trimester of pregnancy - hormonal changes (estrogens) - already from the 2nd week of pregnancy
  - antibiotics, cytostatics, analgetics
  - toxins of some bacteria
  - uremia, hepatic encephalopathy
  - alcohol (high plasma levels + acetaldehyde)
- physical stimuli
  - intracranial hypertension (brain edema, hematomas, tumors, hydrocephalus) - leads to herniation (passage) of the brain through Foramen occipitale magnum = conus occipitalis
  - compression of the brain stem - activates vomiting center = warning signal (develops quickly to death)
  - brain trauma
  - commotion or contusion of the brain - extension of the brain stem activates vomiting center
  - meningeal irritation - bleeding, inflammation
- increased activation of the stato-kinetic apparatus
  - sea sickness, carousel, bus - combined with opto-kinetic nystagmus (repeated changes of visual fixation in viewing through side window) - more frequent in children (sedatives help)
- emotional reactions
  - fear, stress (observation of bloody scenes)
- bad smell
  - particularly in the case of a previously experienced bad smell (from bad meal) which was followed by vomiting (retained in memory for a long time)
- psychic disorders - e.g. in Anorexia mentalis

Pathogenesis and clinical manifestations
- dehydration in prolonged (repeated) vomiting - requires infusion rehydration in babies within 24 hours after onset
- development of metabolic alkalosis (loss of HCl) with subsequent hypoventilation leading to lower oxygenation of blood
- mineral dysbalance - mainly Cl losses
- esophagitis, erosions - Mallory-Weiss sy
- risk of aspiration of vomitus during unconsciousness - in central vomiting due to CNS disorders (intracranial hypertension)
70. Gastric ulcer, duodenal ulcer – pathophysiology

Etiology
- multifactorial, not fully understood
- dysbalance between protective mechanisms and aggressive factors towards gastric wall
  ● protective factors
    - mucin
    - prostaglandins E<sub>2</sub> - inhibit secretion of HCl, induce vasodilation of submucosal vessels - increases elimination of H<sup>+</sup>, oxygen supply, cytoprotective effect via increased secretion of mucin
    - inhibitors of PG E<sub>2</sub> (non-steroid antiinflammatory drugs inhibit cyclooxygenase; glucocorticoids - block phospholipase A<sub>2</sub>) can activate ulcer formation
  ● aggressive factors - intrinsic
    - genetic predisposition - familial, more frequently blood group 0
    - stress - frequent psychosomatic disease (glucocorticoids increase acidity of the gastric fluid, vasoconstriction in splanchnic area - decreased production of mucin, parasympathetic activity increases production of HCl, increased production of gastrin)
    - Helicobacter pylori - in 95% of patients with duodenal ulcer, but also in asymptomatic people, eradication of Helicobacter (combination of ATB) helps in many cases
    - chronic venostasis in right heart failure (with simultaneous high acidity)
    - increased HCl production - gastrin (gastrinoma - Zollinger-Ellison sy), acetylcholine (M1 receptors), histamine (H2 receptors)
  ● aggressive factors - extrinsic
    - nutrition (caffeine, large portions of meat, alcohol, sugar, spicy meals) - worsen protective layer of mucin
    - smoking - causes vasoconstriction, decreases production of mucin
    - non-steroid anti-inflammatory drugs - inhibit formation of PG E<sub>2</sub> and decrease protective mucin layer

Acute stress ulcers
- both gastric and duodenal
- quick formation (in several hours)
- spontaneous recovery after elimination of the stress factors
- tendency to perforation
- main role - disorder of microcirculation - in shock, burns, trauma, surgery

Peptic ulcers = ulcer disease
- chronic disorder, relapses
- slow development
- seasonal appearance - spring, autumn
- mainly around 35 years of age
- typical dysbalance between protective mechanisms and acidity
- dominant pain related to meals
- different symptomatology in gastric and duodenal ulcers, rarely are both combined

Gastric ulcers
- less frequent (4-5 times compared to duodenal)
- not distinct sex differences
- danger of tumorous process
- multiple ulcers mainly in gastrinoma, glucocorticoids and increased HCl secretion
Symptoms: pain usually immediately after meal, periodic character of relapses, dyspepsia, loss of body weight, massive bleedings - hematemesis or melena (dark stool)
Duodenal ulcers
- more frequent
- benign (never cause tumorous process)
- dominant etiological factor - stress, frequently also decreased production of pancreatic fluid (decreased neutralization of acidity in duodenum)

Symptoms: pain in fasting or 2 or more hours after meal, in night, meal (mainly milk)
- decrease pain, tendency to increase of body weight (frequent eating), small chronic bleeding
- occult (= hidden, not evident, detectable via chemical tests of feces) leading to anemia

Complications of ulcers
- bleeding
- perforation - causes peritonitis
- penetration - into some close organs - colon transversum, pancreas, liver, gallbladder
- ulcerative deformity - pylorostenosis
- gastric adenocarcinoma in 10% of patients

Principles of therapy
- change of nutritional habits - regular nutrition, avoid coffee, smoking, alcohol,
- antacids
- inhibitors of the proton pump H⁺/K⁺ ATPase (omeprazole)
- antagonists of M1 and H2 receptors
- surgical treatment - vagotomy (decreases acidity - can cause diarrhea due to the reduced ability of the stomach to kill ingested bacteria), relapses in case that hyperacidity is not the only etiological factor
- gastric resections - Billroth I, II, III (partial and total gastrectomy)
71. Gastritis, postgastrectomy status – pathophysiology

Gastritis
- inflammation of the gastric wall causing erosions (ulcer is a deeper involvement including lamina muscularis mucosae)

Acute gastritis (erosive)
- involvement concerns whole stomach
- mucous membrane is hyperemic, edematous with small multiple erosions and sticky bloody mucin

Etiology
- drugs - aspirin (mainly with no drink or meal), phenylbutazone
- alcoholism, smoking
- spicy meals (in sensitive people - not harmful in adapted subjects)
- acute infections (from meals), candidiasis
- stress

Pathogenesis
- usually quickly healed - in the case of infection simple chemotherapy is sufficient
- appropriate diet in people sensitive to some agents in nutrition (drugs) prevents relapses
- no tendency to chronic process (lasts about 1-3 days only)

Chronic gastritis
- Hypertrophic gastritis (Ménétrier's disease)
  - folds in the stomach become enlarged and swollen
  - often protein loss into stomach
- Atrophic gastritis
  A - fundal = autoimmune gastritis (antibodies against parietal cells)
    - hypoacidity - causes repeated gastrointestinal infections, malabsorption of proteins
    - pernicious anemia - missing intrinsic factor
    - also hypochromic microcytic anemia can develop because of inadequate reduction of Fe³⁺ to Fe²⁺ (the only absorbable form) due to low acidity
  B - antral - chronic inflammation due to Helicobacter pylori
  - can cause ulcers

Postgastrectomy status
- Gastric resections:
  - Billroth I - Removal of lower portion of stomach (pylorus) with end to end anastomosis of the remaining stomach with the duodenum.
  - Billroth II - gastric stump connected to the jejunum
  - Billroth III - Removing the entire stomach is done only for resistant Zollinger-Ellison syndrome or extensive cancers.
- Vagotomy

The stomach serves as the receptive and storage site of ingested food and releases its contents downstream into the duodenum in a controlled fashion. The capacity of the stomach in adults is approximately 1.5-2 liters. Alterations in gastric anatomy after surgery or interference in its extrinsic innervation (vagotomy) may have profound effects on gastric emptying. These effects have been termed postgastrectomy syndromes:
  - small capacity, dumping, bile gastritis, afferent loop syndrome, efferent loop syndrome, anemia, and metabolic bone disease.
Dumping syndrome
- characteristic alimentary and systemic manifestations
- the most common and often disabling postprandial syndrome observed after definitive surgery for peptic ulcer disease
- Dumping syndrome can be separated into early and late forms depending on the occurrence of symptoms in relation to the time elapsed after a meal
- both forms occur because of rapid delivery of large amounts of osmotically active solids and liquids into the duodenum
- an operation in which the pylorus is removed, bypassed, or destroyed increases the rate of gastric emptying
- duodenal feedback inhibition of gastric emptying is lost after a bypass procedure such as gastrojejunostomy
- gastric mucosal function is altered by surgery, and acid and enzymatic secretions are decreased. Also, hormonal secretions that sustain the gastric phase of digestion are affected adversely

Early dumping syndrome
- symptoms of early postprandial dumping syndrome appear 30 - 60 min after meal
- accelerated gastric emptying of hyperosmolar contents into the small bowel leads to fluid shifts from the intravascular compartment into the bowel lumen → rapid small bowel distention and an increase in the frequency of bowel contractions
- bowel distention causes crampy abdominal pain, vomiting, bloating and diarrhea
- intravascular volume contraction due to osmotic fluid shifts is perhaps responsible for the vasomotor symptoms such as tachycardia, sweating and lightheadedness (even hypovolemic circulatory shock could develop in some cases)

Late dumping syndrome (late postprandial syndrome)
- occurs 1 - 3 hours after a meal
- rapid delivery of a meal to the small intestine results in an initial high concentration of carbohydrates in the proximal small bowel and rapid absorption of glucose
- this is countered by a hyperinsulinemic response
- the high insulin levels are responsible for the subsequent hypoglycemia (effect of enhanced insulin release after an enteral glucose load as compared to intravenous glucose administration is called the incretin effect – based on increased release of glucose-dependent insulinotropic peptide and glucagonlike peptide-1 (GLP-1)
- the reason why some patients remain asymptomatic after gastric surgery, while others develop severe symptoms, remains elusive

Malabsorption
- deficit of HCl causes decreased transformation of Fe$^{3+}$ to Fe$^{2+}$, hence lower absorption of iron, and microcytic, hypochromic anemia
- loss of parietal cells leads to deficit of intrinsic factor → pernicious anemia
- malabsorption of proteins (due to hypoacidity) → diarrhea, loss of weight, protein catabolism

(Additional problems after gastrectomy: irritable colon, meteorism = flatulence)

Recommendation for partial prevention of the above specified postgastrectomy syndromes: frequent eating in very small portions and with low concentration of carbohydrates in the diet.
72. Gastro-intestinal bleeding

Gastrointestinal bleeding refers to any bleeding that originates in the gastrointestinal tract, from the mouth to the large bowel. The degree of bleeding can range from nearly undetectable to acute, massive, life-threatening bleeding. Bleeding may originate from any site along the gastrointestinal tract, but is often divided into:
- upper GI bleeding (considered any source located between the mouth and duodenojejunal junction – represents about 90% of all cases)
- lower GI bleeding (from the duodenojejunal junction to the anus, small and large bowel included) – about 10%

**Etiology**
- possible causes of gastrointestinal bleeding include: hemorrhoids, duodenal ulcer, gastric (stomach) ulcer, bleeding diverticulum, ulcerative colitis, Crohn’s disease, esophageal varices, arterio-venous malformations, Mallory-Weiss tear (tear in esophagus after vomiting), esophagitis, dysentery (bloody, infectious diarrhea), ischemic bowel, colon cancer, intestinal polyps, celiac sprue, radiation injury to the bowel, portal hypertensive gastropathy, stomach cancer, intestinal vasculitis, small intestinal cancer, Meckel’s diverticulum, aorto-enteric fistula, cow’s milk allergy, ileus, anal fissure
- acute massive bleeding leads to loss of critical volume of blood (20%) within max. several hours – causes hypovolemic circulatory shock – must be early recognized (according to shock symptomatology) despite its hidden character (with exception of visible hematemesis)
- occult (hidden) chronic small bleeding (without macroscopic evidence) can be clinically silent for a long time – manifested sometimes only after development of sideropenic anemia (due to chronic losses of iron)

**Signs and symptoms**
- hematemesis
  - non-digested fresh (light colored) blood – from esophageal varices, Mallory-Weiss tears after prolonged vomiting, acute perforation of a gastric ulcer
  - digested blood by HCl – coffee like color – peptic ulcers, gastric carcinoma
  - differential diagnosis from “hemoptysis” – expectorated blood from lungs or from epistaxis (bleeding from nose) – swallowed during the night and vomited in the morning
- melena (stools stained black by digested blood pigment or dark blood products)
  - tarry, and foul-smelling stools – caused by bleeding from esophagus, stomach, duodenum (beginning of jejunum)
  - to be visible at least 50-100 ml of blood must contaminate stools
  - lasts usually longer than 3 days
  - important differentiation of artificial staining of stools with medicinal charcoal, blueberries, etc.)
- intestinal hemorrhage (enterorrhagia) – fresh blood in stools – from jejunum to the anus
  - when the blood is only on the surface, this indicates a more distal source of bleeding (hemorrhoids)
  - massive – diverticula, polyps
  - occult – Meckel’s diverticulum, some tumors – proved via biochemical tests of stool

**Pathogenesis**
- acute massive bleeding
  - increased HR, pallor, sweating (stress activation of the sympathetic system)
  - decreased pulse amplitude, BP (↓ MV)
- development of hypovolemic shock → decreased diuresis (↓ GF), abdominal pain (from hypoxia, infarctions and acidosis)

- occult chronic bleeding

- developing fatigue – mainly on exertion (up to unconsciousness) signalises anemia (microcytic hypochromic)
73. Intestinal malabsorption

- **malabsorption** is the inadequate absorption of nutrients from the small intestine
- **maldigestion** is failure of the chemical process of digestion that take place in the intestinal lumen or at the brush border of the intestinal mucosa
- frequently maldigestion and malabsorption are interrelated or occur together, making classification difficult – generally maldigestion is caused by deficiencies of enzymes, and inadequate secretion of bile; malabsorption is the result of mucosal disruption (intestinal disease, vascular disorders, intestinal resection)

Etiology of malabsorption/maldigestion

- **gastric disorders**
  - total gastrectomy or Billroth II gastrectomy - decreased digestive functions and postgastrectomy syndromes leading to chronic diarrhea with malabsorption
  - vagotomy - hypoacidity + motility disorders
  - chronic atrophic gastritis with decreased acidity and pepsin production
- **pancreatic disorders**
  - chronic pancreatitis with decreased exocrine functions
  - cystic fibrosis
  - pancreatic cancer
  - pancreatic resection
- **hepatobiliary diseases**
  - cirrhosis and hepatitis
  - biliary tract obstruction (gallstones)
  - biliary fistula
- **small intestine disorders**
  - non-tropical sprue = celiac disease - enteropathy caused by inborn allergy to cereal protein gluten, chronic inflammation, atrophy (flattening) of villi in proximal jejunum leads to decrease of surface, a gluten-free diet allows recovery of normal functions
  - tropical sprue - suspected infectious background - endemic appearance in South-East Asia, similar histological changes as in celiac disease - shortened villi
  - massive resection of the gut (e.g. in Crohn's disease]
  - selective malabsorptions with congenital enzymatic deficit - lactase, maltase, saccharase - inability to breakdown disaccharides - they stay in the lumen, increase osmolarity, cause a shift of water into lumen, resulting in chronic diarrhea with general malabsorption
  - bacterial or parasitic infections causing chronic diarrhea with malabsorption
  - increased motility of the gut (vagal hyperactivity, hyperthyroidism, drugs) - shortened time for absorption, diarrhea
  - changed pH in the intestine due to hyperacidity - Zollinger-Ellison sy
  - bacterial overgrowth from stasis in afferent loop after Billroth II
  - intestinal ischemia - mesenteric atherosclerosis, thrombosis, heart failure
  - lymphatic obstruction - e.g. intestinal lipodystrophy - Whipple's disease, tumorous obstruction of lymphatic vessels/nodes
  - systemic diseases - amyloidosis, sarcoidosis, scleroderma
  - Crohn's disease, lymphoma
- **large intestine disorders**
  - postresection states (tumors, Crohn's disease) - danger of dehydration (watery diarrhea)
  - dysmicrobia - after wide-spectrum ATB
  - ulcerative colitis
Pathogenesis of malabsorption/maldigestion
- decreased intake of energy - despite tendency to hyperphagia leads to loss of weight, cachexia, catabolic state, anemia, fatigue
- malabsorption of proteins - hypoproteinemia, hypoalbuminemia - edemas, hypoglobulinemia - immunodeficiency, bleeding disorders, wasting of muscles
- lipid malabsorption - hypovitaminoses A,D,E,K with all consequences (prevention should be done with supplementation)
- decreased vit. B12, folate, iron absorption (anemia)
- mineral dysbalance - especially hypokalemia - heart arrhythmias, paralytic ileus
- changes in gas resorption - meteorism (flatulence) - painful distension of the gut can even imitate acute abdominal events of myocardial infarction
- bulky, foul-smelling stools
74. Intestinal obstruction - Ileus,

