A

AARD Abbreviation used sometimes for autoantibody associated rheumatic diseases like systemic lupus erythematosus (SLE), Sjögren's syndrome (SjS), systemic sclerosis (SSc), polymyositis (PM) and dermatomyositis (DM).

α_1-Antitrypsin A serum glycoprotein inhibiting proteolytic enzymes, such as trypsin, chymotrypsin and elastase. It also acts as an acute phase protein. Its serum level rises in inflammatory diseases. The coding gene is located on the 14th chromosome, where it can occur in form of 25 alleles. Some of them code for physiological products (PiMM phenotype), whilst others are related to pathological states, e.g. PiZZ phenotype, which is often associated with emphysema, cirrhosis and cholelithiasis, where its serum levels are diminished (α_1-antitrypsin deficiency).

α-Fetoprotein An oncofoetal antigen that can be found in small concentrations in normal human serum. Its level is high in the foetal serum, where presumably thanks to its immunosuppressive effect, it participates in neonatal immunological tolerance. The α-fetoprotein level is also increased in sera of pregnant women when foetal development is defective (central nervous system defects, immunodeficiency syndromes, gastrointestinal or other abnormalities). An increased serum level can be found in patients with certain neoplastic disorders, especially hepatic cancer and can be used as a marker of hepatocellular carcinoma.

α_1-Microglobulin (α_1M) A protein synthesised in the liver and present in blood, serum and urine. Complexes of α_1M with monomeric immunoglobulin A (IgA) participate in renal IgA nephropathy where the serum level of α_2M is also usually increased.

α_2-Macroglobulin (α_2M) A serum glycoprotein working as inhibitor of a number of proteases including thrombin, plasmin, kallikrein, trypsin, chymotrypsin, elastase, collagenase and cathepsin B and G. α_2M is produced mainly by macrophages and regulates the proteolytic balance in a number of extracellular processes that exert their action mainly in blood coagulation, fibrinolysis and inflammation. α_2M and protease complexes are proteolytically inactive and are eliminated quickly (in

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minutes) from the circulation. Its serum levels are increased especially in nephrotic syndrome, atopic dermatitis, diabetes mellitus and ataxia– telangiectasia.

Abatacept Abatacept (Orencia®) is an injectable, synthetic (man-made) soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc portion of human immunoglobulin G1 (IgG1). Abatacept is produced by recombinant DNA technology in a mammalian cell expression system.

Abatacept belongs to a class of drugs called co-stimulation modulators, shown to inhibit T cell activation by binding to CD80 and CD86, thereby blocking interaction with CD28. Blockade of this interaction has been shown to inhibit the autoimmune T-cell activation that has been implicated in the pathogenesis of rheumatoid arthritis. Abatacept attaches to a protein on the surface of T lymphocytes and blocks both the production of new T lymphocytes and the production of the chemicals that destroy tissue and cause the symptoms and signs of arthritis. Abatacept slows the damage to joints and cartilage and relieves the symptoms and signs of arthritis.

Abatacept is indicated for adult rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) and may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists. Abatacept is distributed for intravenous as well as for subcutaneous application. Intravenously abatacept is infused over 30 min. The initial dose of abatacept is followed by doses 2 and 4 weeks later with further doses every 4 weeks thereafter. Adults weighing <60 kg should receive a 500 mg dose, weighing 60–100 kg a 750 mg dose and weighing >100 kg a 1000 mg dose. Paediatric patients weighing less than 75 kg receive 10 mg/kg intravenously based on the patient's body weight. Paediatric patients weighing 75 kg or more should be administered abatacept following the adult intravenous dosing regimen, not to exceed a maximum dose of 1000 mg.

The solution for subcutaneous injection is only for the use in rheumatoid arthritis. If the patient is taking Orencia for the first time, the infusion with a single iv loading dose of approximately 10 mg/kg bodyweight should be used for the first administration, followed by an injection under the skin the next day and then weekly. The self-injectable formulation is a fixed 125 mg dose.

The most common side effects of abatacept include: back pain, cough, dizziness, headache, high blood pressure, nausea, rash, upper respiratory tract infection and urinary tract infection. Administration of abatacept in patients with chronic obstructive pulmonary disease (COPD) has been associated with exacerbation and increased incidence of COPD symptoms. Patients suffering from both rheumatoid arthritis and COPD who elect to have abatacept therapy should monitor symptoms carefully and in collaboration with their physicians. Concurrent administration of a TNF inhibitor with abatacept has been associated with an increased risk of serious infections and no significant additional efficacy over the use of the TNF antagonists alone. It is recommended not to give live vaccines concurrently with

abatacept or within 3 months of its discontinuation as it might blunt the effectiveness of some immunisations. The long-term effects of abatacept with remission of both clinical symptoms and radiographic joint damage have been demonstrated in several trials.

Abduction Movement of extremities of the body away from the body's midline.

Achilles tendon The common insertion of soleus and both gastrocnemii muscles tendons. It inserts on the posterior side of calcaneus, separated from it by the Achilles bursa. Tendonitis can be part of the clinical picture of spondyloarthritis, especially ankylosing spondylitis. It can remain thickened (by fibrosis) after the inflammation has subsided and nodules may be palpable.

Achillodynia Pain of the Achilles tendon, especially of its insertion, most frequently after a trauma or sporting overload.

Achondroplasia and hypochondroplasia Autosomal dominant hereditary syndrome characterised by a short stature with short extremities. In most cases, it is caused by mutation in the gene encoding fibroblast growth factor receptor 3 (FGFR-3). It affects boys more often. With the incidence of 1 in 15,000–77,000 labours (depending on the ethnic origin), the disease belongs to the most frequently occurring dysplasias. Mutation in the FGFR-3 causes impaired proliferation of chondrocytes in the long bone cartilage. Individuals have normal or above-average intelligence.

Clinical signs: specific development abnormalities lead to the abovementioned phenotype. The spine is usually kyphotic, fingers are shortened (brachydactyly), and the final height of the stature is 120–130 cm. Individuals have pear-shaped head with a protrude forehead, middle part of the face is hypoplastic with a tendency to obstruct the upper respiratory system; there are dysplastic changes in the craniovertebral junction with a tendency of foramen magnum narrowing and medulla oblongata compression and thoracic constriction. The situation may result in the manifestation of 'respiratory distress syndrome in achondroplasia'. Difficulties can be divided into three groups. Mildest manifestations have merely the form of obstructive sleep apnoea (most likely connected with the nasal tonsil hypertrophy); a more severe course of the disease includes episodes of apnoea and upper respiratory system obstructions which persist following adenotomy, often associated with the development of hydrocephalus. Most severe conditions develop into circulatory and respiratory failure with oxygen dependence.

Acquired immunodeficiency syndrome An infectious disease due to the HIV retrovirus (human immunodeficiency virus). Two types of virus exist: HIV-1 and HIV-2. Both cause serious immune system defects. The present pandemics are predominantly due to HIV-1, which is more pathogenic. It is transmitted by homosexual or heterosexual intercourse, transfusion of infected blood and its derivates, IV drug administrations using infected needles, organ transplant from an infected donor or from an infected mother during labour or breast-feeding.

HIV infects cells that possess differential antigen $CD4^+$ on their surface (particularly T lymphocytes and macrophages). Non-specific symptoms occur at an early stage after infection. Subfebrile temperatures, weakness, sweating, arthralgias, myalgia, headache, diarrhoea, lymphadenopathy and also certain neurological symptoms may occur. Such symptoms last for several days to 2 weeks. In the majority of infected individuals, these symptoms may not be apparent. Approximately 2 weeks after virus transmission, the viral antigens (p24, gp41) can be detected in the blood of the infected individual. Later on these antigens disappear and antibodies against certain HIV antigens (anti-p24 and anti-gp41) can be detected in the blood of the infected individual at 2–3 months, which is diagnostic confirmation of infection. The disease now often enters a latent period without any clinical symptoms, except for possible lymphadenopathy. Such a period may last up to 12 years, and it terminates by activation of the disease, which, in untreated cases, leads to death in 6–30 months.