Sudden stop of intestinal passage - total obstruction of the gut

**Etiology**

- **mechanical**
  - obstruction
    - intraluminal - large non-absorbable particles of nutrition, biliary - large gallstone enters the gut via fistula caused by decubitus in the gallbladder, parasites
    - intramural - carcinoma, scar strictures (Crohn's disease, ulcers, diverticula
    - extramural - tumors of the surrounding organs (e.g. gynecological)
  - strangulation - mechanical closure of the intestinal lumen (+ compression of nutritional vessels)
    - compression/stricture via adhesions
    - invagination (intussusception) - proximal part is invaginated to the distal part due to dyscoordination of peristalsis
    - herniation of the gut (e.g. through the inguinal ring)
- **vascular**
  - embolism, thrombosis - infarction of the gut - loss of peristalsis
  - neurogenic (paralytic)
    - after surgery - dysbalance in the tonus of sympathetic innervation or due to pre-medication/anesthesia
    - Multiple sclerosis
    - hypokalemia
    - reflexive - CNS trauma, renal colic, severe retroperitoneal inflammation
    - toxic paralytic states- sepsis, uremia, intoxications
- **spastic**
  - irritable intestinal content (toxins)
  - 3rd stage of syphilis, Tabes dorsalis

**Classification** - upper, lower; acute, subacute, "chronic"

**Pathogenesis**

- **Intra-abdominal changes**
  - increased peristalsis (in non-paralytic ileus) tries to overcome the obstruction - produces very intensive **coli**cky pains (repeated at regular intervals) - later, peristaltic activity stops due to exhaustion
  - accumulation of the intestinal content behind the obstruction causes enormous distension of the intestine
  - compression of vessels leads to decreased resorption of gases and fluids - visible "surfaces" in X-ray examination
  - increased pressure in capillaries → transudation into lumen and into the intestinal wall - edema of the wall
  - transudation into the peritoneal cavity → ascites
  - compression of arteries - intestinal ischemia → increases permeability - toxins and bacteria into peritoneal cavity → peritonitis
  - necrosis and perforation of the intestine
  - in the upper ileus - distention limits diaphragmatic movement → respiratory insufficiency, risk of pneumonia in the most poorly ventilated parts of lungs
- Metabolic consequences
- dehydration - losses of fluid from the circulation into intestinal lumen, peritoneal cavity, losses due to vomiting (earlier onset in the upper ileus)
- metabolic alkalosis in the upper ileus due to early intensive vomiting
- lower ileus and prolonged ileus - tendency to acidosis - no reabsorption of bicarbonates from pancreatic secretion and bile, hypokalemic acidosis and metabolic ketoacidosis caused by starvation
- hypokalemia causes atony of the gut

● Circulatory consequences
- hypovolemia
- first - peripheral vasodilation due to acidosis (ketoacidosis because of fasting and lactacidosis due to respiratory insufficiency) → hypotension
- development of hypovolemic and distributive shock - reaction of the sympathetic system tries to centralise the circulation - still worse perfusion of GIT
- hemoconcentration - increased viscosity - contributes to decreased perfusion of periphery
- circulatory shock makes multi-organ dysfunction

Clinical symptoms
- tachycardia, pallor, sweating - activation of sympathetic system
- abdominal pain - later peritoneal signs develop and fever appears
- no colicky pain in paralytic ileus
- vomiting and defecation stops according to the level of obstruction
- "miserere" - vomiting of intestinal content - in prolonged low ileus
- enlarged abdomen - first with various auscultable sounds, later silent

Principles of therapy
- in obstruction - surgery as soon as possible (within 24 hours)
- prevention of metabolic changes
- in paralytic ileus - parasympathomimetics
75. Dysfunctions of the colon: diarrhea, constipation, irritable colon, flatulence, Crohn’s disease, ulcerative colitis

Diarrhea
Specification is sometimes difficult, what is recognized by a patient as a diarrhea depends on the accustomed defecation regime (temporary change of nutrition can cause differences)

Etiology
● Osmotic
  - disaccharidase deficiencies (e.g. lactase)
  - glucose galactose or fructose malabsorption
  - mannitol, sorbitol ingestion
  - lactulose therapy (for prevention of hepatic/porto-systemic encephalopathy – to decrease production of ammonium by bacteria in the gut via decreased pH, decreases also absorption of ammonium from the gut)
  - some salts (e.g. magnesium sulfate)
  - some antacids (Maalox)
  - generalized malabsorption
● Secretory
  - enterotoxins
  - tumor products (e.g. vasoactive intestinal peptide – VIP, serotonin)
  - laxatives
  - bile acids, fatty acids
  - congenital defects
  - infections – inflammatory exudation/secretion – Shigellosis, Salmonellosis
  - traveler diarrhea – infection of travelers by flora which is saprophytic for local population
● Malabsorption
  - pancreatic enzyme deficiency or inactivation – eg. by hyperacidity in the duodenum
  - defective fat solubilisation – defective bile production (cholecystolithiasis)
  - ingestion of nutrient binding substances
  - bacterial overgrowth
  - loss of enterocytes (irradiation, infection, ischemia)
  - lymphatic obstruction (lymphoma, tuberculosis, tumors)
● Motility disorders
  - chronic stress (anxiety) increases motility via n. vagus activation (very frequent problem – e.g. in “exam fever”)
  - in diabetes mellitus - in early stages (constipation prevails later due to polyneuropathy) – activated mainly as a result of hypoglycemic phases (irritates nervous system)
  - hyperthyroidism
  - irritable colon – fixed hypermotility reaction to either psychic stimuli (psychosomatic disorder) or some irritating substances in the intestinal content (individual variability)

Pathogenesis – consequences
- dehydration – important proportion of the fluid lost relative to the amount of ECF – critical in newborns in case of GIT infections (much more frequent in newborns without breast feeding which substantially increases immunity)
- catabolic state due to loss of nutrients (energy) and breakdown of own lipids, proteins
- lipolysis → ketoacidosis – Kussmaul’s breathing
- mineral dysbalance – loss of Na, K – in chronic diarrhea critical hypokalemia can develop
**Constipation**

Constipation is passage of small amounts of hard, dry stool, usually fewer than three times a week. People who are constipated may have difficult and painful defecation. Many people think they are constipated even when their stool is regular but not every day. However, there is no correct number of daily or weekly bowel movements. Normal may be three times a day or three times a week depending on the person. Also, some people naturally have firmer stools than others.

The hard and dry stools of constipation occur when the colon absorbs too much water or if the colon's muscle contractions are slow or sluggish, causing the stool to move through the colon too slowly.

**Common causes of constipation are:**
- endocrine disorders – hypothyroidism
- neurogenic – spinal cord injuries, Parkinsonism, myenteric plexus hypoactivity (various neuropathies – e.g. diabetic, Multiple sclerosis)
- hypokalemia (low motility of the gut)
- longer dehydration
- mechanical stenosis – hernias
- painful defecation – people try to avoid/postpone (anal fissures, hemorrhoids, perianal abscesses)
- some drugs – antacids (that contain aluminum and calcium), antidepressants, anti-hypertonic drugs (calcium channel blockers), opioids
- not enough fiber in the diet (too much absorbable nutrition, low content of the colon)
- lack of exercise – sitting position decreases motility of the gut
- changes in lifestyle - such as pregnancy, older age, and travel (decrease of motility)
- abuse of laxatives – addiction (habit-forming) leads to decreasing spontaneous defecation
- specific diseases such as stroke (very common)
- systemic disorders (amyloidosis, lupus, scleroderma)
- chronic idiopathic constipation

**Consequences**
- difficult defecation leads to hemorrhoids, anal fissures
- increased intra-thoracic pressure (Valsalva’s maneuver) decreases pre-load of the heart and in older people it can cause syncope
- prolonged time for absorption of potentially toxic substances (products of putrefactive processes) can lead to encephalopathy in people with lower detoxification function of liver (cirrhosis)
- longer contact of intestine with potential cancerogens causes increased incidence of colon cancer, also mechanical influences contribute

**Irritable colon**
- irritable bowel syndrome (IBS) is a functional GI disorder characterized by abdominal pain and altered bowel habits in the absence of specific and unique organic pathology
- criteria for the diagnosis of IBS require that patients must have the following continuous or recurrent symptoms:
- Abdominal pain or discomfort relieved by defecation, associated with a change in stool frequency and stool consistency

**Etiology**
- causes remain poorly defined
- hypothesized are distinct aberrations in small and large bowel motility, visceral hyperalgesia and psychopathology (patients with psychological disturbances relate more frequent illness
than control populations - higher incidence of panic disorder, major depression, anxiety disorder and hypochondriasis)
- recently, even microscopic inflammation has been documented in some patients

Clinical manifestations
- diarrhea is described as small volumes of loose stool, with evacuation preceded by urgency or frequent defecation - postprandial urgency is common
- constipation variably results in complaints of hard stools of narrow caliber, painful or infrequent defecation, and intractability to laxatives
- alternation of both is common - characteristically, one feature predominates in a single patient, but significant variability exists among patients

Principles of treatment
- to acknowledge stressors and to use avoidance techniques
- improvement in GI symptoms with successful treatment of psychiatric comorbidities
- fiber supplementation may improve symptoms of constipation and diarrhea (individually variable - data regarding the effectiveness of fiber are controversial because 40-70% of patients improve with placebo)
- caffeine avoidance may limit anxiety and symptom exacerbation

Meteorism = Flatulence
Flatulence is the state of having excessive stomach or intestinal gas. This can result in uncomfortable feelings of bloating, as well as increased belching or passing of gas from the rectum.
Most people produce about 1-3 pints a day and pass gas about 14 times a day. Flatulence itself, although not life threatening, can definitely cause social embarrassment.
Etiology
- body does not digest and absorb some carbohydrates (for example, the sugar, starches, and fiber) in the small intestine because of a shortage or absence of enzymes
- undigested food then passes from the small intestine into the large intestine, where normal, saprophytic bacteria break down the food, producing hydrogen, carbon dioxide, and, in about a third of all people, methane
- lactase deficiency or some other malabsorption syndromes
- swallowed air (aerophagia) - this can occur with improper swallowing while eating or unconscious swallowing of air, activities that cause swallowing of air include rapid drinking, chewing gum, use of tobacco products, drinking carbonated beverages, hyperventilation in anxious people
Consequences
- abdominal pain and discomfort - when pain is on the left side of the colon, it can be confused with heart disease, on the right side of the colon, it may mimic gallstones or appendicitis

Crohn's disease
- causes inflammation in the small intestine
- usually occurs in the lower part of the small intestine (ileum), but it can affect any part of the digestive tract, from the mouth to the anus
- the inflammation extends deep into the lining of the affected organ, it can cause pain and diarrhea, bleeding, weight loss and fever may also occur

Etiology
- cause is unknown
- suspicion that infection by certain bacteria, such as strains of mycobacterium, may play a role - no convincing evidence that the disease is caused by infection (Crohn's disease is not contagious)
- although diet may affect the symptoms it is unlikely that diet is responsible for the disease
- abnormal activation of the immune system in the intestines appears to be important
- susceptibility to abnormal activation of the immune system is inherited - recently a gene NOD2 has been identified as being associated with Crohn's disease, this gene is important for body responses to some bacterial products

Pathogenesis - complications of Crohn's disease
- blockage of the intestine (due to thickening of the intestinal wall with swelling and scar tissue, narrowing the passage)
- ulcers with fistulas to the surrounding tissues such as the bladder, vagina, or skin (most frequently around the anus and rectum)
- nutritional complications - deficiencies of proteins, calories, and vitamins may be caused by diarrhea or malabsorption
- complications associated with Crohn's disease - arthritis, aphthous ulceration, uveitis, stomatitis, kidney stones, gallstones, cancer of colon

Principles of treatment
- cells affected by Crohn's disease contain TNF - it may be responsible for the inflammation
  Anti-TNF seems particularly helpful
- Interleukin 10 suppresses inflammation
- antibiotics are used to treat the bacterial infections that often accompany Crohn's disease
- Budesonide - new corticosteroid causing fewer side effects
- Methotrexate and cyclosporine - immunosuppressive drugs – seem to work faster than the other immunosuppressive drugs.
- surgery - to remove part of the intestine can help in some complications but cannot cure Crohn’s disease

Ulcerative colitis
- similar predisposing factors as in Crohn’s disease
- localization only in colon, rectum
- similar symptomatology with different frequency of particular problems (more frequent bleeding, less diarrhea, abscesses and fistulas, pain is uncommon but may occur)
Acute and chronic pancreatitis

**Acute pancreatitis**
- acute inflammation with destructive autodigestion of the pancreas and peripancreatic tissues due to escape of activated proteolytic enzymes from the ducts (can cause death within 2 days mainly from hemorrhage and/or sepsis)

**Etiology**
- two major factors: biliary disease and alcohol abuse
  - 40 - 80% of patients without alcoholic etiology (differences among countries) have small gallstones → reflux of bile probably via obstruction at the ampulla of Vater
  - up to 70% caused by alcohol abuse - (after heavy drinking) - mechanism is not clear, it can be direct toxic effect on pancreatic acinar cells or inflammation of sphincter of Oddi with spasm (quite frequently in combination with overeating - especially fatty meals)
- minor factors: trauma, ampullary tumors, viral infection (mumps, Coxsackie B-hepatitis), drug-induced (e.g. azathioprine, valproic acid, corticosteroids, aspirin?), hyperparathyroidism (precipitation of calcium in the pancreatic duct or activation of trypsinogen), hyperlipidemia (especially with chylomicrons), hypothermia, shock, infarction, radiation therapy, duodeno-pancreatic reflux (in the case of some duodenal obstruction - activated enzymes come back into the pancreatic duct)
- 25% idiopathic (can be due to occult biliary microlithiasis, rarely familia)

**Pathogenesis and clinical manifestations**
- pathologic changes result from the action of activated pancreatic enzymes
  - swelling of the gland, necrosis, abscess formation, hemorrhage, ascites (includes blood, fat globules, amylase and other enzymes)
  - fat necrosis around pancreas with soap formation (leads to hypocalcemia)
  - activation of kinins, complement, coagulation factors, plasmin → thrombosis, hemorrhage
  - vasoactive substances → vasodilation, increased permeability → edemas, decreased blood pressure
  - phospholipases interfere with surfactant → ARDS
  - extreme pain (distended ductules, edema, hemorrhage - stretching of the pancreatic capsule)
  - peritonitis
  - nausea, vomiting
  - paralytic ileus (due to hypokalemia)
  - fever (endogenous pyrogens, infectious complications)
  - circulatory shock - hypovolemia (hemorrhage mainly into the retroperitoneal space, accumulation of fluid in the gut) and vasodilation (kinins) - with all possible consequences
  - hyperamylasemia (10 - 20 times over the norm) and hyperlipemia - cardinal laboratory findings (but need not be expressed in some patients)
  - activation of DIC
  - hypoglycemia/hyperglycemia
  - jaundice (in about one fifth of patients) - compression of the bile duct by pancreatic pseudocysts
  - acidosis - first lactic (due to shock), later diabetic ketoacidosis
  - hyperkalemia (release from necrotic cells) develops into hypokalemia after rehydration and compensation of acidosis

**Chronic pancreatitis**

**Etiology**
- obstructive (tumor, post-inflammatory strictures)
- calcificatory - 70 - 80% of chronic pancreatitis (frequently in chronic alcoholism) - precipitation of proteins and calcium - poorer enzyme release → exocrine defect (endocrine function usually normal)
- cystic fibrosis (mucoviscidosis) - too viscose secretion (also in lungs - infections, fibrosis; in the gut - after birth - meconium ileus; sweat glands - high concentration of salt) - stasis predisposes to pancreatitis
- alcoholism leads to decreased function of the pancreas
- familial hereditary (induction of cytochrome P450 → lipid peroxidation by oxygen free-radicals)
- idiopathic

Consequences
- leads first to exocrine, later also endocrine dysfunction
- chronic malabortion (weight loss, deficiency of fat soluble vitamins with consequences)
- diarrhea, pain (intermittent)
- secondary diabetes mellitus
- vit. B12 deficiency due to decreased degradation of B12 binding protein
- thrombosis of the portal vein
- obstructive jaundice
**Hepatitis**

**Etiology**
- inflammation of the liver parenchyme - can be part of some other primary diseases (sarcoidosis, hematological disorders) or viral
- herpes-viruses - CMV, EBV - leads to "infectious mononucleosis"
- toga-viruses - rubella
- hepatotropic viruses - A, B, C (rarely D, E)
  - A - RNA virus, fecal-oral (parenteral, sexual) transmission, incubation period 30 days, acute onset with fever, mild severity, mainly in young people, does not cause chronic hepatitis, prophylaxis by serum globulin
  - B - DNA virus, parenteral, sexual transmission, incubation period 60-180 days, insidious onset, severe process can come to chronicity, any age group, HBV vaccination available, persistent HB-S-Ag = surface Australian antigen
  - C - unknown RNA virus, parenteral transmission, incub. period 35-60 days, insidious onset, subclinical chronic process, difficult diagnostics, prophylaxis - interferon alpha
  - D - RNA virus (defective with HB-S-Ag coat), incubation period 30-180 days, parenteral ?, fecal-oral, sexual transmission, severe chronic process, HBV vaccine
  - E - RNA virus, incubation period. 15-60 days, fecal-oral transmission, acute onset, severe in pregnant women, no chronic processes, mainly in children, no vaccination

**Pathogenesis**
- hepatic cell necrosis, scarring, Kupffer's cell hyperplasia, infiltration by mononuclear phagocytes
- inflammatory edema can obstruct intrahepatic bile canaliculi - cholestasis - obstructive jaundice
- in hepatitis B, C - more severe damage of cells (fulminant hepatitis - in 70-80% leads to death)
- liver encephalopathy, liver failure - high mortality

**Clinical manifestations**
- loss of appetite, nausea, jaundice, acholic light stool, dark urine
- enlarged painful liver
- icteric phase starts 1-2 weeks after prodromal phase (combination of hepatocellular damage and intrahepatic obstruction - increased both unconjugated and conjugated bilirubin)
- increased bile acids in blood cause itching
- ↑ ALT, AST, AP
- acute hepatitis - strict diet is necessary - glucose
- chronic active hepatitis - continuing destruction of hepatocytes
- posthepatitic cirrhosis - liver failure
- after hepatitis - prolonged diet with exclusion of alcohol and fats
- resting regime (without physical activity) contributes to recovery of liver functions

**Infectious mononucleosis**
- EBV, CMV oral infection (personal contact) - incubation period 2-3 weeks
- mainly in adolescence
- starts as tonsillitis, lymphadenopathy - *if ATB are ineffective it is necessary to verify Dg of mononucleosis*
- hepatosplenomegaly, increased monocytes (large lymphocytes) in peripheral blood, fever
- complications - myocarditis, superinfections, rarely severe liver involvement
78. Cholelithiasis and cholecystitis

**Cholelithiasis**
- much more frequent in developed countries - 10-20% of population
- cholesterol stones are more common than pigmented (bilirubin)
- risk factors for cholesterol stones: obesity, middle age, female gender, gall-bladder, pancreatic or ileal disease, familial incidence
- pigmented stones in older age appear in cirrhosis

**Etiology**
- cholesterol gallstones are formed from cholesterol crystals which develop in hyper-saturated bile with cholesterol
- causes of hyper-saturation: enzymatic defect in cholesterol secretion (especially in obese people), female gender (2x more frequent), decreased production of bile acids promoting cholesterol insolubility, decreased resorption of cholesterol in the ileum-decreases bile acid pool (e.g. after resection of the gut), hyperlipoproteinemia, drugs and hormones (estrogens in gravidity), high content of cholesterol in nutrition, DM, liver cirrhosis, also in low stimulation of secretion - starvation or in parenteral nutrition
- stability of cholesterol in bile is also influenced by pH - decreased pH (e.g. in inflammation - cholecystitis) activates formation of crystals (microstones)
- pigmented stones associated with biliary infection of increased unconjugated bilirubin in bile

**Clinical manifestations and complications**
- stones can be "silent" or can obstruct cystic or common duct and cause colicky pain (especially after a fatty meal) radiating from the right subcostal area under the right scapula
- intolerance of some meals - fats and cabbage
- stones in gallbladder evoke cholecystitis
- cholangitis (dilation of the intrahepatic bile canaliculi)
- posthepatic obstructive jaundice
- pancreatitis
- large stones can produce decubitus in the gallbladder - communication with the duodenum (fistula) - stone can cause obstruction of the gut - biliary ileus

**Principles of treatment**
- either standard laparoscopic cholecystectomy or microsurgery with stone removal (usually relapses)
- dissolution of stones - e.g. with the use of chenodeoxycholic acid - a lot of toxic side effects, relapses
- extracorporeal shock wave-lithotripsy - if small particles are not eliminated via cystic duct, they can again increase size

**Cholecystitis**
- acute or chronic
- typically caused by stones
- after surgery, traumas, severe burns, shock status, complicated baby delivery, dehydration, infections
- distended gallbladder is ischemic - necrosis and perforation is possible - intense pain similar to that caused by gallstones can also imitate acute pancreatitis, myocardial infarction, acute pyelonephritis - cholangiography or radioactive scan can confirm a diagnosis
- fever, leukocytosis, increased bilirubin, amylases
- cholecystectomy is usually necessary
- chronic process can be asymptomatic
79. Classification of jaundice - etiology and pathogenesis

- daily production of bilirubin is about 300 mg - 80% from hemoglobin (destroyed old red blood cells → heme → biliverdin → unconjugated bilirubin (lipid soluble) + albumin = soluble in blood + glucuronic acid - soluble in water, eliminated with bile to stools → bacterial action → uroblinogen → urine

- **Icterus** - yellowish color of tissues caused by increased plasmatic level of bilirubin (either conjugated or unconjugated) - norm is below 20μmol/l - affinity for collagen fibers - causes yellow color mainly of skin, sclera, mouth epithelium
- false icterus - caused by increased level of carotenoids in blood - mucous membranes and sclera have normal color

**Classification of icterus**

- **Prehepatic** - excessive red blood cell destruction
  - hemolytic blood transfusion reaction
  - hereditary disorders of the red blood cell
    - Sickle cell anemia
    - Thalassemia
    - Spherocytosis
  - acquired hemolytic disorders:
    - hemolytic disease of the newborn (premature birth, fetal erythroblastosis)
    - autoimmune hemolytic anemias
    - toxic - chemicals, drugs (snake venom)
    - infectious - malaria
    - mechanical (artificial valves, prolonged marching)
    - large hematomas, infarctions

**Characteristics** - increased unconjugated bilirubin, conjugated bilirubin is normal, increased uroblinogen in urine, no bilirubin in urine, normal or darker color of stool, normal liver tests, decreased hematocrit

- **Intrahepatic** - dysfunction of hepatocytes, decreased conjugation and excretion into bile canaliculi
  - Gilbert's disease - inborn decreased bilirubin uptake by the liver and decreased conjugation
  - Crigler-Najjar sy - enzymatic defect of bilirubin conjugation
  - Decreased conjugation of bilirubin - hepatocellular damage
  - hepatitis, cirrhosis, cancer of the liver
  - drug induced intrahepatic cholestasis

**Characteristics** - increased unconjugated bilirubin (also conjugated in the case of some remaining liver function and intrahepatic obstruction due to inflammatory edema), bilirubin in urine, normal color of stool, pathologic liver tests

- **Posthepatic icterus** (cholestatic) - obstruction of bile flow
  - structural disorders of the bile duct
  - cholelithiasis
  - congenital atresia of the extrahepatic bile ducts
  - bile duct obstruction caused by tumors
  - some pharmacals inhibit membrane transport
  - primary biliary cirrhosis - immune reaction against bile canaliculi epithelium - deficient passage
  - pancreatic and liver cysts, pseudocysts
  - parasites

**Characteristics** - increased conjugated bilirubin only, dark urine (bilirubin), no uroblinogen in urine, pale color of stool, liver tests normal or pathological (in the case of activation of biliary cirrhosis), steamm Hghea, deficit of fat soluble vitamins, increased bile acids
in plasma - inhibit acetylcholinesterase, increased nerve irritability, irritation of free neural endings → intense itching, increased lipids and cholesterol → xanthelasma

● Physiological icterus of newborns
  - higher level of unconjugated bilirubin (hemolysis - HbF → HbA) - immature conjugation mechanisms
  - penetration into CNS due to immature hemato-encephalic barrier, deposits in basal ganglia (rich in lipids) → kernicterus (apathy, hypotonicity, encephalopathy, rigidity, chorea, deafness)
  - blue light changes bilirubin to isomer which can be better conjugated
  - exchange blood transfusion in the worst cases
80. Cirrhosis of the liver, Portal hypertension

Liver cirrhosis is represented by a large diffuse nodular scarring process causing liver failure and portal hypertension.
- micronodular (< 3 mm), macronodular - is not influenced by etiology
- active, passive- in former alcoholics after they stop drinking

Etiology
- alcoholic cirrhosis - Laenec cirrhosis (fatty cirrhosis), 50% - toxic effects of chronic excessive alcohol intake (toxicity of acetaldehyde formed by alcohol metabolism - damages hepatocytes, disorganization of the lipid portion of cell membranes) - causes fatty liver, inflammation, derangement of the lobular architecture - necrosis, fibrosis (cirrhosis)
  - lower resistance to alcohol in women (positive effects of alcohol max. up to 20 g of pure alcohol per day)
- postnecrotic cirrhosis, 20 - 40% - after viral hepatitis, drugs, toxins (tetrachlomethane), autoimmune destruction - replacement of necrotic tissue with fibrous cirrhotic tissue
- biliary cirrhosis
  - primary biliary cirrhosis (unknown, possibly autoimmune mechanism - scarring of lobular bile ducts
  - secondary biliary cirrhosis - obstruction by neoplasms, strictures, gallstones - causes inflammation and scarring
  - Wilson's disease (abnormal storage of copper due to its decreased excretion - autosomal recessive heredity, also CNS disorders - dementia), Hemochromatosis (increased deposits of iron - autosomal recessive disease, increased absorption, much more frequent in men - toxic effect of iron - formation of aggressive free radicals, compensatory mechanisms exhausted after 40 years of age, liver cirrhosis, heart failure, pancreas - bronze diabetes, treatment - regular venipuncture), galactosemia, glycogenosis - IV. type, deficit of α1 antitrypsin
- venostatic - in right heart failure, stasis of blood in liver, leads to hypoxia - centrilobular!!!, venostatic induration of liver develops into cirrhosis
- idiopathic - 10 -15%

Pathogenesis
- toxic effect (acetaldehyde, copper, viruses), deficiency of ATP, increased oxygen free-radicals, low anti-oxidative capacity (glutathione peroxidase, superoxide-dismutase etc.)
- injured hepatocytes release cytokines → activation of Kupffer's cells, fibroblasts and Ito's cells → production of collagen

Clinical manifestations and complications of liver cirrhosis
- portal hypertension - due to fibrosis and scarring- lower blood flow in the portal system
  - ascites - increased hydrostatic pressure (over 18 mm Hgs = 2.4 kPa) ↑ filtration, ↓ oncotic pressure due to hypoalbuminemia in failing liver, secondary hyperaldosteronism (low degradation of aldosterone in liver and activation of the renin, angiotensin aldosterone system due to large volume shift to peritoneal cavity), complete evacuation not recommended - leads to renewed formation and further loss of proteins to the ascitic fluid, danger of bacterial peritonitis
  - edemas - due to hypoalbuminemia
  - splenomegaly - leads to anemia, thrombocytopenia, leukopenia
  - varices - esophageal (most critical, cause massive bleeding), hemorrhoids, superficial abdominal veins (caput medusae) - these spontaneous porto-systemic shunts induce liver encephalopathy (see below)
- low immunity - porto-systemic shunts cause loss of phagocytosing capacity of liver (50% of the total reticuloendothelial system)
- malabsorption - due to venostasis in GIT
- bleeding disorders - thrombocytopenia, decreased production of coagulation factors in liver
- icterus - in larger involvement of liver - indicator of liver failure

Other symptoms of failing liver are described in the next chapter.

Prevention of bleeding from esophageal varices (and large ascites formation)
- TIPS = transjugular intrahepatic porto-systemic shunt - represents large artificial shunting of blood to systemic circulation (via spiral stent ensuring communication) - can lead to development of porto-systemic encephalopathy (similar symptoms as in liver encephalopathy - see below) - in such cases the diameter of the stent should be decreased to limit the volume of shunted blood going directly to the brain without undergoing residual detoxification in the liver

Other causes of portal hypertension
- prehepatic - thrombosis of the portal vein or v. lienalis (trauma, thrombophlebitis, compressive tumors, hypercoagulability)
- intrahepatic - compression of interlobular branches of the portal vein, congenital periportal fibrosis, periportal infiltration in myeloproliferative states, sinusoidal portal hypertension in all forms of cirrhosis
- posthepatic - thrombosis of v. hepatica, compression by tumors (Grawitz, hepatocellular carcinoma), venostasis (right heart failure)
81. Hepatic failure, hepatic coma

Since there is a high reserve in functional capacity of the liver, about 90% of the parenchyme must be damaged in order to lead to failure of metabolic, detoxication, proteosynthetic, immunologic and other functions.