Activation of the disease is manifested by decreasing antibodies against the HIV antigens (anti-p24) and concurrent reoccurrence of these antigens in the blood. Such an event is referred to as seroconversion. The number of T lymphocytes in peripheral blood decreases. If the number of T lymphocytes is less the 0.2×10^9/l, then the infected individual is considered to have severe AIDS, even though the patient may be asymptomatic. AIDS symptoms include infections due to normal, non-pathogenic microorganisms (pneumonia due to *Pneumocystis carinii* – in 50 % of all patients) and certain malignancies with rapid course (Kaposi sarcoma – approximately 1/3 of all patients). Dementia and changes of psychomotor functions, which are very likely due to direct HIV infection of glial cells in the brain, occur in approximately 2/3 of all patients. The typical clinical picture of AIDS does not develop in certain patients; however, these patients suffer from a group of symptoms referred to as ARC (AIDS-related complex) in which infections and tumours are not present. ARC may or may not progress to full-blown AIDS.

The diagnosis of AIDS consists of serological assessment, immunological assessment (determination of $CD4^+$ lymphocytes or the $CD4^+/CD8^+$ ratio in peripheral blood), clinical assessment and relevant medical history. Contemporary treatment is only partial, and generally it allows inhibition of HIV replication in infected cells (azidothymidine, zidovudine) and thereby prolongs the period free of any clinical symptoms. However, after development of the symptoms, treatment cannot cure the disease.

ACR classification criteria for diagnosis of rheumatoid arthritis 1987 – see Rheumatoid arthritis (RA), classification criteria.

Actemra Trade name of tocilizumab in Switzerland and in the USA.

Action potential Electrical activity in the nerve axon or muscle fibre according to the ‘all or nothing’ type, when the membrane potential polarity ceases or is restored abruptly.

Acupuncture (AC) Used in rheumatology for pain relief. Metallic needles are inserted into specific body points by rotation movement. Acupuncture should induce a balance between "yang" (spirit) and "yin" (blood) principles that run in 14 meridians comprising 361 acupuncture points. AC has been considered as a form of neuromodulation. Its effects have been explained by the gate theory of pain relief and also by a presumption that the insertion of the needle acts as a noxa, inducing the production of endogenous opiate-like substances (opioids). The locations of acupuncture points often overlap myofascial trigger points and painful muscle points.

Electro-acupuncture refers to the stimulation of the acupuncture points with needles plugged into a source of electrical current or by the application of small electrodes on those points. Similarly, laserpuncture and magnetopuncture are used.

Acupressure refers to a method when acupuncture points are influenced by pressure from the fingers or rounded sticks.

Acute conditions in rheumatic diseases

The patient should be immediately admitted to hospital (orthopaedic, rheumatology, neurosurgery or traumatology departments).

- Septic bacterial arthritis
- Baker's cyst rupture or rupture of the joint capsule of the knee joint that mimics the symptoms of deep vein thrombosis.
- Tunnel or compression syndromes that cause great pain and nerve compression or cause disorders of blood circulation.
- Compression fracture of osteoporotic vertebra without neurological complications.
- Administration of analgesics is needed.
- Dislocation of atlantoaxial joint in RA and AS, which causes compression of the medulla oblongata.
- Peripheral paresis or spinal cord compression caused by cervical or thoracic disc herniation.
- Peripheral paresis or cauda syndrome caused by lumbar disc herniation.
- Radiculopathy of upper or lower extremities, causing intensive pain, administration of analgesics, packs for relief of sciatic pain and bed rest.

Acute conditions in diffuse connective tissue disease Clinical symptoms suspecting CNS vasculitis, comatose states, exacerbation of disease, acute onset of oliguria, anuria, hyperviscosity syndrome, hypertension crisis, eclampsia, acute abdomen, hemorrhagic states, thrombosis, muscle weakness causing breathing problems, polyneuropathy and Guillain–Barré syndrome.

The patient should be admitted to the department of internal medicine or neurology, which have experiences with the treatment of the disease.

Acute polyarthritis with fever The patient should be admitted to the rheumatology department.

Treatment complications

Anaphylactic shock, laryngeal oedema
In young patients epinephrine and large dose of glucocorticoids intravenously are administered, or coniotomy is performed. Immediate admission to the intensive care unit or ENT department is necessary.
Bleeding in the stomach, abdominal or intestinal perforation
Anti-shock therapy should be immediately started; in patients on long-term glucocorticoid treatment, 100 mg of hydrocortisone should be administered. Patient should be admitted to the department of surgery or internal medicine.

Agranulocytosis The patient should be admitted to the department of rheumatology, internal medicine or haematology.

Treatment complications can include hypokalemia, which may often occur after administration of glucocorticoids and may cause heart rhythm problems or acute muscle weakness. Potassium should be administered.

Adrenal insufficiency often arises when glucocorticoids are administered or when their administration is interrupted, sometimes even if it is not reduced; however, in some conditions (intercurrent illness, stress conditions), the endogenous need increased. It is necessary to increase the dose of glucocorticoids and, where appropriate, to admit the patient to the hospital.

Hypercalcaemic crisis The patient should be admitted to the intensive care unit, fluids should be given, diuresis forced and glucocorticoids administered.

Pneumothorax It may result from local injection in the area of the chest wall; the patient should be admitted to the department of internal medicine or pneumology.

When applying a local anaesthetic intradurally, the patient must be admitted to the intensive care unit.

Perineurial injection may cause transient paresis or hypoesthesia. Bed rest is indicated, until the effect of the anaesthetic vanishes.

Acute febrile neutrophilic dermatosis (Sweet's syndrome) A rare disease of unknown aetiology characterised by marked inflammatory neutrophilic skin infiltrates.

► *Symptoms and signs:*
- Painful nodules and red-violet maculae on the skin of the shoulders, torso or head; ulceration usually doesn't occur.
- Lesions generally heal without scarring.
- Concomitant high fever.
- Leucocytes with polymorph nuclear predominance.
- Tendency to relapse.

Acute phase proteins (APPs) Glycoprotein mediators whose production is significantly modified after activation of the inflammatory response or any other kind of tissue damage. That is why they are also referred to as acute phase (of inflammation) reactants. They are produced mainly by hepatocytes but also by monocytes, endothelial cells, fibroblasts and other cells. They are divided into positive and negative APPs. The concentration of positive APPs increases in the course of inflammation, whilst the concentration of negative APPs decreases. Albumin is an example for a negative APP. The increase of the major APPs can be greater than a 1000-fold, whilst the concentration of other positive APPs increases only by less than threefold. C-reactive protein (CRP) and serum amyloid A (SAA) are the most strongly reactive positive APPs in humans. Their main biological functions include direct neutralisation of inflammatory reactions, minimising the damage due to inflammation, involvement in reparatory mechanisms and regeneration of damaged tissues. TNF-α, IL-1, IL-6, IL-11 and other cytokines stimulate the transcription of genes encoding APPs, whereas glucocorticoids and insulin inhibit the transcription.

Acute phase reactants – see Acute phase proteins.

Acute prolapse of cervical intervertebral disc Protrusion of the intervertebral disc with intact annulus fibrosus and prolapse of the intervertebral disc with nucleus pulposus prolapse through the perforated annulus fibrosus are the consequence of degenerative changes in intervertebral disc tissues. Prolapse of the disc is usually directed posteriorly through a weak dorsal longitudinal ligament.

► *Symptoms and signs*
Medial protrusion of the disc can cause compression of the spinal cord and lead to development of spastic paraparesis, dorsal column syndrome and urinary bladder dysfunction. More frequently posterolateral prolapse of the disc causes isolated compression of the corresponding spinal nerve. In most patients the symptoms include pain projecting into corresponding dermatome, movement limitation of the cervical spine and spasm of the paravertebral muscles. Initially the neck pain can be provoked by ambulation and later manifests itself by a typical radicular syndrome.

Acute shoulder pain Pain caused by irritation of the phrenic nerve and recognised as shoulder pain (Eiselsberg's phenomenon; first described by the Viennese surgeon Anton von Eiselsberg, Vienna, 1860–1939). This includes pain in angina pectoris, myocardial infarction, gall bladder disorders, trauma of the spleen, neoplasms, diseases of thyroid gland and pleuritis. Also bursitis calcarea, impingement syndrome of one of the rotator cuff tendons, most frequently the supraspinatus muscle, may radiate to the shoulder.