**Acute liver failure**
- poisoning - organic solvents, phalloidin (mushroom Amanita phalloides)
- fulminant hepatitis
- Reye's (virosis + acetylsalycilic acid)

**Chronic liver failure**
- viral hepatitis
- alcoholic cirrhosis
- drugs, venostasis, metabolic cirrhosis, cholestasis, mucoviscidosis, tumors

**Symptoms**
- cholestasis - malnutrition, hypovitaminosis K, icterus
- hypoproteinemia
- bleeding disorders
- fetor hepaticus (breath smells like a freshly open corpse - caused by methylmercaptan from gut)
- spider nevi, palmar erythema (unmetabolized vasoactive substances)
- hepatorenal sy (either due to primary predominance of vasoconstrictive substances or secondary due to activation of sympathetic system - because of general vasodilation caused by unmetabolized vasoactive substances, there is low perfusion of kidney leading to critical decrease of glomerular filtration) - elevated serum creatinine, azotemia
- gynecomastia (unmetabolized female sexual hormones)
- loss of sexual hair, testicular atrophy (dysbalance in sexual hormones)
- menstrual dysfunction (hyperestrogenemia)
- liver "flap" = flapping tremor - non-specific hand tremor
- bleeding disorders (decreased prothrombin and other coagulation factors)
- edemas
- anemia
- hypoglycemia - impaired gluconeogenesis
- hyperammonemias - decreased ability to convert ammonia to urea
- nausea, vomiting, anorexia, loss of body weight

**Hepatic/porto-systemic encephalopathy**
- set of psychiatric and neurologic symptoms appearing in acute or chronic liver failure - usually reversible functional abnormalities without morphological changes - however when it reaches the stage of coma it can be irreversible and cause death
- main pathogenetic factors are probably increased ammonemia, dysbalance among plasmatic levels of aromatic and branched aminoacids, changes in neurotransmitters
- it is caused by failure of liver detoxication and metabolic functions
- important is production of potential toxins (especially ammonia produced by bacterial action onto proteins in the gut, phenols, amines, bacterial toxins) - disadvantageous is a high content on proteins (mainly animal proteins) in nutrition - can be positively influenced by low-protein diet, preferably plant proteins (but positive nitrogen balance must be ensured!!!), wide spectrum antibiotics to eliminate bacterial flora in the gut, and by administration of lactulose (a synthetic disaccharid) which decreases intestinal pH (thus
trapping ammonia as ammonium ion and reducing its absorption), and influences the bacterial flora
- increased production of ammonia and worsening of encephalopathy appears after bleeding from esophageal varices - blood = source of proteins for ammonia formation
- insufficient hepatocytes do not have normal detoxication capacity
- contributing factor is shunting of blood, by-passing the liver and arriving directly at the brain with potential toxins

**Pathogenetic mechanisms of hepatic encephalopathy**
- high ammonia levels → increased formation of glutamine with consumption of glutamate (deficiency decreases excitability of the brain) and α-oxoglutaric acid (deficiency leads to low production of ATP in the brain)
- increased ratio of aromatic/branched aminoacids (due to hyperinsulinemia - causes increased input of branched aminoacids into muscles)
- increased phenylalanine → production of false neurotransmitter phenyletanolamine
- increased tryptophan blocks conversion of tyrosine to DOPA → instead of noradrenaline octopamine is produced (false neurotransmitter) - besides CNS disorders it causes also hyperkinetic circulation and can contribute to hepato-renal syndrome
- increased GABA - inhibitory neurotransmitter

**Symptomatology of hepatic/porto-systemic encephalopathy**
- sleeplessness, increased fatigue, flapping tremor (changes in neurotransmitters)
- intracranial hypertension (increased permeability of blood-brain barrier, formation of brain edema) - together with toxic effects contributes to development of coma
- apraxia (inability to sign)
- changes of behavior

**Detection of early (subclinical) phase of hepatic encephalopathy (for prevention of irreversible changes)**
- since no morphological changes are detectable it is necessary to make functional tests
- psychophysical tests may not be completely objective
- electrophysiological testing of CNS is helpful:
  - frequency analysis of EEG displays slowing of EEG - increased amount of slow frequencies in delta and theta bands (normally alpha activity dominates in resting conditions with eyes closed), slowing of dominant activity from normal about 10 Hz below 8 Hz
  - delayed reactions to sensory stimuli → prolongation of cortical evoked potential latencies
82. Starvation, malnutrition
malnutrition = a condition caused by inadequate intake or digestion of nutrients
• Quantitative - hyponutrition
  - simple starvation
  - protein energy malnutrition (PEM)
  - overnutrition
• Qualitative - Kwashiorkor, Vitamin deficiencies etc.

Simple starvation
= lack of calorie intake
= results from
  inability to earn food
  starvation diets
  specific clinical situations (tumor, trauma, burns, psychiatric diseases)

Fuel stores:
1) fat – cca 15 kg (135 000 kcal)
2) glycogen – 0.2 kg (800 kcal)
3) proteins - 6 kg (24 000 kcal, available only 1/3)

Time course
1) Short-term starvation - first few days
   a) post-absorptive starvation – 4-6 hours after last meal
      - Energy covered from recently received food
      - Glycogenolysis (liver) - peaks 4-8 hr., ends 12-18 hr. after the last meal
      - Gluconeogenesis (liver) - onset 12-18 hr.
   b) early (non-adapted) starving (cca 4-5 days)
      - glycogen stores are depleted
      - full gluconeogenesis from: lactate, pyruvate, glycerol, AK (in this period rapid depletion of proteins)
2) Long-term starvation (adapted) - after several days (cca 4-5)
   - gluconeogenesis ↓ (to 1/3), esp. that from AK
   - lipolysis – fatty acids
     → Energy for heart
     → ketoacidosis (acetoacetate, 3-hydroxybutyrate, acetone)
     → 2/3 energy for brain
3) Death from starvation
   - towards the end – fat resources depleted → rapid depletion of proteins when body proteins drop to 1/2 → death
   - severe alteration of electrolyte balance

Symptoms
- body weight reduction up to 50%
- organ weight reduction (intestine, liver > heart, kidneys > CNS)
- skin - pale, dry, inelastic, cold, hair - dry, falls out easily
- gonadal atrophy, loss of libido, amenorrhea
- weakness, apathy/irritability
- blood pressure ↓
- GIT - achlorhydria, diarrhea
- anaemia
**Hyponutrition** - causes
- inadequate intake
  - developing countries - poverty
  - psychiatric disorders - anorexia, bulimia
  - disorders of consciousness
- digestion disorders
  - gastrectomy
  - pancreatic diseases
  - shortage of bile
  - enzymatic defects
- resorption disorders
  - chronic inflammations of intestine (Crohn, amyloidosis)
  - too short intestine – resections (tumors)
  - laxatives, chronic diarrhea
- metabolic disorders
  - higher losses, higher consumption (tumors, sepsis, burn, polytrauma)

**Classification**
Protein-energy malnutrition - (dry, thin, desiccated)
Protein malnutrition - Kwashiorkor (wet, edematous, swollen)
Combined

1) **Protein-energy malnutrition (PEM)**
   ↓ intake of protein as well as non-protein nutrients = dry form
Grade = determined by calculating weight as a % of expected weight for the height using international standards
- normal state  90 to 110%
- mild PEM  85 to 90%
- moderate  75 to 85%
- severe  < 75%

*Marasmus (Infantile Atrophy, Inanition, Athrepsia)*
= severe form of PEM (near starvation)
- prolonged adapted starvation
- predominant form in developing countries
Symptoms - similar to simple starvation

**Kwashiorkor**
= disease of “displaced” child
less common than PEM (rural Africa, the Caribbean and Pacific islands)

**Etiology:**
- non sufficient intake of proteins
  - foods are protein deficient (yam, cassava, sweet potato, and green banana)
  - pure quality of proteins (wrong balance of AA)
- catabolic states - loss of proteins (burns, trauma, sepsis – so called ”stress starvation”)

**Pathogenesis:**
- first ↓ plasmatic proteins → hypoalbuminemia → hypoproteinemia → edema
- impaired lipoprotein synthesis causes fatty liver
- ↓ transferrin ⇒ anemia
- ↓ immunoglobulins ⇒ infections (resembles AIDS, but event. reversible)

**Symptoms:**
- ↓ muscle mass
- retarded growth
- parenchymatous organs (heart, CNS) preserved
- adipose tissues preserved
- dermatitis, changes in skin pigment
- hair changes (thinning, discoloration event. "striped flag" appearance)
- edema
- large protuberant belly
- enlarged steatotic liver
- anaemia, bleeding
- ↓ immunity
- irritability, lethargy

**Anorexia**

= loss of appetite or desire to eat
- psychologic reasons - A. nervosa
- damage to lateral H (hunger center)
- cancer (anorexia appears in 15% to 25% of patients at the time of diagnosis and becomes universal in widely metastatic disease)

**Cachexia**

= body status characterized by:
- severe weakness
- marked and progressive loss of body weight, fat, and muscle

results from:
- anorexia
- starvation
- adequate nutrition, but malabsorption
- cancer (anorexia and/or higher metabolic needs of tumor cells, BMR is not adaptive!)

**Psychiatric nutrition disorders**

**Anorexia nervosa**

= Eating disorder associated with a distorted body image
↓ calorie intake ⇒ severe weight loss
+ decreased or absent menstruation („critical body fat“ theory)

Risk factors:
- upper or middle economic background
- female
- goal-oriented family or personality

**Bulimia (recurrent binge eating; binge eating)**

= Eating disorder characterized by eating more than needed to satisfy the hunger followed by self-induced vomiting or use of laxatives
83. Obesity

= chronic disease characterized by an excess of adipose tissue
= 20% above desirable weight according to tables
Body mass index (BMI) = body weight (in kg)/height (in m²)

Underweight       BMI < 18.5
Normal weight     BMI 18.5 – 24.9
Overweight        BMI 25 – 29.9
Obesity           BMI > 30

Etiology
= multifactorial disease

● Genetic factors - 33% of the BMI is attributable to genetics
  - single gene disorder (e.g. Bardet Biedl, Cohen sy) - rare!
    - obesity gene (rare)
      Genetically aberrant OB gene (very rare)
      ↓ transportation of leptin across HEB
      aberrant receptors for leptin in the hypothalamus
    - mutations in gene encoding adipose beta-3 receptors
    - genes encoding glucocorticoid receptor and Na-K-ATPase
  - Environmental factors:
    - increased food consumption
    - sedentary lifestyle
    - smoking cessation
  ● Symptom of another disease
    - tumor (damage) in medial H (satiety center)
    - Cushing sy
  - Diabetes mellitus type 2 - hyperinsulinemia:
    → production of free fatty acids (FFA, non-esterified)
    → production of triacylglycerols ⇒ ↑ deposition in lipid tissues
    → lipo-mobilisation (↓ hormone-sensitive lipase)
    → Carnitin acyl-transferase (↓ beta oxidation)

Adipose tissue distribution:

Upper body obesity (”apple” shape, android, or central fat distribution)
  More dangerous – visceral fat is more metabolically active
Lower body obesity (”pear” shape, peripheral fat distribution)

Obesity consequences:

● hypertriglyceridemia
● glucose intolerance and diabetes mellitus type 2, insulin insensitivity
  - high intake of lipids + low activity:
    → fat in muscles (replaces proteins)
    → ↑ of “white” glycolytic fibres and ↓ of “red” insulin sensitive oxidative fibres
    → insulin resistance in muscles → hyperinsulinemia + hyperglycaemia
    → more FFA in portal vein → liver
    → ↓ insulin uptake → higher release of glu → insulin resistance + hyperglycaemia
    → ↑ visceral fat – release of TNFα + cytokine → ↑ insulin resistance

● non-alcoholic steatohepatitis
● hypertension, coronary heart disease, stroke
● reproductive problems, certain types of cancer
• aromatase (enzyme converting androgens to estrogens) - in obese - more aromatase in adipose tissues than in gonads → in women - infertility, polycystic ovaries, risk of hormone sensitive tu (breast, cervix, ovary, endometrium)
  → in men - infertility, tu of prostate, colon, rectum
• cardiomyopathy
• gallbladder disease
• osteoarthritis
• sleep apnea
a. Alterations in peripheral nervous system and motor function

afferent fibers - sensory
efferent fibers – motor + vegetative
spinal nerves - all 3 components x cranial nerves - various combinations

Disorders of afferent fibers
- Alterations in sensory sensitivity
  - anesthesia, hypesthesia
  - hyperesthesia
  - paresthesia
- Alterations in pain sensitivity
  - neuralgia
  - phantom pain

Disorders of efferent fibres
- Lower motoneuron - flaccid paralysis
- Vegetative fibers - RSD, causalgia

Mononeuropathies
- trauma, infection, compression affects only one spinal nerve, plexus or peripheral nerve

Degeneration + regeneration of peripheral nerves
- axon interruption - degeneration of peripheral part = 1. Wallerian law
- central part – regeneration = 2. Wallerian law

Trigeminal neuralgia
Paresis of facial nerve
Carpal tunnel sy
- relatively common compression of the median nerve in canal made by carpal bones
+ transverse carpal ligament
Etiology: wrist injuries, wrist exertion, pregnancy
Symptoms: wrist pain (worsens at night), numbness of thumb + 2 fingers, paresthesia,
  thumb abductor atrophy

Polyneuropathies
- sensory, motor, vegetative or mixed deficits
- toxic agents
  - arsenic, lead, alcohol → general polyneuropathy
  - whilst Streptomycin affects VIII. cranial nerve, antimalarial drugs affect II. cranial nerve
- nutrition defects – vitamin B hypovitaminosis
- metabolic diseases - diabetes, uremia
- immune mechanisms - Guillain-Barré sy

Guillain-Barré syndrome (GBS)
neurological emergency!
most common neuropathic cause of paralysis in post-polio era
- acute inflammatory demyelinating polyneuropathy
- in 60% postviral (postbacterial),
  immune mediated attack on the peripheral nerve system antigens
  Weakness, paresthesias, pain, paralysis, respiratory insufficiency

Charcot-Marie-Tooth disease
- hereditary demyelinating neuropathy
**Postherpetic neuralgia**
herpes zoster – childhood chicken pox
virus travels from dorsal root ganglia to corresponding dermatomes → vesicular eruption - shingles + hyperpathia - abnormally exaggerated subjective response to pain - 1 month after onset in 70% of cases
2 forms
- allodynia – hypersensitivity to touch and heat
- spontaneous constant pain

**Disorders of neuromuscular junction**
- Drug influence on NM junction
  - curare - blocks Ach receptors on postsynaptic membrane → flaccid paralysis
  - physostigmine, neostigmine - block of Ach-esterase → prolonged contraction
  - botulotoxin - block of Ach release from presynaptic part → flaccid paralysis
  - Hypocalcemia - tetany - block of complete closure of Na channels → Na enters and can cause action potentials → tetanic cramps
- **Myasthenia gravis**
  = acquired autoimmune disorder
  Antibodies x Ach receptor at postsynaptic part of neuromuscular junction
  Etiology
  - Drugs: penicillinamine, ampicillin, prednisone, lithium
  - Herpes simplex virus
  Symptoms
  - weakness of skeletal muscles, increases on exertion
  - progression: from ocular to facial muscles, then to truncal and limb muscles
- **Lambert-Eaton Myasthenic Syndrome**
  Etiology
  - abnormal Ach release at neuromuscular junction
  = autoimmune attack against voltage-gated calcium channels
  - on presynaptic motor nerve terminal (accompanies e.g. small cell lung tu)
  Symptoms
  - Progressive muscle weakness and muscle pain
  - proximal muscles affected > distal muscles (esp. lower limbs)
  - Oropharyngeal and ocular m. - affected mildly
  - Respiratory muscles usually are not affected

**Skeletal muscle disorders (myopathies)**
- myopathy = disease of voluntary muscles
- myositis - inflammation
- atrophy = ↓ muscle mass
- dystrophy = defect in muscle fibers
- myotonic disorders

**Muscle atrophy**
- disuse atrophy – in unused muscles
- denervation atrophy - death of LMN
- secondary atrophy - e.g. Cushing sy (breakdown of proteins), thyreotoxicosis, catabolic states (starving)

**Muscle dystrophy**
= primary muscle diseases (do not involve nerve system)
- genetic disorders → progressive deterioration of skeletal muscles → muscle cell hypertrophy, atrophy, necrosis
- necrosis of muscle cells → muscle fibers are replaced by fat and connective tissue → muscle weakness

*Duchenne’s dystrophy*
Inherited, recessive, bound to X chromosome - dystrophin gene is damaged or missing from X chromosome
- first involvement of posterior hip + shoulder muscles
  → dysbalance between agonists/antagonists → abnormal posture
- progressive deterioration of muscle functions, death from respiratory insufficiency

*Myotonic disorders*
myotonia = continued muscle contraction after cessation of voluntary effort
= channelopathy = defective ion membrane conductance

*Rhabdomyolysis*
= breakdown of muscle fibers with leakage of potentially toxic cellular contents to circulation

**Etiology**
- inherited enzymatic defects
- excessive muscular activity (epilepsy, psychosis, marathon)
- traumatic events (burns, near drowning)
- Toxins (Ethanol, Heroin, Methadone, Cocaine, LSD)

**Consequences**
- Hypovolemia (sequestration of plasma water in injured myocytes)
- Hyperkalemia (release of cellular K to circulation)
- Metabolic acidosis (release of cellular phosphate and sulfate)
- Acute renal failure (nephrotoxic effects of liberated myocyte components)
- Disseminated intravascular coagulation
85. Pathophysiology of the spinal cord

Role of the spinal cord
simple motor and vegetative reflexes - segmental organization
transmission of signals to and from brain

Spinal cord and root compression

Etiology:
- Spinal cord and root compression
- Infection (e.g. epidural abscess)
- Disc disease and spondylosis
- Haematoma
- Cystic lesions

Compression can affect:
- pyramidal pathway → voluntary movement disorders
- extrapyramidal pathways → disorders of muscle tone
  + extrapyramidal influence on voluntary movements
- somatosensory pathway
- vegetative nervous system
- spinal reflexes

Pyramidal pathway disorders
● central (upper) motoneuron (UMN)
  - cortex - discrete paresis
  - corticospinal (corticobulbar) tract - spastic paresis - hyperreflexia + increased muscle tone
● peripheral (lower) motoneuron (LMN)
  - spinal cord + peripheral nn. - flaccid paralysis - hyporeflexia + ↓ muscle tone

Clinical picture of spinal cord compression depends on:
● site of lesion
  - root – lower motoneuron + sensory afferent nerves - pain – sharp, shooting, radiating to
cutaneous distribution (dermatomes) + muscle groups, ↑ with movement
  - segment - interruption of ascendent (sensory) and descendent (upper motoneuron+vegetative) tract pain - continuous, deep, whole leg, half body, not influenced by
  movement
● speed of onset - gradual development of dysfunction / spinal shock

Spinal cord injury

Pathological processes:
- at site of injury (primary damage) mechanical neuron disruption + hemorrhage + edema
- at more distant location (event. later = secondary damage) - due to release of vasoactive
  subst.- NorA, serotonin, dopamine, histamine → vasospasm, edema – ischemia

Classification of spinal syndromes
according to a part of body affected:
  monoplegia
  paraplegia
  hemiplegia
  quadriplegia
according to the part of spinal cord affected:
  Central cord sy
  Anterior cord sy
Conus medullaris sy
Brown-Sequard sy
= transsection of only one half of spinal cord at the side of damage
  - hypersensitivity = root sy
  - damage to position sensitivity + vibration sensitivity + spastic paralysis at the other
    side of body
  - damage to pain + thermal sensitivity

**Spinal shock**
= sudden acute spinal transversal section
  first phase:
  - flaccid (weak) paralysis below the injury level regardless to eventual UMN/LMN
    involvement
  - complete areflexia (no tendon or vegetative reflexes)
  - vasodilation + decrease of blood pressure (transsection of the sympathetic trunk - danger of
    the circulatory shock!!!)
  - incontinence vera (urinary + fecal)
  - lasts usually 3 - 4 weeks
  later phase:
  - normalization of blood pressure (occurrence of spontaneous activity of vessel muscles)
  - occurrence of simple autonomic reflexes (e.g. autonomic bladder)

**Vegetative hyperreflexia**
- can occur any time after spinal shock resolves (when spinal cord transsection is situated at
  Th6 and above)
- stimulation of receptors below lesion → abnormal reflex sympathetic response →
  vasoconstriction → severe hypertension → baroreceptor reflex in the region above lesion →
  vasodilation (headache, sweating, flush) + activation of parasympathetic system
  (bradycardia)

**Tabes dorsalis (locomotor ataxia)**
= form of neurosyphilis
= progressive destruction of posterior columns in spinal cord
Symptoms
- stabbing pain in the legs
- weakness of legs, unsteady gait
- paresthesias
- dementia

**Amyotrophic Lateral Sclerosis (ALS) - Lou Gehrig's disease**
progressive incurable disease
middle age, more men
unknown etiology - partially hereditary
- ? environmental agents ⇒ ↑ glutamine to toxic level
- ? autoimmunity
affects motoneurons in cortex (UMN) and in anterior horn of spinal cord
+ event. cranial motor nuclei (LMN)
→ muscle atrophy (paralysis, swallowing + aspiration problems)
LMN are more affected than UMN - distal terminals are affected first, centripetal progress
loss of UMN - lateral column degeneration with gliosis = "sclerosis"

**Syringomyelia**
- cavitation and gliosis of the spinal cord (usually cervical or thoracic), medulla, or both
- Clinical features: Variable depending on anatomical involvement
  - anterior horns – weakness – esp arms
  - posterior horns – loss of pain and temp sensation esp. arms + trunk
  - syringobulbia - + cranial nerves
- slow progression

**Poliomyelitis**
- polio virus - specific damage to anterior horn motoneurons
- acute phase - fever, myalgia
- later (not always) - paralysis - spinal nn., event. + cranial nerves

**Tetanus**
- tetanospanmin (clostridium tetani) via blood and lymph to neuromuscular plate, then
  - diffusion along nerves up to spinal cord - block of inhibitory neurons GABA, glycine)

Clinical picture:
- prolonged painful spasms (of both antagonists and agonists), first short peripheral nerves,
  risus sardonicus
86. Autonomic nervous system dysfunctions
autonomic nerve system controls visceral functions
efferent pathway – 2 neurons – preganglionic, postganglionic
sympathetic nervous system
- thoraco-lumbalis
  - preganglionic nerves release Ach, postganglionic neurons release mainly Norepinephrine - with one exception – sweat glands - Ach
- effect on $\alpha$ (eye, vessels – vasoconstriction), $\beta_1$ (heart), $\beta_2$ (bronchi, vessels – vasodilation, GIT) and $\beta_3$ (lipid tissue) receptors
parasympathetic nervous system
- cranio-sacralis
- both pre- and postganglionic nerves release Ach

Autonomic nerve system is under the influence of centers in medulla oblongata and hypothalamus.

Autonomic nerve dysfunctions
- organs innervated by autonomic nerve system always have some autonomy (interruption of nerve fibers does not cause complete loss of function)

Dennervation hypersensitivity
= ↑ of number of receptors after denervation → ↑ sensitivity to hormones from adrenal gland

Central vegetative system disorders
- disorders of hypothalamus - e.g. – hyperphagia, anorexia (damage to medial, lateral hypothalamus)
- disorders of brainstem – e.g. conus medullaris
- Progresive autonomic disorder = degenerative disorder of central + peripheral ANS neurons
  idioopathic, event. accompanying e.g. Parkinsonismus, spinal cord trauma
  Anhidrosis, sphincter disorders, orthostatic hypotension,
  symptoms get worse in heat, after meal
- Damage to descendent autonomic nerve tracts in spinal cord
  sudden spinal cord transsection – spinal shock (see above)
  vegetative hyperreflexia (see above)

Peripheral vegetative system disorders
Acute vegetative pandysautonomia
  includes both parasympathetic and sympathetic dysfunction – manifestations in cardiovascular, gastrointestinal and sudomotor functions
  an immunologic basis remains most likely, often with onset after a viral illness can accompany Guillain-Barré syndrome

Familial dysautonomia
  Rare, hereditary, decreased number of peripheral sensitive and vegetative nerve fibers
  - newborns - swallowing problems, crying without tears
  - orthostatic hypotension
  - excessive sweating
  - decreased perception of pain
  - thermoregulation disorders

Reflex Sympathetic Dystrophy (RSD) - Causalgia
= abnormal response of nervous system after a disease or an injury
  - severe pain + hypersensitivity to touch
- changes in blood flow to the skin, swelling
- ↑↓ sweating
- muscle spasms, stiffness

Causalgia = RSD after a known traumatic event (brachial plexus injury)

*Bürger's disease* (Claudicatio intermittens) - possible etiology in some patients = sympathetic hypertonicity

*Raynaud sy* - (whitening of fingers with insensitivity) - activation of sympathetic fibers by cold, vibrations leads to vasospasm

**Eye function disorders**
- **Horner’s triad** - transection of upper thoracic segment + symp. innervation to head
  - reduction of eye slit
  - enopthalmus
  - miosis
- **Adie’s sy** - tonic pupil ( neurological phenomenon in which one or both pupils is dilated and responds slowly or not at all to light and a near stimulus
  - miosis
  - pupil is larger, does not react to light, gets small at near sight
  - damage to ciliary ggl. (PS) + abn. regeneration (fibers originally innervating m. ciliaris innervate sphincter m.)
- **Argyll-Robertson sy**
  - eye does not react to light, accommodation is normal
  - pupils are smaller, irregular
  - neurosyphilis, diabetes mellitus, tumor of brainstem

**Disorders of sweat glands**
- **Hyperhidrosis** - ↑ sweating
  - emotional states
  - hormonal changes - pheoeochromocytoma, menopause
  - causalgia
- **Anhidrosis**
  - disorder of sympathetic innervation (e.g. diabetic neuropathy – legs + trunk)
  - degeneration of sweat glands – older people
  - ↓ sensitivity to Ach

**Disorders of cardiovascular system**
- Orthostatic and postural hypotension
- Syncope, collapse
- Pheoeochromocytoma

**Disorders of GIT**
- **Achalasia** - cardiospasm
  - disorder of relaxation of lower oesophagus
  - results from abnormal PS innervation (absence or degeneration of ggl. cells in intramural plexus)
  - swallowing disorders, event. vomiting
- **Hirschprung disease** - congenital megacolon
  - inborn defect of ggl. cells of intramural plexus of large intestine
  - constipation at birth, empty rectum, extended colon, vomiting, pathogenesis is different from *Toxic megacolon*: = acute toxic colitis with non-obstructive dilatation of the colon
- either idiopathic or caused by medications (anticholinergics, antidepressants, opioids) or procedures (barium enema or colonoscopy)
  - the hallmark = inflammation extending beyond the mucosa into the smooth-muscle layers and serosa, myenteric plexus involvement is not consistent and probably does not contribute to dilatation

• **Irritable Bowel Syndrome**
  = a functional GI disorder characterized by abdominal pain and altered bowel habits in the absence of specific and unique organic pathology.
  Altered motility
  - variations in slow-wave frequency and a late, postprandial response of spike potentials
  - a generalized smooth muscle hyper responsiveness
  Visceral hyperalgesia
  - ↑ perception of normal motility and visceral pain to rectosigmoid and small bowel inflation
87. Brain blood circulation disorders, break of blood - brain barrier

Cerebral blood flow = constant throughout mean arterial pressure of 60 - 160 mmHg (= autoregulation - local influence of O₂, CO₂, H)

Cerebrovascular accident
- Transient – Transient ischemic attack (TIA)
- Complete “Stroke” - Cerebrovascular “accident” (CVA)
  85% - ischemic stroke
  15% - hemorrhage

Etiology of cerebrovascular accident
- Occlusion (50%)
  - thrombotic
  - non-thrombotic - disease of vessel walls
    - collagen d. - systemic lupus erythematosus
    - vasculitis - polyarteritis nodosa, temporal arteritis
- Embolisation (20%)
  - from extra- or intracranial arteries, heart - fat, air, tumor emboli
- Hemorrhage (15%) - Rupture of vessel wall - Aneurysm, Hypertension, AV malformation, trauma, tu
- Disturbance of normal properties of blood (5%)
  - polycythemia, hyperfibrinogenemia ⇒ ischemia, DIC, Haemophilia, thrombocytopenia ⇒ hemorrhage

Cerebral ischemia
Transient ischemic attack (TIA)
= episode of focal neurological symptoms due to inadequate blood supply to brain
- sudden, lasts less than 24 hours, leaves no residual deficit
- micro emboli (80%) - (from heart, aorta, extracranial arteries)
- reduced flow - (e.g. fall of perfusion pressure)

Cerebral infarction
sudden onset, with irreversible functional changes

Ischemic cascade
Ischemia = imbalance between cerebral blood flow and metabolic needs → ATP shortage → ion channel disorder – inhibition of Na/K ATPase (K outflux, Na influx), swelling, electrical properties disorder + Ca influx → Glutamate ECF excess → Ca influx → activation of intracellular enzymes – NOS + xanthine oxidase → Free radicals → cell death!!!
Anaerobic metabolism → hypercapnia, lactacidosis

Therapeutic implications
- in both brain infarction and brain haemorrhage vasoconstrictors are recommended - cause decrease in bleeding, and in infarction improve perfusion via increased blood pressure (the theoretical conclusion that vasodilators could improve blood flow is not correct!!! - vasodilation takes place only at the periphery of the infarction, whereas in the hypoxic center the vessels do not react - thus perfusion in the peripheral vessels increases, but at the expense of perfusion in the infarction zone, which decreases = "steal effect")
- Ca antagonists - block of Ca influx
- Glutamate antagonists
- free radical scavengers
- Barbiturates - ↓ cerebral metabolism

Clinical syndromes
According to the part of brain affected
Lacunar necrosis = occlusion of penetrating arterioles
can cause multi-infarction dementia

Intracerebral hemorrhage
- clinically difficult to distinguish from infarction according to the initial symptomatology at the beginning
- usually accompanied by headache, vomiting
- x-ray positive

Etiology:
- aneurysm
- arterial hypertension
- blood clotting (due to medicaments)

Blood-brain barrier
Blood-cerebrospinal fluid barrier and the blood-brain barrier (BBB) represent substantial protection for the brain against undesirable blood substances. These barriers are very permeable to water, O₂, CO₂ and small lipid-soluble substances, somewhat permeable to small electrolytes - and special transport systems exist for some other specific molecules such as essential amino acids. The barriers are the result of endothelial cells which line capillary walls - and glial cells called astrocytes which wrap the capillaries with fibers.
The blood-brain barrier creates a protected chemical environment for the brain wherein certain molecules can perform functions independent of the functions those molecules perform in the rest of the body. This is particularly important for the neurotransmitters serotonin (which is highly concentrated in platelets & the intestine) and norepinephrine (which affects blood pressure & metabolism).