Acute shoulder pain without movement limitation may be caused by radicular syndrome of C5, herpes zoster (shingles), diseases of the bones around the

shoulder, Paget–Schroetter syndrome and subclavian, axillary or brachial vein thrombophlebitis leading to livid oedema of the hand.

Limitation of active movement (passive movements are unlimited) is caused by complete disruption of the rotator cuff usually following trauma, overload, mechanical friction or trauma to the rotator tendons with break up or rupture. Commonly the supraspinatus muscle tendon is affected. In the case of complete rupture, active abduction to the extent of 0–30° is impossible, and the anterior tip of the acromion is tender upon palpation. Sooner or later, the supraspinatus muscle atrophies. In some cases, the X-ray shows calcification in the supraspinatus muscle tendon. Ultrasound or magnetic resonance imaging can confirm disruption of the tendon.

► *Treatment*
Bed rest, extremity positioning, analgesics, physiotherapy and surgical reconstruction.

Adalimumab Adalimumab (Humira®) is a recombinant human IgG1 monoclonal antibody specific for human tumour necrosis factor (TNF). Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). Adalimumab was first approved by FDA in December 2002 for reducing signs and symptoms and inhibiting the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). Adalimumab can be used alone or in combination with methotrexate (MTX) or other DMARDs. Adalimumab has also been approved for moderate to severe polyarticular juvenile idiopathic arthritis (JIA) in children 4 years of age and older, psoriatic arthritis (PsA) in adults and in ankylosing spondylitis (AS) in adults. Besides these indications in rheumatic diseases, adalimumab has approvement to treat moderate to severe Crohn's disease (CD) in adults, moderate to severe Crohn's disease (CD) in children 6 years and older, moderate to severe ulcerative colitis (UC) and moderate to severe chronic plaque psoriasis (Ps) in adults. Adalimumab 40 mg is administered using a prefilled ready to use syringe or pen by subcutaneous injection once every other week.

Adduction Movement of extremities of the body towards the midline.

Adenosine deaminase (ADA) An enzyme in humans and mammals catalysing the deamination of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively. In the case of deficiency, the metabolism of DNA is impaired, resulting in severe disruption of T-lymphocyte function (adenosine deaminase deficiency).

Adhesion Abnormal union of parts that are normally separate. Increased tissue adhesion, caused in rheumatology most frequently by inflammation, is expressed by limited reciprocal movement of tissues.

Adhesive capsulitis (frozen shoulder) This is characterised by pain and gradual progressive limitation in shoulder movements due to contraction of the glenohumeral capsule. There is often partial or complete resolution over months to years. It is the most common in later life and can be associated with neurodystrophy, for example, in the 'shoulder-hand' syndrome, following strokes, metabolic disorders (especially insulin-dependent diabetes mellitus), etc.

Adhesive molecules Glycoproteins or lectins taking part in interactions between immune system cells, especially during colonisation of primary and secondary lymphatic organs and within inflammatory reactions. They belong to several families, such as selectins, integrins, members of the immunoglobulin super family (ICAM-1, VCAM-1, PECAM) and cadherins.

Adjuvant A supplemental agent that increases the effect of the main drug. In immunology, it is an agent of organic or inorganic origin that is capable of potentiating the immune response to a concomitantly administered antigen (e.g. Freund's adjuvant).

Adson's test Test to examine for impingement of the subclavian artery. During the examination, the patient is upright with the upper extremity extended to 40° and his/her head rotated to the examined side. When inspiring and elevating the chin, there is a diminution of the radial pulse on the side of the extended upper extremity, which indicates evidence of impingement of the subclavian artery.

Agammaglobulinaemia A condition in which the total serum immunoglobulin level in the individual is lower than 1 g/L (immunodeficiency). It is caused by genetically conditioned insufficient production of immunoglobulins. There are two forms: Bruton's or Swiss type. Bruton's type is congenital, sex-linked agammaglobulinaemia in boys. The clinical picture is dominated by pyogenic infections. No antibodies are produced after vaccination.

► *Treatment*
Infusion of intravenous preparations of Ig (IVIg).

The Swiss type of idiopathic agammaglobulinaemia with lymphopenia is a severe combined immunodeficiency (SCID). The clinical picture is dominated by systemic fungal infections, mainly candidiasis, together with bacterial infections such as in Bruton's type. The mere repletion of immunoglobulins is rarely therapeutically successful, so bone marrow transplantation should be considered (immunoglobulin deficiency).

Agonist The principal acting muscle (prime mover) responsible for the movement in the required direction. The antagonist acts in the opposite direction to the agonist. The synergist co-acts in the direction of the agonist.

Albers–Schönberg disease – see Osteopetrosis.

Alendronate Alendronic acid belonging to bisphosphonates, which are substances registered for the treatment and prevention of osteoporotic fractures in

postmenopausal women, patients with glucocorticoid-induced osteoporosis and osteoporosis in men. It is taken orally once a week, in the form of sodium salt in the dose of 70 mg. The preparation must be taken strictly on an empty stomach in upright position and with a larger amount of water. After swallowing, it is necessary to remain in upright position for at least 30 min. This regimen is a prevention of irritation of the lower part of oesophagus. Less than 1 % of swallowed substance is absorbed, which then binds to the bone surface with a half-life of approximately 10 years. The primary effect of alendronate is the suppression of osteoclastic resorption of bone tissue.

Alexander technique – see Exercise techniques.

Algodystrophic syndrome (ADS) ADS is characterised as a complex of symptoms elicited by a nociceptive stimulus.

► *Symptoms and signs*
The clinical picture is characterised by severe burning pain, autonomic vasomotor dysfunction, skin changes and subsequent locomotor malfunction of the affected extremity. Radiographically, it is characterised by regional osteoporosis in the affected area.
ADS – synonyms: algoneurodystrophy, reflex sympathetic dystrophy, Sudeck's atrophy, complex regional pain syndrome (CRPS), shoulder–hand syndrome and causalgia. The complex of symptoms includes regional pain, vasomotor disturbances, skin changes and sensory disturbances. Any region on the upper and lower extremities may be affected.

The development of ADS can be divided into:

- *Acute phase* – This begins usually 10 days after an injury. It is characterised by intensive, dull, roughly circumscribed pain, oedema with reddening to cyanosis of the skin that is glossy and sweaty. The aim of physical therapy is to improve local blood perfusion without increased afferentation from the affected region. Diadynamic currents and pulse ultrasound are advisable or interferential currents in analgesic doses (transcutaneous nerve stimulator). Vacuum–compressive therapy (cautiously), passive positioning of the extremity and active exercise of the fingers.
- *Dystrophic phase* – This begins 2–4 weeks after the injury or damage. The skin goes pale, the oedema decreases, and a spotty or diffuse osteoporosis of the whole affected region occurs on the X-ray image. In this stage Basset currents or vacuum–compressive treatment is advisable. Passive exercise of the extremity, beginning with antigravity exercises.
- *Atrophic phase* – This is characterised by persisting trophic changes in the skin and dermis, limitation of passive and active movements up to ankylosis. Functional changes in this stage are very difficult to influence; application of pulse, low-frequency magnetotherapy or distance electrotherapy (Basset currents) may be applied. Intensive locomotor treatment, exercise in a sling, hydrokinesiotherapy and thermotherapy.

Prevention of ADS: early active mobilisation of the affected extremity focusing on functional training.

Algodystrophy, Sudeck's syndrome or reflex sympathetic dystrophy syndrome (algoneurodystrophy syndrome)

It is often a post-traumatic condition which develops after pulling, dislocation, fracture, wrong plastering or nerve interruption.

It is a neurogenic inflammation causing pain with the substance P being excreted in pain-sensitive receptors.

At the same time, a slight synovitis develops, in association with modified microcirculation in the bone and periarticular tissue.

At acute stage, the arm, leg or affected joint and surrounding areas are red or purple, swollen, warm and sensitive to pressure or moving, and the patient experiences a burning sensation. At subacute stage, the joint or the relevant part of the body is wet, cold, having white or purple colour.

At chronic stage, a periarticular fibrosis develops, with thickened skin and subcutaneous tissue and with contracture of the joints. A special case is the hand–arm syndrome, which causes arm contracture with diffuse swelling of the hand and fingers. Besides trauma, it often develops in a reflexive manner following infarction and strokes.

Laboratory anomalies are not present; sedimentation is normal.

Radiological signs. At the initial stage of the disease, the isotopic examination detects accumulation of the pharmaceutical agent. Later, characteristic spotty bone atrophy develops which at the third stage turns into a hypertrophic atrophy with thickening of certain trabeculae.

Therapy. At first, bed rest, analgesics, beta-blockers, vasodilators and sympatholytic agents (also intra-arterial) or regional sympathetic blockers are indicated. To improve circulation, calcium channel blockers, glucocorticoids per os and blood vessel massage (vasotrain) may be administered, followed by step-by-step mobilisation, loading. At the chronic stage, intensive mobilisation, thermotherapy and ultrasound are indicated.

Algometry (evaluation of pain threshold)

- Instrumental measurement of the pressure on a joint or muscle already causing pain.
  Using the Phyaction device (ultrasound + mid-frequency currents), one can, according to current density and ultrasound frequency, localise a painful trigger point.
  Using thermovision, it is possible to localise tender or trigger points on the skin surface:
- Thermal by measuring thermal stimulus endurance
- Different types of visual analogue scales (VAS; on a vector from 0 to 10, or 100 with plus values on the right side and minus values on the left) horizontally and vertically

- Verbal, e.g. Likert 5° scale
- Pain evaluation using questionnaire systems
- Melsack's questionnaire where pain can be expressed by 78 words divided into four groups. Furthermore, the questionnaire contains three indexes with a degree scale from 1 to 5:
  - NWC – number of words chosen.
  - PRI – pain rating index.
  - PPI – present pain intensity.

The evaluation of pain is an integral part of each evaluation system in rheumatology, e.g. HAQ, RADAI, WOMAC, Lequesne index, AIMS and others.

Alkalising agents Compounds used in cytostatic treatment. They act as agents alkalising DNA, thereby blocking cell division, which is why they are used in the treatment of neoplasms. Rarely some of them are used as immunosuppressants (cyclophosphamide).

Alkaptonuria and ochronosis Alkaptonuria is a rare inborn (autosomal recessive) error of the metabolism of aromatic amino acids phenylalanine and tyrosine where, due to a defective activity of the enzyme called homogentisic acid oxidase, there is no cleavage of homogentisic acid (alkapton) causing accumulation in the body and excretion in urine. Its polymer – ochronotic pigment – impregnates the bradytrophic tissues.

► *Symptoms and signs*
- Presence of homogentisic acid in the urine (turns dark when left standing)
- Visible, black-grey pigmentation on eyes and ears
- Degenerative changes of locomotor organs, especially the spine

Allodynia Pain elicited by a stimulus normally insufficient to cause pain.

Allopurinol Acts as an inhibitor of xanthine oxidase. The recommended starting dose is 100 mg daily, with many patients requiring a dose of 300 mg or more daily, whilst with others a dose of 100 mg a day is enough. 100 and 300 mg tablets are available. In severe tophaceous gout, orally, once a day 400–600 mg may be taken.

Alphacalcidol (1-Alpha-hydroxycholecalcipherol) is intended for the treatment of postmenopausal, senile or glucocorticoid-induced osteoporosis. It only requires liver hydroxylation to quickly turn into active calcitriol; therefore, it may be used in renal insufficiency. Whilst on treatment with alphacalcidol, there is no sense of examining the plasma concentration of 25-hydroxycholecalcipherol (standard marker of vitamin D saturation in the body), as this substance is circumvented with this therapy. The primary final effect of the treatment is the increased calcium and phosphate absorption from the gut. Blood levels of these minerals should be regularly monitored during the therapy.

Amyloid A family of fibrillar proteins depositing in different tissues in primary and secondary amyloidosis. Their molecules have a typical folded leaf structure

(anti-parallel β-structure). Chemically they are composed of the two different types AL (amyloid light) and AA (amyloid associated). The amyloid AL fibres consist of light-chain immunoglobulins or their fragments, whereas amyloid AA consists of non-immunoglobulin fibroproteins. The precursor of amyloid A is a serum amyloid P (SAP) which belongs to an important group of acute phase proteins and is an integral part of high-density lipoproteins (HDL). Besides these two forms AL and AA, amyloid deposits comprise to a lesser extent the amyloid P (AP) component, whose precursor is serum amyloid P.

Deposition of amyloid can result from an inflammatory, hereditary or neoplastic origin. Primary (genetically predisposed) amyloidosis is rare. Secondary and reactive amyloidosis is occasionally the consequence of a number of chronic and recurrent diseases, e.g. leprosy, tuberculosis, bronchiectasis, systemic lupus erythematosus, juvenile idiopathic arthritis and rheumatoid arthritis. It is characterised by extracellular deposition of insoluble protein fibres in a number of tissues, including the spleen, liver, kidneys and lymphatic nodes, leading eventually to death. In the liver, the vessels of the portal system are most affected; sometimes, in the advanced stage, the space of Disse is filled with amyloid. In the myocardium, the amyloid is deposited in the vessels and basal membranes of cardiomyocytes, whilst in kidneys it is deposited in the mesangial loop and in the advanced stage in the perimeter of the glomeruli. Primary systemic amyloidosis is caused by the overproduction and insufficient elimination of light-chain immunoglobulins (mainly lambda) and occurs in multiple myeloma (approximately 20 % of myelomas). Secondary amyloidosis is caused by deficient elimination of acute phase protein cleavage products and accompanies chronic autoimmune and systemic inflammatory processes. The deposits consist of 85–90 % of amyloid A and 10–15 % of amyloid P. It is therefore referred to as amyloidosis AA. The AP component can be found also in other forms of amyloid plaques, including those present in the brain in Alzheimer's disease. Amyloidosis AL with fibrillar deposits formed by light-chain immunoglobulins occurs frequently in multiple myeloma or Waldenström's macroglobulinaemia. Usually it affects the heart, gastrointestinal and respiratory systems, peripheral nerves and the tongue. Amyloidosis can also occur due to age.

► *Symptoms and signs*

- Latent course.
- Prominent weakness, dyspnoea, oedema, weight loss, orthostatic collapse and macroglossia.
- Subsequently there are signs of nephrotic syndrome, cardiomyopathy, speech disorders and polyneuropathy.

Amyopathic dermatomyositis A dermatomyositis subgroup – see Idiopathic inflammatory myopathies (IIM). Patients have skin changes characteristic of dermatomyositis, but without muscle weakness. Some patients show subclinical signs of myositis (laboratory, electromyographic, histological), in which case the disease is

classified as hypomyopathic dermatomyositis. Patients with amyopathic and hypomyopathic dermatomyositis may develop conventional dermatomyositis within 6 months.

Anabolic steroids Anabolic steroids having a generalised anabolic effect but are no longer recommended in treating osteoporosis because of their adverse effects (virilisation, hepatopathy, unfavourable influence on the metabolism of lipids, etc.). Theoretically it can be used in elderly women with low bone turnover. In male osteoporosis secondary to hypogonadism, testosterone derivatives are the treatment of choice.

Anaesthesia dolorosa Severe spontaneous pain occurring in an anaesthetised region.

Anakinra Anakinra (Kineret®) is a competitive antagonist at interleukin 1 (IL-1) cell surface receptors, but without any agonist activity. Anakinra inhibits the biological activity of interleukin 1α and 1β (IL-1α and IL-1β).

IL-1 is considered to be a critical mediator of inflammation and joint damage in rheumatoid arthritis. In November 2001 the FDA approved anakinra, for rheumatoid arthritis patients who have failed one or more disease-modifying antirheumatic drugs (DMARD). Anakinra is given 100 mg per day subcutaneously using a prefilled syringe. Though not approved by FDA or EMA, anakinra is sometimes used for adult-onset Still's disease, gout and pseudogout, juvenile arthritis, ankylosing spondylitis, uveitis and autoinflammatory syndromes.