Development after birth - bile pigments released due to severe hemolysis in newborns can enter basal ganglia → "Kernicterus"

Parts without hematencephalic barrier:
- fenestrated capillaries, high permeability - no barrier
- release of hormones
  - neurohypophysis (neurosecretion)
  - adenohypophysis releases hormones to blood
  - epiphysis
- chemoreceptive zones
  - area postrema (chemoreceptive area for vomiting)
  - organum vasculosum laminae terminalis (osmoreception for ADH control)
  - subfornical organ - chemoreception for angiotensin II - fluid intake regulation

Disruption of blood-brain barrier
→ vasogenic edema

Etiology:
- hyposmolarity, decreased oncotic pressure
- acidosis (increases permeability)
- inflammation (histamine, serotonin, bradykinin)
- hepatic, uremic encephalopathy
- brain injury, neuro-surgery, tumors
- ischemia, hypoxia
- heat stroke; hypothermia, fever (especially in children!!!)
- tricyclic antidepressants (e.g. chlorpromazine)
- Multiple sclerosis
88. Brain edema, intracranial hypertension

Intracranial pressure = depends on stability of 3 volumes
- brain tissue
- blood
- cerebrospinal fluid

**Intracranial hypertension** = raised intracranial pressure

**Etiology:**
- disorders of CSF drainage
- swelling of brain tissue - cerebral edema
- increase of blood volume
- intra-cerebral haemorrhage
- intra-cranial haematomas
- tumors (even benign brain tumors (inoperable) can cause death through intracranial hypertension)
- benign intracranial hypertension („pseudotumour cerebri“) - no evidence of “mass” lesion or hydrocephalus (obesity, endocrine - pregnancy, menstrual abnormalities, drugs - contraceptives, tetracyclin)

**General symptoms of intra-cranial hypertension**
- headache, vomiting, impaired upward gaze, changed behavior, confusion, unconsciousness, coma
- visual problems – Papilledema, diplopia, blurring, ev. loss of vision

**Herniation**
- a condition in which a portion of the brain is displaced because of increased pressure inside the skull
- brain herniation can:
  - block cerebro-spinal fluid flow → hydrocephalus
  - block local blood supply → ischemia
  - most dangerous = tonsillar herniation (“conus occipitalis”) = *downward displacement of the brain stem through the foramen occipitale magnum* → compression of brainstem (vital centers) → cardiac, respiratory arrest → death

**Cerebrospinal fluid disorders**
- fluid in ventricles + subarachnoid space

Excessive accumulation of cerebrospinal fluid
- in infants, children → hydrocephalus - enlargement of the skull (not fixed up to about one year of age)
- in adults - fixed size of skull → intracranial hypertension

**Hydrocephalus**

**Etiology:**
- Congenital - e.g. Aqueductal stenosis, Dandy Walker sy - atresia of foramina Luschkae and Magendi, overproduction of CSF, decreased absorption in subarachnoid space (Paccione's granulations)
- Secondary -acquired:
  - traumatic head injury
  - subarachnoid hemorrhage
  - brain tumors
  - meningitis
Types:
- communicating (external) hydrocephalus
  - higher secretion of CSF (hypersecretion)
  - obstruction in subarachnoid space (hyporesorption)
- non-communicating (internal) Hydrocephalus
  - obstruction within ventricular system
- hydrocephalus Ex-Vacuo: shrinking of brain (e.g. Alzheimer's Disease), this type does not lead to intracranial hypertension!

Symptoms:
- intracranial hypertension - vomiting, sleepiness, irritability
- rapid increase in head circumference (in children) - unusually large head size
- downward deviation of the eyes ("sunsetting")
- seizures
- gradual onset - mental retardation - in children without herniation

Brain edema
= abnormal accumulation of fluid within brain parenchyma (intra or extracellular) producing a volumetric enlargement of brain tissue

Types of brain edema
- vasogenic
  - disruption of blood brain barrier
  - plasma or a filtrate enter EC space of the brain
- neurotoxic
  - swelling of neurons - IC retention of H2O and Na due to failure of Na/K pump
- osmotic
  - accumulation of excess IC water in response to hypo-osmolarity of plasma (intact blood brain barrier)
- hydrostatic
  - transcapillary movement of protein-free transudation to EC space due to capillary dilatation in acute hypertension
- interstitial
  - fluid in periventricular white matter - consequence of acute hydrocephalus

Therapeutic use of osmotic solutions:
- only in intact blood brain barrier
- restricts transport via BBB
- Mannitol
  - opens blood brain barrier by dehydrating endothelial cells and separating tight junctions
  - has antioxidant effect
  - ↑ flexibility of erythrocytes
  - ↓ blood viscosity
  - ↓ CSF production
  - ↓ cerebral blood volume

Intracranial hemorrhage
Epi(extra) dural hematoma
Often rupture to middle meningeal artery
- rapid (arterial origin)
- blood clot between dura and overlying bone - usually located in temporal area
Sub dural haematoma
Rupture of bridging veins between cortex surface and dural sinuses
- gradual and slow progress (danger because of late manifestation when development of intracranial hypertension may not be being monitored and the subject can die!!!)
89. CNS neurotransmitters – disorders

The three major categories of substances that act as neurotransmitters are:
- amino acids (primarily glutamic acid, GABA, aspartic acid & glycine)
- peptides (vasopressin, somatostatin, neurotensin, etc.)
- monoamines (norepinephrine, dopamine & serotonin) plus acetylcholine.

**Glutamic acid (glutamate)**
= the most common neurotransmitter in the brain
= always excitatory, usually due to simple receptors that ↑ the flow of positive ions by opening ion-channels.
*NMDA glutamate receptor* (N-Methyl-D-Aspartate = a synthetic chemical that binds specifically to the NMDA glutamate receptor)
= the only known receptor which is regulated both by a ligand (glutamate) and by voltage.
- has a capacity for an activity-dependent increase in synaptic efficiency known as LTP (Long-Term Potentiation), which may be crucial to some forms of learning and memory
- are most densely concentrated in the cerebral cortex (esp. hippocampus, amygdala, and basal ganglia).
- are particularly vulnerable to glutamic acid excitotoxicity, ie.,

  - *Excitotoxicity* due to glutamic acid (damaging effects due to excessive excitatory neurotransmitter release) = a major destructive process seen in strokes and other forms of brain ischemia.
  - dysbalance between glutamate and GABA plays an important role in pathogenesis of epilepsy
  - increased alertness (or anxiety) due to caffeine may be mainly due to blockade of adenosine receptors which normally inhibit glutamate release.
  - inhibition of NMDA receptors (and LTP) is believed to be an important part of the way ethanol affects brain functions.

**GABA (γ-aminobutyrate)**
= a major inhibitor of presynaptic transmission in the CNS
= most highly concentrated in the substantia nigra and globus pallidus nuclei of the basal ganglia, followed by the hypothalamus, the periaqueductal grey matter and the hippocampus
- seizures in Vitamin B6 deficiency are mediated by ↓ of GABA (The vitamin B6 derivative *pyridoxal phosphate* is a cofactor in the synthesis of GABA).
- Benzodiazepines and ethanol ↑ activity of GABA postsynaptic receptors (↑ Cl influx)
  Prolonged use of benzodiazepines results in adaptation of the receptors to their use. Receptors may increase in number and/or sensitivity to GABA - tolerance. Withdrawal of the drug can result in GABA receptor hypoactivity producing symptoms worse than the ones that the patient originally sought treatment for - withdrawal.
- Dysbalance between glutamate and GABA plays an important role in pathogenesis of epilepsy
  - plays a role in some of the basal ganglia disorders
    - *chorea* = damage to striate body of basal ganglia
    - loss of inhibitory effect (↓ production of GABA) → ↑ motor activity + ↓ muscle tone = hyperkinetic hypotonic syndrome
    - degenerative - Huntington disease
    - children - streptococcal infection - „St Vitus dance“
    - rapid, irregular, aimless, involuntary movements of muscles of limbs, face, and trunk *athetosis* -“indian dancer“
    - damage - striatum + globus pallidus
- constant, slow, involuntary, writhing movement of fingers/hands or feet/toes + often mental retardation
- hemiballismus - high amplitude flailing of the limbs on one side of the body

**Dopamine**
Belongs together with norepinephrine and epinephrine to catecholamines

*Parkinson's disease*
- damage to substantia nigra + globus pallidus
- results from selective degeneration of substantia nigra (pigmented substantia nigra neurons)
- idiopathic or due to viral infection infection (Spanish flu)
- shortage of dopamine in substantia nigra → excess of Ach → ↑ of GABA in striatum → ↑effect of BG → suppression of motor cortex → hypokinesia
- damage to globus pallidus → ↓ inhibitory effect in reticular formation → rigidity ⇒ hypokinetic - hypertonic disease
- Clinical picture:
  - rigidity - ↑ elementary postural reflexes, hypomimic face, ↓ motor activity - walking difficulties + problems initiating a movement
  - tremor at rest

**Drug addiction**
dopamine = neurotransmitter stimulating centrum of pleasure
- Cocaine prevents dopamine reuptake by binding to proteins normally transporting dopamine
  → prolonged dopamine effect
- Amphetamine also ↑ dopamine levels
Frequent repeated over-stimulation → ↓ number of receptors + remaining receptors become less sensitive → tolerance to drugs (addiction)

**Schizophrenia**
Schizophrenia is thought to be due to an overstimulation of D2 receptors in the mesolimbic and mesocortical systems. Evidence for the "excess dopamine" theory of schizophrenia comes largely from the fact that D2 antagonist drugs alleviate the symptoms, whereas substances which increase D2 stimulation, such as amphetamines, can induce psychotic symptoms (which are reversible with D2 antagonists).
Recent view supposes accompanying disorder in serotonin + glutamate systems
Etiology
- Genetic predisposition?
- Viral infection?

**Attention deficit hyperactivity disorder**
- excess of dopamine causes restlessness and hyperactivity
- improper balance between dopamine + serotonin

**Acetylcholine**
- Ach receptors are comparatively few in the brain but outside the brain Ach is the major neurotransmitter controlling the muscles.
- in the brain Ach is produced by interneurons in the striatum, the nucleus accumbens and the basal nucleus of Meynert that provides cholinergic input to the cerebral cortex and the basolateral amygdala, the basal ganglia and the reticular nucleus of the thalamus.

**Alzheimer's Disease**
= most common type of dementia in elderly
= gradually progressive cognitive decline that results in loss of memory, language skills and activities of daily living
- incidence increases with age

**Etiology** - not known

- genetics - 19 or 21 chromosome? (only some cases)
- external factors - enviromental toxins - aluminium?

**Pathogenesis:**

- neuritic plaques (outside neurons) = aggregates of filaments of β-amyloid (neurotoxic)
  - limbic syst - hippocampus
  - parietal lobes
- neurofibrillary tangles (inside neurons, close to nucleus) = tau-protein
  - pyramidal cells of neocortex
- markers of inflammation
  - production of free radicals → neurone degeneration
- progressive deterioration of cholinergic neurons especially in the basal nucleus of Meynert and hippocampus
  - ↓ of Acetylcholine-transferase
  - Ach levels are decreased up to 90% of norm
- loss in norepinephrine and 5-HT
  - non-cognitive symptoms of AD - e.g. depression and aggression
- cerebral atrophy - widened sulci and narrowed gyri, esp. in frontal and parietal regions

**Serotonin (5-hydroxytryptamine, 5HT)**

- There is no equilibration between body and brain serotonin - the serotonin in the brain is independently synthesized from tryptophan transported across the blood-brain barrier.
  - Insulin facilitates the transport of tryptophan across the blood-brain barrier. The resultant improvement of mood and drowsiness induced by serotonin is a common effect of a large carbohydrate meal.
  - ↓ Serotonin → overeating, bulimia
  - ↓ Serotonin → anxiety and endogenous depression (inhibitors of serotonin reuptake – SSRI are helpful in depression and bulimia treatment)
- high-estrogen contraceptives may contribute to depression by lowering serotonin levels in the brain.

**Seasonal Affective Disorder (SAD)** - “winter blues” = autumn or early winter depression

**Symptoms:**

- tendency to sleep more, eat more, crave carbohydrates and sweets, gain weight
- loss interest in sex
- irritability

**Pathogenesis:**

In the pineal body Serotonin is not used as a transmitter but for synthesis of melatonin.

- Melatonin regulates diurnal (circadian) and seasonal behavior in mammals (the pineal body has been called a "third eye" because its activity is influenced by light - noradrenergic neurons near the optic nerve are inhibited by light but in darkness, norepinephrine stimulation of pineal cells causes change of serotonin to melatonin).

With decrease of sun light (autumn) more melatonin is produced (higher consumption of tryptophan → ↓ serotonin in brain → depression, melatonin has depressive/hypnotic effect - used as hypnotics or for prevention of "jet lag" - shift in time)
90. Epilepsy - etiology and pathogenesis

Epilepsy = episodic spontaneous seizures resulting from paroxysmal uncontrolled discharge of neurons within CNS
Results from dysbalance between excitatory and inhibitory neurotransmitter systems

main inhibitory neurotransmitter - GABA
  glutamate = precursor of GABA
  glutamate decarboxylase - controls GABA amount
Possible role of GABA in epilepsy
  - low GABA inhibitory effect → ↓ inhibitory influence on excitatory system
  - insufficient GABA synthesis (e.g. B1 hypovitaminosis)
  - ↓GABA transporting proteins in cellular membr.
  - insufficient glucose decarboxylase
  - ischemic effect

most important excitatory neurotransmitter = glutamate
Possible role of glutamate in epilepsy
  - shortage of GABA → relative/absolute excess of glutamate
  - disorder of glutamate reuptake to astrocytes + neurons → shortage of glutamate for new GABA formation
  - damage to neurons e.g. hypoxia → rapid leakage of glutamate to EC + disorder of “reuptake” system
  - tetanic stimulation causes LTPP, reduction of inhibition

Etiology of Epilepsy
● primary – idiopathic – 75%
● secondary - 25% - structural brain disorders:
  - ischemia, hemorrhage (13%)
  - developmental brain disorders
  - injuries, tu, inflammations
  - chemical and physical factors:
    - hypo-, hyper osmolar states
    - damage to Na/K pump → ↑K in EC
    - hypoglycemia, uremia, toxic substances
    - metabolic amino acid disorders (e.g. insufficient formation of GABA - e.g. in vit B1 shortage)

Epileptogenic focus
Present mainly at focal epilepsy
= pathologically changed region – focus of epilepsy origin - e.g. ischemic focus
  - non-active center
  - intermediary zone - source of hyperactivity

Seizure readiness
= predisposition of the brain to epileptic discharges
● genetic abnormalities
  - children - immature brain (febrile cramps)
  - acquired abnormalities – e.g. hypovitaminosis B1
  - ↑K in EC space → ↓ output of K from cell → ↓ lateral inhibition - enables spread of discharge
● ↓Ca in EC → ↓ release of GABA → ↓ inhibition
hypoxia, hypoglycemia – shortage of energetic substrate
frequent repetition of epileptic discharges \(\rightarrow\) \(\downarrow\) effect of inhibition (desensitization) \(\rightarrow\) generalization

**Causes of epileptic discharge**
- "epileptic" neurons exhibit electrical dysbalance
  - changed membrane transport of K, Na and Ca
  - repetitive depolarization = paroxysmal depolarization "shift" \(\rightarrow\) produce \(\uparrow\) frequency of action potentials \(\rightarrow\) action potentials arise also in dendrites
- "Kindling" = process by which the epileptic activity can be caused by electric or chemical stimuli
  - takes place esp. in limbic system
  - few neurons ensure widespread seizure – hypersynchronisation
  - after discharge \(\rightarrow\) higher amplitude of EEG

**Epileptogenic stimulus** - not always necessary
- sudden change of endogenous or exogenous setting eliciting epileptic seizure
  - infection, intoxication, hormonal dysbalance
  - psychic burden, visual, auditory stimuli

Some **functional circuits** within brain **play role in epilepsy propagation**
- cortico-thalamic circuit - active in sleep - sleep spindles
  - petit mal - often at night, \(\downarrow\) during arousal
- cortico-hippocampal circuit - circuit of Papéz (assoc. cortex - hippocampus – corp. mamillaria - amygdala – limbic cortex)
  - key for explicit memory
  - basic hyperactivity in generalized E
- cortico-amygdaloid circuit
- cortico-cortical circuit
- cortico-striate circuit - important for event. propagation or cessation of propagation of seizure