Analgesia Painful stimulus does not elicit pain. It can be linked to a change of perception of other modalities.

ANCA Autoantibodies against the cytoplasm of neutrophils (antineutrophil cytoplasmic antibodies). ANCA participate in the pathogenesis of systemic vasculitides and glomerulonephritis. These antibodies are directed against several enzymes or other proteins located, predominantly, in the azurophilic granules of neutrophils. Using the indirect immunofluorescence method, it is possible to differentiate three types of ANCA during a reaction with the neutrophils:

1. Diffuse fine granular cytoplasmic fluorescence (c-ANCA) can be found in most cases of granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA). Protease 3 is the specific antigen (PR3-ANCA).
2. Perinuclear fluorescence (p-ANCA) is found in eosinophilic granulomatosis with polyangiitis (EGPA). These antibodies are often directed against myeloperoxidase, elastase, cathepsin G, lactoferrin, lysozyme and beta-glucuronidase.
3. 'Atypical' ANCA includes neutrophil nuclear fluorescence and some unusual cytoplasmic patterns, and whilst a few of the target antigens are shared with p-ANCA, the others have not been identified. p-ANCA or atypical ANCA occur in ulcerative colitis, primary sclerosing cholangitis, Crohn's disease, rheumatoid arthritis and SLE.

Ankylosing hyperostosis – see Diffuse idiopathic skeletal hyperostosis (DISH; ankylosing hyperostosis; Forestier's disease)

Ankylosing spondylitis (AS; Bechterev's disease) A chronic systemic inflammatory disorder belonging to the group of seronegative spondylarthritides affecting predominantly the axial skeleton, sacroiliac, apophyseal and costovertebral joints of the spine. Much of the pathology occurs at the entheses. Secondary metaplasia of the inflamed tissue of anterior and lateral borders of the vertebrae causes a gradual ossification of the peripheral part of fibrous annulus of the intervertebral disc and adjacent ligaments. Occasionally, peripheral joints are also affected. The shoulder and hip joints are affected in up to 50 %, with other joints affected in about 20 %. Extraspinal organ involvement such as iritis and aortal valve disease is less frequent than in rheumatoid arthritis, but inflammatory bowel disease can occur in 5–10 % of patients. Pulmonary fibrosis, amyloidosis and neurological signs of compression can be observed in late disease.

► *Symptoms and signs*
- Pain with stiffness in the back of inflammatory nature
- Movement limitation of the spine in all three planes
- A trend towards development of spinal deformity
- Occasionally, peripheral arthritis, mostly of hip and shoulder joints and joints of the lower extremities
- Extraspinal organ manifestations (ocular, skin, mucosal, cardiovascular, pulmonary, neurological, IgA nephropathy and amyloidosis)
- Radiological presence of sacroiliitis, syndesmophytes and peripheral enthesopathy
- High association with HLA-B27 antigen

Anorexia nervosa A disorder characterised by low body weight (BMI usually under 17.5) with an intense wish to remain thin, amenorrhoea and relative hypercorticism. It most commonly affects adolescents. All these factors cause a significantly decreased bone density in women with anorexia nervosa.

Antibodies Immunoglobulins produced by plasma cells that originate from B lymphocytes after specific antigen stimulation. They play two major roles in the humoral immune system. The first is antibody specificity, the essence of which represents the recognition and binding to complementary antigen determinants (recognising function). The second role includes specific biological functions, which are referred to as effector functions. These represent the ability to bind to specific Fc receptors of various cells, to activate complement, to transfer through the placenta, etc. All of these activities are induced by interaction with specific antigen, but different parts of immunoglobulin than the binding side are responsible for these functions. Antibodies are present in serum and other body fluids or inside the producing cells. They can be divided depending on their structure (different classes of immunoglobulins), how they are produced (conventional and monoclonal antibodies) or depending on their properties (anti-idiotypic, cytophilic, cytotoxic, etc.).

Antibodies against cyclic citrullinated peptides (anti-CCP antibodies; anti-citrullinated peptide antibodies, ACPA) Anti-CCP antibodies (ACPA) have a high specificity and sensitivity for rheumatoid arthritis (RA). They belong to the IgG class and have more than 56 % sensitivity and more than 90 % specificity for RA, depending on the assay kit used. They are directed against peptides and proteins, which possess the unusual, non-standard amino acid citrulline. Citrullinated proteins develop during enzymatic posttranslation enzymatic deimination of arginine residues catalysed by peptidylarginine deiminases in the presence of Ca^{2+}. Such posttranslational modification of proteins leads to loss of the positive charge of arginine residues with subsequent modification of antigenicity of the proteins. Antiperinuclear factor, antikeratin antibodies (both directed against citrullinated filaggrin), anti-Sa antibodies (against citrullinated vimentin) and cyclic citrullinated peptide antibodies (anti-CCP) are amongst the best-known citrullinated reactive antibodies associated with RA. Recently, it has been shown that the basic component of the antigenic epitope of filaggrin and vimentin is citrulline. The formation of citrullinated antigens is a dynamic process that takes place in inflamed synovia in the presence of peptidylarginine deiminases (PADs). Five subtypes (PAD 1, 2, 3, 4 and 6) are known. Expression of PAD4 isotype with increased enzymatic activity is typical for RA. Anti-CP antibodies (ACPA) are produced in the area of inflammation and pannus, probably by plasma cells and B cells.

Apart from high specificity, antibodies against citrullinated peptides are typically present in the very early stage of RA. Their presence is associated with the more active and severe forms of the disease. A combination of these antibodies with rheumatoid factor increases the specificity and positive predictive value of these markers and enables early intervention. Currently, ELISA methods are used to assess antibodies against citrullinated peptides and cyclic citrullinated peptide antibodies (anti-CCP). Measurement of ACPA is now the most frequent assay in clinical practice.

Antibodies against Ku antigen Ku antigen is a heterodimer of two peptides consisting of units with MW = 70 kDa and MW = 80 kDa, which are present in the nucleus and nucleolus. Ku protein is a component of DNA-dependent protein kinase. Ku antigen binds the enzyme to DNA and helps in DNA repair. Anti-Ku antibodies were first found in patients with scleroderma–polymyositis overlap syndrome in Japan. Apart from Japan, these antibodies are frequently found in patients with systemic lupus erythematosus or mixed connective tissue disease. In addition, such antibodies have been found in some patients (23 %) with primary pulmonary hypertension. Anti-Ku antibodies induce macular fluorescence of the nucleus with nucleolar fluorescence when cells are in the G1 phase of the cell cycle.

Antibodies against U1RNP and Sm antigen Antibodies present in systemic lupus erythematosus (SLE) directed against small nuclear ribonucleoprotein particles (smRNP). They are usually autoantibodies against proteins complexed with small nuclear RNA. Anti-Sm antibodies (antibodies against Sm antigen or Smith antigen named in honour of the first patient with SLE where anti-Sm antibodies were found)

are very specific to SLE. However, their sensitivity is low (10–30 % of patients with SLE). Anti-Sm antibodies are almost always accompanied by the presence of anti-U1RNP antibodies; a contrary relationship does not apply.

The clinical correlation of anti-Sm is not significant, some studies report a more frequent presence in central nervous system disease, nephritis, lung disease, pericarditis and their correlation with disease activity. In 1972, Sharp described antibodies against an extractable nuclear antigen (subsequently defined as U1RNP) and its association with mixed connective tissue disease (MCTD, Sharp's syndrome; first described 1972 by Gordon C. Sharp, American physician). Antibody against U1RNP is also found in SLE but usually with low titres. Interestingly, many of the features of MCTD, particularly fibrosing alveolitis, myositis, arthritis and Raynaud's phenomenon, were found in these patients.

Anticardiolipin antibodies – see Antiphospholipid syndrome (APS).

Anticentromere antibodies – see Systemic sclerosis (SSc).

Anti-citrullinated peptide antibodies – see Antibodies against cyclic citrullinated peptides.