**Classification of epilepsy**
- focal origin \(\rightarrow\) Partial epilepsy
  - Simple epilepsy - without loss of awareness
  - Complex epilepsy - diminished or lost awareness
- origin in large region or in many sites simultaneously \(\rightarrow\) Generalized epilepsy
  - Petit mal
  - Grand mal

**Time course of epileptic seizure**
1) Prodrome = mood or behavioral change preceding attack
2) Aura = symptoms just before attack (specific sensation - smell…)
3) Attack = seizure
4) Post-seizure period = time immediately after attack - confusion, disorientation, automatic behavior

**Jacksonian epilepsy** (JE)
= partial, simplex epilepsy (consciousness preserved)

Epileptic discharge extends to:
- precentral gyrus → typical motoric seizure - motoric JE
- postcentral gyrus → sensitive JE - dysesthesias
- cramps (dysesthesias) start in restricted body region (face, hand, leg) and extend to homolateral half of the body
- after seizure sometimes → transitory paresis = Todd paralysis

**Psychomotoric seizure**
= partial, complex epilepsy - focus = in temporal lobe, hippocampus or amygdala
- motoric and sensor symptoms are accompanied by:
  - vegetative signs (gastric aura)
  - emotional signs (anxiety, dreamy states, depersonalization, amnesia)
  - mechanical automatisms
EEG - potentials with frequency of 4-7 Hz (Theta)

**Generalized E**
sudden affection of both hemispheres - loss of consciousness

*Petit mal*
Usually appears in children, 3 forms
1) Absentia petit mal (<30 seconds)
   - sudden loss of consciousness - break of activity,
   - EEG - “spike, round wave”
2) Myoclonic petit mal
   - in puberty, sudden cramp of upper limbs, without loss of consciousness
   - EEG - several spikes, round wave
3) Akinetic petit mal (Lennox sy)
   - in preschool age, sudden flexory cramp, loss of postural tone and fall,
   - short unconsciousness

*Grand mal*
Causes deep unconsciousness, fall
  - Tonic phase
    - generalized spasm of muscles
    - break of respiration - cyanosis
    - mydriasis, no light reaction of pupils
  - Clonic phase - about 2 min
    - symmetrical clonic cramps
    - EEG - high freq. spikes (100 Hz)
  - Post-paroxysmal phase
    - unconsciousness, respiratory difficulties,
    - confusion, aggressiveness, amnesia

**Status epilepticus**
= serious complication (5-10% ends by death)
uninterrupted grand mal seizures, constant unconsciousness
life emergency - heart, lung failure, brain edema
91. Pathophysiology of demyelination (Multiple Sclerosis)

1) Acute demyelinations:

**Guillain-Barré syndrome**
neurological emergency!
most common neuropathic cause of paralysis in post-polio era
= acute inflammatory demyelinating polyneuropathy
- in 60% postviral (postbacterial), immune mediated attack on the peripheral nerve system antigens
- weakness, paresthesias, pain, paralysis, respiratory insufficiency

**Acute disseminated encephalomyelitis**
acute postviral - *Hurst disease* - headache, sleepiness,
*postvaccination encephalopathy* (smallpox)

**Optic neuritis**
- transitory loss of vision

2) Chronic demyelination

**Multiple sclerosis**
= characterized by occurrence of demyelination plaques (= focus of demyelination and inflammation) disseminated in space and time

Affects about 1% of population (geographic differences – more in north than in south),
women are affected more frequently than men,
Age of onset – usually in the range of 20 - 30 years of age,

**Etiology**
Supposed is some viral or bacterial infection (EB virus?, herpes virus?, Roseola virus?),
to which genetically predisposed persons react with autoimmune damage to myelin

**Histology:**
- perivascular cellular infiltrates - T, B lymphocytes, macrophages + axonal transsection

**Pathogenesis**
autoimmune process is directed against
  - myelin
  - neuron antigens
  - oligodenrocytes (myelin production)
Initial systematic event (virus infection) → Activation of CD4+ T cells by exogenous antigen
→ Activation of CD+ T cells for autoantigen (molecular mimicry?)
→ Penetration via blood brain barrier → Recruitment of lymphoid cells and establishment of retention of antigen-reactive T cells in CNS → Cell mediated inflammation and secretion of cytokines, proteinases and antibodies → demyelination

**Classification of MS**
● according to time course:
  1) attacks, remissions, progressions (more frequent)
  2) chronic progressive - without remissions
● according to extent of damage
  - cerebrospinal - starts usually by Retrobulbar neuritis
  - spinal
- polyneuritic – peripheral nerves

Symptoms of MS
● usually starts with non-specific symptoms - paresthesias, weakness of lower limbs, and vision problems
● sensory problems (diplopia, blurred vision, ↑sensitivity to heat)
● motoric problems
  - pyramidal pathways - central - spastic paresis
  - cerebellar (less frequently) - intention tremor, ataxia, dysarthria
● vegetative problems - sphincter disorders
● depression (usually reactive)

Demyelination (and symptoms hardly discernible from multiple sclerosis) may be also part of Neuroborreliosis (disorder of CNS in Borreliosis – Lyme disease)
92. Pathophysiology of immature newborns

- body weight of a hypotrophic newborn is below the 10th percentile for the given gestation age
- improvement in the health care help survival of very hypotrophic newborns with body weight below 600 g (born in the 26th week or even earlier)
- however, this situation raises the issue that the future development (related to many perinatal complications) carries increased risk, and that a much higher number of health problems appear in these individuals

Health problems in premature newborns:

- cardiovascular system
  - because of low blood saturation with oxygen - compensatory increased heart rate
  - in the case of energy deficit and hypoxia - low heart contractility, bradycardia - hypotension, hypoperfusion of the brain - irreversible changes
  - persistent Ductus arteriosus of Botallo - low perfusion of lungs

- respiratory system
  - HbF - higher affinity to oxygen - shift of the dissociation curve to the left - lower oxygenation of tissues
  - surfactant - produced by mature pneumocytes, increases surface tension of alveoli preventing their collapse (increased permeability for proteins- formation of hyaline membranes)- sufficient amount of surfactant from the 35th week - in immature newborns artificial hypertonic ventilation is necessary
  - spontaneous breathing dependent on maturity of the brain stem (respiratory center) reacting to hypoxia during birth

- renal system
  - from the 34th week - number of nephrons is completed - but without full function, there is high vascular resistance decreasing perfusion
  - after birth - increase of diuresis but not normal concentration capacity - even in mature newborns it is not possible to add salt into nutrition, since up to about 1 year of age infants are not able to eliminate it without loss of water

- GIT
  - only from about 38th week are there normal suction and swallow reflexes - earlier either gastric tube or parenteral nutrition is necessary
  - immature intestine does not have normal absorption capacity (malabsorption diarrhea) and simultaneously it is more permeable for proteins, bacteria (allergic reactions, infections)
  - necrotic enterocolitis - disorder in intestinal microcirculation

- hematology
  - immature conjugation of bilirubin in liver - jaundice - in critical levels it is necessary to carry out exchange transfusion to prevent "kern icterus", blue light helps conjugation (bilirubin is transformed in the skin to a different isomer)
  - low production of coagulation factors in liver (hypovit. K) - bleeding disorders (critical is intracranial bleeding)
  - anemia - due to bleeding, Rh incompatibility, catabolic state - low erythropoesis
  - polyglobulia - only in the case of a delayed cutting off the umbilical cord = placental-fetal transfusion

- immune system
  - immature immune system has low activity of both T and B lymphocytes
  - low phagocytic activity
  - deficit of chemotactic factors
  - low function of barriers - increased risk of infection
- in the case of missing immunoglobulin supply from mother milk, there is much higher probability of severe infections - mainly GIT infections causing diarrhea and vomiting leading to critical dehydration and mineral dysbalance

● nervous system
  - immature sensory functions
  - incomplete myelination (positive Babinsky's sign)
  - problems with central regulation of blood pressure
  - respiratory insufficiency due to missing activity of the respiratory center
  - missing important reflexes (e.g. for normal feeding)
  - risk of periventricular leukomalacia - due to hypotension, hypoxia
  - periventricular hemorrhage - after ischemic phase - reperfusion with increased volume causes rupture of capillaries

● thermoregulation
  - high ratio body surface/body weight is demanding for the maintenance of constant body temperature
  - very low amount of subdermal fat in immature newborns - low insulation and low energy source
  - brown fat is formed only after 26th week - low capacity for non-shivering thermogenesis

● metabolism
  - low glycogen stores - hypoglycemia (below 1.7 mmol/l during the first day)
  - low GIT activity
  - despite all nutritional attempts - decrease of body weight after birth
  - hypocalcemia - ionized calcium below 1 mmol/l - in 5-10% of all newborns (due to the lost parathormone supply from mother, vit. D insufficiency, high calcitonin in immature newborns

**Immature newborn** – any birth before completion of 37th week of pregnancy

**Etiology of premature birth**
- health problems of mother
- loss of amniotic fluid
- disease of the fetus
- Rh incompatibility

**Risks of intensive care**
- retinopathy - due to changes in retinal vessels in prolonged oxygenation with pO₂ > 100 mm Hg
- bleeding after compensation of circulation (due to increased pressure - ruptures of vessels - especially in CNS)
93. Aging

Now that a lot of formerly critical health problems have been solved, or at least people successfully survive thanks to new treatments, the average age of the human population is increasing, and more attention has to be paid to aging processes to improve also quality of life in the elderly.

Speculation about theoretical limits to human longevity came recently to the conclusion that in the case of optimal health care (i.e. when non-treatable diseases would exist) the maximum age could be about 120 years (this seems to be determined by some biological limits of the cell reproductive cycle - e.g. shortening of telomeres).

Theories of aging
- somatic mutations - exposure to mutagenic factors - irradiation, chemicals - cell injury, death
- theory of "oxidative stress" - induced mainly by "oxygen free-radicals" or loss of anti-oxidative capacity - lipoperoxidation of phospholipids in cell membranes (malondialdehyde - potential marker of cell aging)
- lipofuscin - "aging pigment" - marker of aging (produced by oxidation of lipids and proteins)
- antioxidative effects (oxygen free-radical scavengers) - enzymes (superoxide dismutase, glutathione peroxidase, catalase), antioxidative substances - vit. E, A, C and melatonin in CNS
- immunologic theory of aging - functional capacity of the immune system decreases with age
  - this includes also ability to recognize own antigens → autoimmune diseases in elderly
- neuro-endocrine theory - based on control of aging via hypothalamo-pituitary system
- theory of non-enzymatic glycation of proteins - increasing with age (also in uremia, hyperglycemia - DM, oxidative stress) - leads to changed function of cells and their death
- theory of programmed aging - shortening of telomeres (high activity of telomerase in stem cells enables multiple reproduction - also in tumorous cells)
- mitochondrial disorder (either through gene mutations or oxygen free-radicals effects) leads to decrease of intracellular energy production

Functional changes during aging
- all tissues, organs and systems undergo aging - they decrease functional reserve and adaptation capacity

● Cardiovascular changes
  - decreased number of myocytes, increased lipofuscin, collagen and fat → fibrosis, decreased contractility and MV
  - decreased pacemaking and conduction tissues - arrhythmias, blocks
  - decreased coronary artery blood flow - decreased MV - heart failure
  - rigidity and thickening of valves - contributes to heart failure
  - decreased elasticity of vessels → increased systemic vascular resistance - afterload → hypertension, left ventricle hypertrophy and failure

● Changes in the respiratory system
  - decreased elastin and increased collagen → decreased compliance of the chest wall and decreased lung elasticity → decreased vital capacity
  - decreased number and motility of cilia + chronic bronchitis = obstruction → enlargement of alveoli - rupture of septa → emphysema = decreased surface/increased dead space, increased residual volume - decreased vital capacity, respiratory insufficiency

● GIT changes
  - gastric atrophy - decreased HCl and pepsin → malabsorption of proteins, anemia, infections
- decreased production of bile and pancreatic enzymes with atrophy of intestinal epithelium → generalized malabsorption
- muscular atrophy, decreased peristalsis → constipation - difficult defecation with possible collapses (Valsalva's maneuver)
- decreased liver functions - hypoglycemia, low tolerance of alcohol, low degradation of pharmacs (necessary lower dosage)
  ● Endocrine changes
    - decreased target organ sensitivity
    - decreased levels of hormones with exception of: noradrenaline, parathyroid hormone, insulin, glucagon and atrial natriuretic peptide (these are increased)
    - lower production of hormones is compensated by slower degradation (elimination)
  ● Changes in the renal system
    - decreased GF - renal insufficiency → decreased excretion of drugs and metabolites
    - decreased concentration capacity (dehydration in low intake of fluids)
    - decreased pH compensatory capacity
    - decreased bladder capacity, decreased innervation (sensation of filling), decreased sphincter tone → incontinence, nocturia
  ● CNS changes
    - decreased cerebral blood flow - senile dementia
    - Alzheimer disease - so far no specific treatment
    - increased lipofuscin in neurons
    - astrocyte degeneration
    - decreased synthesis of neurotransmitters - decreased function of CNS
    - decreased inhibitory functions → increased repetitive movements and tremor
    - degeneration of myelin - prolonged reflexes
  ● Changes in the immune system
    - atrophy of thymus (deficiency of T-cells)
    - decreased antibody response
    - increased production of autoantibodies

Senile CNS changes and muscular atrophy and weakness does not allow to old people to be self-sufficient. They require constant assistance, which is financially more demanding than attempts to prevent the above specified changes.
94. Pathophysiological view on "alternative/complementary" medicine

Complementary medicine includes many different techniques (see below a short description of some examples). Only some of these methods are actually used for any length of time as is claimed by those who practice them. All providers of these techniques argue that compared to standard (allopathic) medicine "they treat the patient as a whole person" rather than single symptoms and signs. This statement misuses one of the weak points of the standard medicine as it is currently practiced - namely the fact that a lot of doctors (not all of them!!) ignore the necessity of a very complex assessment for the treatment of any disease. It is a misinterpretation of the basic aims of modern medicine to put it into conflict with the principle of "whole person" treatment. As was specified in the Introduction to this review of Pathophysiology and in many subsequent chapters – a good standard of medical practice is attained only by complex understanding of multi-factorial etiology (including psychosomatic relationships) and non-schematic individual treatment for prevention of secondary processes and complications. It is only poor quality medicine (with missing psychological support for patients and the necessary explanations of their health status, in terms of a clear description of the existing possibilities for influencing it) which provides the space for manipulation with complementary medicine.

Examples of general arguments against acceptance of complementary medicine
- There is usually no tendency (or even willingness) to use standard methods for assessing the principles and significance of beneficial effects (e.g. statistical methods) – the proclaimed success can be explained by the existing probability of spontaneous health recovery.
- Any possible psychotherapeutic effect is interpreted, for example, as a special ability to manipulate using some kinds of energy, an interpretation which has so far not been proven, and for which no reliable studies have yet been performed.
- "Complementary" methods can cause avoidance of or delay to an urgent existing causal therapy (e.g. use of antibiotics in severe bacterial infections)
- It results in financial loss for patients who are willing (especially in the case of children) to pay enormous sums of money for unrecognized methods.