Anti-DFS70 antibodies Autoantibodies directed against a 70 kD protein in the cell nucleus. Anti-DFS70 antibodies may be recognised within the routine screening test for ANA by indirect immunofluorescence on HEp-2 cells showing a uniformly distributed fine speckled nuclear staining in interphase cells and a positive fine speckled fluorescence in the chromosomes of mitotic cells. Confirmation is given by specific immunoassays. Anti-DFS70 antibodies have been proposed as useful biomarkers to exclude systemic autoimmune rheumatic diseases (SARD).

Anti-dsDNA antibodies

Anti-DNA antibodies form a heterogeneous group directed against different antigen determinants of DNA. Several groups are differentiated:

Antibodies reacting only with the double-stranded DNA (dsDNA). These antibodies form the majority and are found in the sera of 65 % patient sera with systemic lupus erythematosus (SLE) react with dsDNA.

Antibodies cross-reacting with dsDNA and ssDNA (single-stranded DNA). These antibodies are the most frequent in SLE.

Antibodies reacting solely with ssDNA.

Antibodies reacting with Z conformational DNA (Z-DNA).

Clinical importance of anti-dsDNA antibodies:

- High levels of anti-dsDNA antibodies are associated especially with SLE.
- Circulating anti-dsDNA can be found in IgM, IgG and sometimes IgA classes.
- IgG antibodies are more significant than IgM; their presence correlates with the activity of the disease and severity of glomerulonephritis.

- This correlation to glomerulonephritis can be found mainly with complement fixating and activating antibodies especially IgG anti-DNA.
- IgG antibodies occur in four subgroups with prevalence of IgG1 and IgG3.
- Single-shot assessment of anti-dsDNA is highly diagnostic, though for determining prognosis longitudinal follow-up is recommended. In most cases a rise in anti-dsDNA levels indicates an exacerbation of the SLE.

Mechanism of renal impairment by anti-dsDNA antibodies in SLE:

- Anti-dsDNA binds to histone complexes and DNA having affinity to heparin sulphate of glomerular basement membrane.
- Anti-dsDNA with the ability to cross-react with several other antigens like A- and D-peptides of small nuclear RNP or ribosomal P-protein can have a direct impairing influence on renal cells by penetration into cytoplasm and nucleus or by binding to the cell surface with subsequent binding of the complement and cytolysis.

Antiepileptic drug-induced osteopathy Approximately half of patients on long-term treatment with antiepileptic drugs have biochemical manifestations of osteopathy (hypocalcaemia, hypercalciuria, hypovitaminosis D, increased osteoresorption markers, hyperparathyroidism), and in some these manifestations are connected with reduced bone mineral density which increases the patient's risk of fracture. The number of fractures in epilepsy patients is twice the number suffered by the remaining population. The aetiopathogenesis of the interference of antiepileptic drugs with the bone metabolism has not been fully explained yet. The antiepileptic drug-induced osteopathy becomes clinically relevant in particular in combination with other risk factors of osteoporosis (see Osteoporosis – Risk factors). Cytochrome P 450 inducers (especially phenytoin) accelerate degradation of vitamin D metabolites and therefore are the cause of the most serious osteopathias – osteopenia and osteoporosis; in a group of epilepsy patients treated at inpatient institution, they were also the cause of high number of osteomalacia (see Osteomalacia). The use of valproate, which inhibits cytochrome P450, is associated with higher incidence of osteoporosis and osteoporotic fractures; however, the cause has not been explained. Topiramate and zonisamide are antiepileptic drugs inhibiting carbonic anhydrase and may cause acidosis and hypercalciuria meaning that they present a risk for the patients in the form of osteoporosis and formation of uric stones. Novel antiepileptic agents, e.g. lamotrigine, seem safe in adult patients in terms of the osteopathy risk, or there are missing data regarding their adverse effects on the skeleton.

Antigen presentation Modification of antigen into a form that can be recognised by T lymphocytes and thus activate the immune response. Currently, most of the available information relates to the presentation of protein antigens. The presentation of exogenous and endogenous protein antigens differs slightly. In the exogenous pathway of antigen presentation, the antigen must first be phagocytosed by antigen-presenting cells (APC) where its further transformation takes place. This is a complicated process in the course of which its molecule is fragmented within endosomes of APC to immunogenic fragments (peptides containing usually 12–20

amino acids), which bind to a certain location (binding channel) in the molecule of MHC (HLA class II in humans) products (antigens). This complex is transferred to the surface of APC and recognised by T-helper lymphocytes. The T_H lymphocyte through its antigen receptor (TCR) recognises only complexes in which immunogenic peptide is firmly bound in the binding channel of HLA class II molecules. The T_H lymphocyte does not recognise free or weakly bound peptide fragments, and this is the basis of the specificity of the subsequent immune response. The binding of immunogenic peptide to TCR is the first signal to 'attract the attention' of the specific T_H cell clone. For their activation and initiation of the immune response, T_H lymphocytes must also obtain the second (confirming, co-stimulating) signal, which mediates interaction of co-stimulation molecules (e.g. CD28 on the surface of T lymphocyte and CD80 on the surface of APC).

Antigens originating from cells infected by viruses or antigens associated with malignancies are subject to an endogenous pathway of presentation. Moreover, in this case, the antigen is first degraded in the cytoplasm of the affected (target) cell in an organelle referred to as proteasome. Thereby, immunogenic peptides, containing mainly 8–9 amino acid units, are formed, and these peptides bind to synthesised HLA class I molecules. This complex is transferred to the surface of the cell where it is recognised by cytotoxic T lymphocytes, which initiate lysis of the 'target' cell. The capability of T_H lymphocytes to recognise immunogenic peptide incorporated only into HLA class II molecules and T_C lymphocytes only into HLA class I molecules is referred to as immunologic restriction. A significant majority of antigens undergo such a presentation. The exceptions are certain polysaccharide antigens, which can be recognised directly by B lymphocytes without T_H lymphocytes and superantigens that non-specifically activate a large number of T_H lymphocyte clones. Other exceptions are glycolipid and lipid antigens that are presented by CD1 molecules instead of HLA molecules.

Antigen targets of antinuclear antibodies (ANA) in the cell (antibodies against intranuclear antigens).

- Chromatin – essential components of the chromatin are DNA, histones and non-histone nuclear proteins.
- Nuclear membrane and pores.
- Nucleolus.
- RNA complex with the proteins (ribonucleoproteins; RNP).
- Matrix–fibrillar skeleton of the nucleus.
- Different components of cytoplasm, e.g. enzymes, ribosomes or RNP.

Antihistone antibodies and antinucleosome antibodies Histones are alkaline nuclear proteins containing a great amount of positively charged amino acids (lysine, arginine). They are present in eukaryotic cells associated with DNA. There are five main types of histones – H1, H2, H2B, H3 and H4. Histones rich in H3 and H4 form a tetramere, binding lysine-rich dimers of H2A-H2B on both sides. These histones form a central core encircled by two threads of a 146-nucleotide long

segment of DNA. This structure is called a nucleosome, and individual nucleosomes are interconnected by a segment of DNA with a bound H1 histone.

Anti-idiotypic antibodies Antibodies directed against idiotypic determinants of immunoglobulins (immunoglobulins, idiotypes). Antigenic determinants created by the combining site of an antibody (immunoglobulin) are called idiotypes, and antibodies directed against these idiotypes are anti-idiotypic antibodies.

Anti-immunoglobulin antibodies Antibodies directed against antigenic determinants, which are present on the surface of immunoglobulin molecules. Basically they can be divided into anti-isotypic, anti-allotypic or anti-idiotypic antibodies. Antibodies against isotypic determinants define the competence of antibodies to particular classes and subclasses of immunoglobulins and are utilised in the diagnostic assessment of their concentrations in various immunochemical methods.

Anti-Jo-1 antibodies – see Antisynthetase syndrome.

Anti-La antibodies – see Anti-SSA/Ro and anti-SSB/La antibodies.

Antimalarial drugs Misleading nomenclature for drugs used in rheumatology as not all preparations applied for the treatment of malaria are used in rheumatology as well. It applies only to quinoline derivates, namely, only the two 4-aminoquinoline derivates chloroquine and hydroxychloroquine that differ from each other only by substitution of the hydroxyethyl group for the ethyl one on the tertiary nitrogen atom on the lateral chloroquine chain.

Mechanism of action in autoimmune diseases The exact mechanism of action of antimalarial drugs is unknown. Possible mechanisms are shown in Table 1. Probably intensive accumulation of chloroquine in the intracellular lysosomal system of lymphocytes, fibroblasts and polymorphonuclear cells is needed. This, in consequence, affects different functions of cellular functions, such as protein glycosylation, membrane lipid digestion and cell receptor development, which can be influenced by alkalisation of normally acidic lysosomal pH or by influencing the elimination and function of acidic proteases. Antimalarial drugs further inhibit multiple functions of

Table 1 Mechanism of action of antimalarial drugs in autoimmune diseases

Accumulation in lysosomes
Affects antigen processing
Decreases antibody formation
Decreases activity of NK cells
Decreased release of IL-1, IL-2 and TNF-α
Prevention of receptor-dependent lysosomal endocytosis
Decreases receptor formation at lower density
Decreases influenza and adenoviral receptor internalisation
In *Plasmodium malariae* infection
Decreases activity of lysosomal acidic proteases and so the degradation of haemoglobin-invaded erythrocytes

phagocytes, including the release of reactive oxygen species. Antimalarial drugs can also influence the antigen processing ability of the monocyte–macrophage system, thus inhibiting the function of lymphocytes. The release of interleukin-1 is also inhibited.

Further action of antimalarial drugs (decrease in lipidaemia, anti-platelet aggregation effects and hypoglycaemic effects) The decrease in platelet aggregation with antimalarial drugs has been known for some time. Unlike the similar effect of salicylates, no prolongation of bleeding time has been observed in antimalarial drugs. This led Charnley, otherwise a pioneer in total hip joint replacements, to use antimalarial drugs as a prophylactic treatment against deep venous thromboses after implantation of hip joint prostheses. A study was carried out involving 10,000 patients who were administered 600–800 mg of hydroxychloroquine per day 1 to 2 weeks after surgery; a significant drop in the rate of thrombotic complications was observed. Retrospective and prospective studies showed a lower incidence of venous, as well as arterial, thrombotic complications in patients with systemic lupus erythematosus (SLE) treated with antimalarial drugs. Even in the group of patients at high risk with the presence of antiphospholipid antibodies, there was a decrease in the rate of thrombembolic events. In a study spread over 9 years, in a group of 54 patients treated with hydroxychloroquine, there were only 2 (4 %) thrombembolic events, whereas in the group without hydroxychloroquine this figure was 20 %.

In studies, it was also shown that antimalarial drugs decreased the total cholesterol, LDL-cholesterol and triglycerides by 10–15 % in patients treated over the long term. This is indirectly related to a possible decrease in steroid dose in these patients. Antimalarial drugs increase the number of LDL receptors and decrease the cholesterol synthesis in the liver. The hypoglycaemic effect of antimalarial drugs has not been completely explained so far; it is likely to be due to an increase in insulin binding to its receptor.

A combination of corticosteroid-sparing effect, hypoglycaemic effect, lipid-lowering effect and anti-platelet aggregation effect leads to an overall decrease in cardiovascular events with antimalarial drugs.

► *Pharmacokinetics*

Chloroquine and hydroxychloroquine are rapidly absorbed after oral administration. The bioavailability varies between 75 and 90 %. The average time needed for absorption of 50 % of the preparation is 4.3 h.

The biological half-life of antimalarial drugs is very long, up to 40 days, which means a steady state is reached in 3–4 months. Antimalarials accumulate predominantly in the acidic environment of lysosomes. This explains their high accumulation in the liver that is rich in lysosomes and low accumulation in muscle, which have a low amount of lysosomes. A significant accumulation can also occur in ocular tissues, especially those containing melanin. The majority of the absorbed drug is excreted in urine in an unaltered state; only 1/3 of the drug is metabolised through removing of ethyl group on the terminal amino ethyl group of the lateral

chain. The therapeutically effective serum concentration of chloroquine is thought to be in the range 700–1200 ng/mL, but this has not been entirely confirmed.

► *Dosage*

The recommended daily dose of chloroquine is 250 mg/day. The therapeutic effect of antimalarial drugs takes up to 3 months of continuous daily administration. In the course of treatment, it is essential to have regular eye checks, including ophthalmic examination, visual acuity and colour vision (every 12 months). In patients over 60 years of age, it is advisable to have an ophthalmic assessment prior to initiating treatment because of the stronger probability of developing degenerative changes, especially with coincident disorders (arterial hypertension and diabetes mellitus). In recent years, hydroxychloroquine has been favoured more than chloroquine as it has a safer profile with far less ocular toxicity. It is commenced at 200 mg twice a day and then reduced to 200 mg daily after 3 months if effective. It is now often combined with methotrexate in moderate to severe rheumatoid arthritis.

► *Clinical efficacy*

The results of long-term controlled clinical trials performed over the last 40 years have shown that chloroquine and hydroxychloroquine are effective in mild rheumatoid arthritis (RA). When administered, they have demonstrably better efficacy compared to placebo and can decrease the clinical activity of the inflammatory process measured. Antimalarial drugs decrease the activity of acute phase reactants but have failed to slow the rate of erosive progress on X-rays in clinical trials. Its efficacy is comparable to d-penicillamine but lower than sulphasalazine and intramuscular administration of gold compounds. Antimalarial drugs are indicated in rheumatoid arthritis with mild clinical activity, especially in cases without unfavourable prognostic signs.

Furthermore, antimalarial drugs are used in juvenile idiopathic arthritis, SLE and psoriatic arthritis.

► *Adverse effects related to treatment with chloroquine and hydroxychloroquine*

- *Gastrointestinal*: anorexia, nausea, vomiting, epigastric pain, spasms, diarrhoea and weight loss
- *Skin*: rashes, pruritus, pigmentations of the skin and nails, photosensitivity and exacerbation of psoriasis
- *Neurological*: headache, drowsiness, insomnia, irritability, tinnitus, proximal myopathy, myasthenic syndrome, polyneuropathy and lowered threshold for seizures
- *Haematological*: toxic granulation of leukocytes, leucopenia, agranulocytosis, aplastic anaemia
- *Ocular*: accommodation disturbances, diplopia, corneal deposits, retinopathy,
- *Other*: arrhythmia, cardiomyopathy and porphyria

Anti-Mi-2 – see Idiopathic inflammatory myopathies (IIM).

Antineutrophil cytoplasmic antibodies – see ANCA.

Antinuclear antibodies (ANA) Antinuclear antibodies (ANAs) are antibodies recognising a naturally occurring protein (or self-protein) as foreign and might start

a cascade of inflammation, causing the body to attack itself. The recommended screening test for ANA is the indirect immunofluorescence test on HEp-2 cells. ANA subtypes (anti-ENA antibodies) may be identified by specific tests (immunoassays). ANAs are a useful and initial cost-effective screening test for patients suspected of having a systemic

Anti-PCNA/cyclin antibodies (proliferating cell nuclear antigen) DNA-polymerase delta-associated protein with a molecular weight of 36 kDa. The antibodies are highly specific for systemic lupus erythematosus, but they are rare (approximately in 6 %). One suggestion is that anti-PCNA-positive patients more frequently have diffuse proliferative glomerulonephritis and lymphadenopathy. Positive immunofluorescence of the nuclei occurs only in rapidly dividing cells because the amount of PCNA rises proportionally to synthesis and cell growth.

Antiphospholipid syndrome (APS) A syndrome with the following:

► S*ymptoms and signs*
Venous or arterial thrombosis, or both, often multiple, repeated miscarriages and pregnancy failures and moderate thrombocytopenia; all with the presence of lupus anticoagulant (LA), elevated aCL (anticardiolipin antibodies), or both.