Some reasons for the relatively high attraction of complementary medicine in the population
- People have a tendency to trust to "miracles" when they are in critical health state (without appropriate information from the doctor’s side).
- There is inadequate evaluation (comments) of these methods in the media - naive editors help to distribute false advertisement
- A positive psychological effect can be a dominant experience (especially when adequate psychological support from the GP or a specialist is missing) experience.
- Since it is quite popular among patients to combine standard treatment with application of complementary methods, some doctors who are trying to attract patients are open to a cooperation with anybody, without any effort to understand a possible background (e.g. in the case of an improvement in, or even total recovery from "untreatable" tumors, it is possible to understand it as a spontaneous improvement in immunological processes resulting from the beneficial psychological effect helping to eliminate prolonged stress, thus leading to destruction of tumorous)

Examples of complementary methods (in alphabetical order):
- Acupressure - pressure from fingers is applied where appropriate (acupuncture points) - usually only on sole of foot
- Acupuncture - classic Chinese variant uses whole body (energy centers) - one of the oldest methods with some possible logical explanations (release of endorphins, Head’s zones, irritation of inhibition interneurones in the dorsal roots of the spinal cord)

- Aqua touch - a whole body treatment given in water

- Auricular acupuncture - a variant of acupuncture trying to affect the whole body from the ear

- Bowan therapeutic touch - light touch used in certain sequences should release energy blockages

- Chinese medicine - provides a comprehensive range of treatments for problems arising in physical, mental, emotional and spiritual parts of the consciousness

- Colonic hydrotherapy - warm water is pumped into the colon, the central point is that poisons are flushed out

- Color therapy – belief in the benefits of colored light on the skin

- Crystal healing - according to this method crystals transmit energy which is claimed to be able to tune bodies, crystals are chosen according to their energy

- Geopathic stress (geopathogenic zones) - concept of energy patterns which are created by the Earth that can adversely affect the body - people should move from geopathogenic zones not to be ill (zones are recognized by water diviners) - never physically proved; theoretically it is not possible that e.g. on the level of a high floor (in some high building) the borders of the geopathogenic zones could be so sharp as it is indicated by providers of this method (one corner in a bedroom is recognised as unhealthy and in one meter distance there is a „healthy place“)

- Healing - supposes that healing energy is part of every person and that certain people "sensibles" are able to channel these energies, healers say that they have a special ability, what is a gift from God (no one official religion accepted this)

- Homeopathy - treating the vital force to enable the body to "re-energize" its own repair mechanism; the homeopathic remedy may not even contain a single molecule of the healing substance (because of enormously low concentration) any molecule of the healing substance - it should work only via "information" about that substance present in the solution; placebo effect is most probable

- Iridology (iris diagnostics) - should be able to make any diagnosis only from the iris of the eye where nerve endings should be exposed

- Music therapy - sound and music produce vibrations and these should have marked effects on healing (however, the positive psychogenic effect of music is not disputable)

- Philippine surgery - non-bloody surgery used mainly for removal of tumors (this trick can have a quite distinct psychogenic effect)

- Reiki - a Japanese healing discipline - principles are similar to healing techniques but the system follows a pre-determined set of hand positions

- Tai Chi - slow movements and breathing technique help to regulate the flow of Chi energy

It is not the aim of this chapter to refute automatically all existing methods of this kind. This is a reminder of the need for doctors try to understand the background and the reason for the use of any treatment, and they should verify quantitatively its effect in order to compare it with some other kinds of treatment. Doctors should not practise as do naive and fanatic healers using obscure methods, without correctly naming their background and making serious attempts to evaluate their effectiveness.
95. Pathophysiology of infertility and sexual disorders

- the number of infertile couples is increasing - recently about 15 - 20% of them 40% represents male infertility

Male infertility
- production of sperm is normally fairly constant up to high elderly, but many endogenous or external factors can influence sperm quality
- number of sperms - the average volume of semen produced at ejaculation is 2 to 5ml, and the concentration of spermatozoa should be at least 20 million per ml
- sperm kinetics - at least 75 per cent of the spermatozoa should be alive (it is normal for up to 25 per cent to be dead), and at least 25 per cent of the spermatozoa should be swimming with rapid forward movement
- male fertility seems to be declining
- many environmental factors that can affect male fertility (more today than 50 years ago):
  - endocrine disrupters, toxic pollutants, sexually transmitted infections, zinc deficiency, alcoholism, smoking, anabolic steroid use, ionizing radiation, low physical activity
- potential toxins - phthalates, phenols, pesticides, dioxins, phytoestrogens (soya products)
- wearing of tight (leather) trousers and tight plastic underwear changes testicle microclimate (temperature) - can influence sperm quality (motility)
- stress influences
- endogenous factors - genetics (Klinefelter's sy, cystic fibrosis), hormonal effects (gonadotropins), inborn disorders of germ cells, angioathies, autoimmune processes,

Female infertility
- ca one month after birth all eggs are created - later there is only their periodical release

Risk factors:
- during aging fertility declines - infertility in older women appears mostly due to a higher risk for chromosomal abnormalities
  - chances for pregnancy - by age 34 = 90%, by age 40 - declining to 67%, by age 45 - declining to 15%
- weight factors - 30% of estrogens are produced in fat cells- extreme weight levels (high or low) influence fertility
  - obesity is highly associated with polycystic ovarian syndrome
  - amenorrhea is also highly associated with DM type II
  - underweight (10 - 15% below norm) can stop the reproductive process (anorexia, restrictive diets, strict vegetarians with B12, iron, zinc and folic acid deficiency)
- extreme exercise -marathon runners, dancers, and others who exercise very intensely (works via lower body fat but other mechanisms are also involved)
- smoking - those who started smoking before the age of 18 are at greater risk for infertility, smoking also increases the risk for still births and low birth-weight babies, marijuana smoking appears to adversely affect fertility in both males and females
- caffeine - a correlation has been found between caffeine consumption and infertility, possibly because it has estrogen-like effects
- irradiation
- stress - severely elevated levels of stress hormone can shut down menstruation

Endogenous factors
- hormonal dysbalance (besides primary endocrine problems it can be influenced by stress)
- anatomical - strictures of ovarian (fallopian) tubes, salpingitis, torsion, cancer, cysts
- immunological
- genetic (Turner's sy, cystic fibrosis)

**Frequency of sexual intercourse**
- egg fertility - about 1 day
- sperms survival (in ovarian tubes - about 3-4 days)
- needed frequency of sexual intercourse - at least twice a week

**Sexual disorders**
- problems in sexual behavior, reactions and feelings upon normal sexual stimulation
- more problems in people with higher IQ
- substantially dependent on acute or chronic stress conditions
- better recognizable in men but with more severe consequences in the case of sexual frustration

**Males**
- higher sexual appetite (on average)
- abstinence leads to stress, depression with a lot of psychosomatic disorders
- erectile dysfunction:
  - organic causes - cardiovascular disorders (left heart insufficiency, atherosclerosis, DM) - VIAGRA helps via 5-phosphodiesterase blockage (leads to increased levels of cGMP and NO)
  - anorganic etiology - psychological stress (low self-confidence), hormonal disorders, drugs especially antihypertensives, antidepressives, steroids), alcohol, marihuana
- premature ejaculation - before or soon after penetration - usually psychological background

**Females**
- problems with appetite - primary (inborn), secondary - after some bad experience, some genital disorders, drugs, social factors
- excitement inability - low perfusion of external genital area, low lubrication, inflammatory processes
- anorgasmia (total anorgasmia in about 8% of women) - otherwise dependent on appropriate sexual act and psychosocial factors
- dyspareunia - unpleasant/painful sexual intercourse
- incontinence (during orgasm)
- vaginism (contraction of vaginal muscles - usually as a stress reaction)

Majority of anorganic (functional) sexual disorders in both sexes can be solved with well cooperating partner.
96. Electric bio-potentials - recording and diagnostic use

Despite existence of modern diagnostic imaging, biochemical and other techniques that enable detection of morphological and chemical changes within the body, there are also various functional disturbances sometimes detectable only via analysis of electric potentials produced by some organs (tissues) as a manifestation of their function (ECG, EEG, EMG, ERG, EOG and others). These methods can also be preferable in some cases because of their non-invasive character and economical efficiency.

Evaluation of these signal is performed either in the "time domain" (detection of particular specific peaks and wave complexes – „grapho-elements“ - and description of their time and amplitude characteristics) or in the "frequency domain" (frequency spectrum characteristics). At present this is done almost exclusively with the use of computers. Since electrical activity analysis serves mainly for recognition of functional changes, pathophysiology deals with some of these signals (mainly with ECG, EEG) and instructs basic interpretation of some pathological findings. It is important to understand basically the methodology of these techniques, in order to be aware of the limits of these methods and to recognize possible artifacts changing significantly the interpretation of acquired recordings.

Important recording conditions and parameters

Location of recording electrodes
- preferred non-invasive character of electrophysiological methods requires using of surface electrodes which should be located as close as possible to the source of the signal
- more recording sites are necessary in the case of mapping of a signal distribution
- besides active electrodes, for the unipolar recording also an indifferent (reference) electrode (having approximately zero potential) is necessary
- before placement of the electrodes, the skin surface should be cleaned (e.g. with alcohol) to remove any superficial fatty film which would increase electric resistance (which is of high importance particularly in the recording of very small potentials such as brain evoked potentials)

Signal amplification
- according to the voltage (amplitude) of the recorded signal, a different level of amplification is used
- for the further computer processing of the signal it is important to achieve a signal amplitude of at least 1 V (Volt) - since the majority of signals (e.g. electrocardiogram -ECG) have amplitude of several millivolts, amplification of about 1,000-times is used - such level of amplification does not represent any problem and is not usually accompanied with larger noise (such as contamination with alternating current - oscillations of 50 Hz in Europe, 60 Hz in USA)
- in the case of the electroencephalogram (EEG), the necessary amplification is about 20 times higher (ca 20,000-times) because this signal has amplitude of tens of microvolts only - such an amplification requires much higher quality of amplifiers (having low level of intrinsic noise), more careful recording electrode montage (with low skin-electrode transmission resistance), and also in some cases electromagnetic shielding (Faraday cage) in some cases is needed (to increase useful signal-to-noise ratio) to achieve a good quality of signal recording
- signal filtering - each amplification should concern only “useful” signal frequencies - thus high pass and low pass filters are used to eliminate “not-interesting” frequencies (like alternating current from grid)
Analog/digital conversion

- for saving of the analog signal into a digital computer (and for further digital processing), it is necessary to convert it to into series of discrete digits describing the amplitude of the signal at selected points with a given frequency (sampling rate)
- for sufficiently precise digital description of the signal, the required frequency of A/D conversion (sampling rate) depends on the highest frequency which is present (and important) in the recorded signal - the sampling rate should be two times higher than the frequency which we need to recognize in the signal (= Nyquist frequency - see the picture provided to this chapter at our Web page specified in Introduction)
- standard A/D converters discriminate the amplitude with 12 bit accuracy (= 4,096 recognized levels – but A/D converters with higher resolution are also available) – thus in the case of amplitude about 1V (after amplification), it is possible to recognize about one hundredth of a microvolt in the raw signal (this is more than adequate for standard use)

Sources of artificial activity (artifacts)

● exogenous
- electromagnetic noise (alternating current – coming from the power supply) - recognizable according to its regular frequency and constant amplitude (simply removable with analog or digital filters)
- electrochemical DC current changes (caused by movement of electrodes - not well fixed) - slow potentials of high amplitude

● endogenous
- muscle artifacts - either muscle contractions (eye blinking in EEG) or muscle tremor (e.g. shivering in cold conditions during ECG recordings)
- ECG contamination in EEG signal (usually when non-cephalic reference electrode is used)

Artifacts can be removed automatically during computer recording of the signal (“on-line”) or during visual inspection selected segments are eliminated (“off-line”).

Most frequently used electric bio-signal evaluation

ECG description - evaluation in the “time domain” - amplitude and duration of single peaks and waves is evaluated, automatic computer description with offered interpretation is available

EEG description in the "time domain" – e.g. detection of graphoelements specific for particular types of epileptic seizures

EEG description in the “frequency domain” - frequency spectrum is changed in any pathology of the brain - non-specific slowing of EEG - increased frequencies in delta and theta bands, slow "dominant frequency" - normally it is about 10 Hz (alpha band)

Evoked potentials - reaction to sensory stimuli (averaged response to repeated stimuli is evaluated in the "time domain") - due to inter-individual variability of amplitudes mainly latencies are important for diagnostics - delayed latencies in visual, acoustic or somatosensory evoked potentials are found e.g. in demyelination processes

EMG (electromyography) - detection of myasthenia, muscular atrophies, myotony - frequency and amplitude in electrical stimulation is evaluated

ERG (electroretinography) - detection of retinal potentials in scotopic and photopic conditions enables objective recognition of various functional disorders - e.g. diabetic retinopathy, uremic retinopathy, retinitis pigmentosa, toxic effects of pharmac (amiodarone, antimalarials)

EOG (electrooculography) - detection of some retinal disorders and oculomotor disturbances
97. Principles and possibilities of (auto)-biofeedback

Many body functions are outside of voluntary control. Some of them cannot be intentionally influenced because the subject does not have any information about changes of the particular parameter. For example we cannot interfere into regulation of our blood pressure since we do not know its actual changes and we cannot recognize what are the influences that play a role in it.

When we provide the missing information about the development of some parameter (e.g. blood pressure), the subject can learn to influence this parameter after some experience of to which conditions lead to its increase or decrease. Thus some hypertonic people (those with psychogenic/stress background to their hypertension) can learn to eliminate/depress such states of mind which evidently are increasing their blood pressure.

The way of information providing can be very simple - the information from an artificial (technical) sensor is analyzed (with the use of micro-processor) and in the event that some specified level is exceeded it can be indicated to the subject - e.g. by switching on off of a light. Even more detailed information can be mediated e.g. by increasing and decreasing the frequency of a tone indicating that the regulated parameter is either coming closer to or receding from the ideal level.

There is quite a large spectrum of parameters which we can try to influence with the use of auto-biofeedback. One of the most frequently recommended is EEG-biofeedback.

EEG biofeedback (neuro-feedback) was originally oriented only to the possibility of improving laxation ability via increase of EEG alpha activity (instead of autogenic training such as yoga that not all people are able/willing to practice). Alpha activity represents mainly the “resting” EEG frequency and thus its increase is recognized as a sign of relaxation. In chronically stressed people who find themselves unable to relax effectively, EEG analysis can provide information about changes in the actual amount of their alpha activity. When a subject tries to recognize which states of mind lead to increase of alpha activity, after some training it can help them to achieve a much higher alpha activity and probably also a better relaxation state. So far it has been proved in reliable studies that this kind of EEG bio-feedback can be officially recommended to patients with some psychosomatic disorders related to chronic stress, some cases of epilepsy or brain hyperactivity.

However, in recent times another kind of EEG-biofeedback has also been practised, based on some computer games (e.g. a simulated task to keep a car on a road) that could influence various EEG parameters (such as sensory-motor rhythm or theta frequency). It is claimed that the achieved ability to drive the car in the middle of the road (after some training) represents complex change of brain EEG parameters and functioning that should be helpful in a large spectrum of psychological, neurological and social problems (fatigue, loss of concentration, insomnia, depressions, alcoholism, smoking, drug abuse, migraine, anorexia, bulimia, chronic fatigue syndrome, immunodeficiency, hyperactivity in children, specific learning disorders - dyslexia etc.). Nevertheless, it has so far not been proved that it could help in these diagnoses, and it seems that false information is being distributed (virtual researchers are cited) about these applications!!!. Since particularly in the case of children parents do not hesitate to pay money for each session, it seems to be a lucrative business. Some of the reported improvements with the use of this kind of EEG-biofeedback in children can be attributed to the fact that some attention is regularly paid to these children, which can have more or less the same positive effect as any game that could be played with them.

Thus, despite the promising perspectives of auto-bio-feedback applications, their non-verified variants should be subject to a fair degree of scepticism, as they probably represent only commercial activities.