Diagnostic criteria of primary/secondary APS:

- Clinical signs: venous thrombosis, arterial thrombosis and repeated miscarriages (pregnancy failures)
- Laboratory findings: thrombocytopenia, IgG-aCL (moderate/high levels), IgM-aCL (moderate/high levels) and positive test for LA

Diagnostic criteria for APS: one clinical sign including thrombocytopenia and the presence of aCL (>20 GPL units) or presence of LA; evidence of antiphospholipid antibodies (aPL) on two occasions at least 6 weeks apart; up to 5-year follow-up of the patient to eliminate systemic lupus erythematosus (SLE) or other autoimmune disease

In principle we distinguish primary APS, i.e. it is impossible to show evidence of other concomitant autoimmune disorder, especially SLE, over at least 5 years, and secondary APS when the patient, besides APS, also suffers from SLE or drug-induced lupus or another autoimmune disorder.

Some authors broaden out the possible disorders, likely related to the presence of aPL, into two basic groups:

1. Disorders elicited by aPL without a direct connection to thrombosis
   - *Neurological*: Guillain-Barré syndrome, transversal myelitis, chorea and migraine
   - *Obstetric*: pre-eclamptic toxaemia and eclampsia and postpartum serositis
   - *Other*: non-thrombogenic (idiopathic) pulmonary hypertension, avascular necrosis of the bone.

2. Disorders elicited by aPL with a direct connection to thrombotic vascular signs
   - Veins:
     Limbs: thrombophlebitis
     Liver:
     – Major vessels, Budd–Chiari syndrome
     – Hepatomegaly and increased concentration of enzymes
     Adrenal glands: Addison's disease and adrenal insufficiency
     Lungs: pulmonary embolism and thrombembolic pulmonary hypertension
     Skin: livedo reticularis, skin nodules, chronic venous ulcers and superficial purpura resembling a vasculitis
     Eyes: venous thrombosis of the retina
   - Arteries:
     Limbs: ischaemia and gangrene
     Brain:
     – Major vessels: acute stroke and transient ischemic attack
     – Minor vessels: acute ischaemic encephalopathy and multi-infarct dementia
     Heart:
     – Major vessels: myocardial infarction
     – Minor vessels: acute (circulatory collapse and cardiac arrest) and chronic (cardiomyopathy, arrhythmia and bradycardia)
     Kidneys:
     – Major vessels: renal artery thrombosis
     – Minor: thrombotic renal microangiopathy
     Liver: infarction of the liver
     Aorta:
     – Upper part: aortic arch syndrome
     – Abdominal part: claudication
     Skin: gangrene of the fingers
     Eyes: thrombosis of arteries and arterioles of the retina
     Endocardium and valve
     – Acute: vegetations, 'pseudoinfectious endocarditis'
     – Chronic: valvular dysfunction (regurgitation, stenosis)
     Sneddon's syndrome – coincidence of stroke, hypertension and livedo reticularis

A proposal of new classification criteria of APS (Sapporo 1999 [revised 2006]; Wilson et al. 1999; Miyakis et al. 2006; Lockshin et al. 2000; Weber et al. 2001; Garg and Deodhar 2012):

Antiphospholipid antibodies – the presence of aPL (aCL or LA) demonstrated at least twice at least 6 weeks apart with one or more clinical signs.

► *Clinical symptoms and signs*

- Arterial or venous thrombosis (or both) demonstrated radiographically, by ultrasound or histologically
- Three or more consecutive miscarriages (up to 10th week) unexplained by other reasons, or one or more deaths of morphologically normal foetus after

the 10th week of pregnancy, or one or more still births after the 34th week of pregnancy accompanied by serious pre-eclampsia or placental insufficiency
- Two or more episodes of reversible cerebral ischemia
- Occurrence of multiple sclerosis-like syndrome or otherwise unexplainable focal neurological deficit

Additional features, no criteria:
- Thrombocytopenia below 100,000/mm^3
- Haemolytic anaemia with reticulocytosis and positive Coombs test
- Otherwise unexplainable transversal myelopathy
- Livedo reticularis
- Otherwise unexplainable thickening of mitral or aortal valve and regurgitation demonstrated on echocardiography
- Unexplained chorea observed by a physician
- Migraine lasting 1 year with concomitant presence of aPL in the serum

Anti-Ro antibodies – see Anti-SSA/Ro and anti-SSB/La antibodies.

Anti-SRP antibodies – see Idiopathic inflammatory myopathies (IIM).

Anti-SSA/Ro and anti-SSB/La antibodies Anti-La antibodies occur practically together with anti-SSA/Ro antibodies, but not vice versa as in the case of the relation between anti-Sm and anti-U1RNP antibodies. Anti-SSA/Ro can be found in primary Sjögren's syndrome and systemic lupus erythematosus (SLE). There are two Ro antigen peptides (Ro60 and Ro52) differing from one another according to molecular weight. The bond with Ro60 and Ro52 is in some cases distinct in SLE and systemic sclerosis (SSc). Approximately 40 % of patients with SSc who are anti-Ro positive have antibody only to Ro52 and 20 % of sera from SLE patients to only Ro60. Other patients in both groups have antibodies to both Ro peptides, which is why this difference doesn't have much clinical significance.

The presence of anti-SSA/Ro and anti-SSB/La antibodies is clinically significant because of their association with several SLE subtypes: subacute cutaneous lupus, neonatal lupus and SLE in C2 and C4 deficiencies. Likewise, there exists an association between patients with pneumonitis and renal disturbance with the presence of anti-SSA/Ro antibodies in the serum.

There are certain differences amongst patients with only anti-SSA/Ro or in combination with anti-SSB/La.

Characteristics of patients with anti-SSA/Ro and anti-SSB/La antibodies

Anti-SSA/Ro	*Anti-SSA/Ro + Anti-SSB/La*
More frequent HLA-DR2	More frequent HLA-DR3
Young patients	SLE in the elderly
Frequent homozygotes for C2 and C4 deficiencies	No relation with complement deficiency

Association between the presence of anti-SSA/Ro or anti-SSB/La and congenital heart block The risk of congenital heart block is probably highest when the mother's serum contains a combination of anti-SSA/Ro and anti-SSB/La and in the case of antibodies against Ro52 antigen.

Anti-SSB/La antibodies – see Anti-SSA/Ro and anti-SSB/La antibodies.

Antisynthetase syndrome Myositis and interstitial pulmonary fibrosis with fever, arthritis, Raynaud's phenomenon and thickened, fissured radial margins of index fingers on both hands (the so-called car mechanics' hands). Typically, serum antibodies against cytoplasmic enzymes are present (aminoacyl-tRNA synthetases), e.g. anti-Jo-1.

Apoptosis Programmed cell death in multicellular organisms. It can be regarded as the opposite of mitosis. Multicellular organisms keep their integrity not only based on the ability to form new cells as a replacement for those worn-down and withered but also by regulated apoptosis. This is an active process going on by continuously eliminating unwanted and unnecessary cells. It is applied, for example, in disposing of those T lymphocytes that are able to react with self-antigens and so cause an autoimmune response. It is, however, a common biological event and not unique to the immune system. Apoptosis is regulated by growth factors, several cytokines and oncogenes. Cells undergoing apoptosis are mainly proliferating ones that failed to get the necessary signalling ensured by growth factors during their development or, on the contrary, got an apoptotic signalling. The signalling is often produced by TNF, lymphotoxin or Fas-ligand. In the cell, the apoptotic signalling causes water loss and an increase in intracellular ionised calcium concentration. This leads to chromatin condensation and activation of the endonucleases that split the DNA to 50–300 kb fragments, leading to cell death and its disintegration into smaller fragments ingested by surrounding phagocytes without the development of an inflammatory reaction. Proteolytic enzymes mainly the so-called caspases participate in this process. The second mechanism of terminating cells in a multicellular organism is necrosis. It is, however, morphologically and by its mechanism, distinct form apoptosis.

Apremilast A drug (Otelza®) belonging to the group of so-called small molecules. Apremilast is an oral selective inhibitor of phosphodiesterase 4 (PDE4) approved in two therapeutic indications. For the treatment of moderate-to-severe chronic plaque psoriasis in adult patients who failed to respond to or, who have a contraindication to or are intolerant to other systemic therapy including cyclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA). Apremilast is indicated alone or in combination with DMARDs for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy.

Apremilast works intracellularly to modulate a network of pro-inflammatory mediators. PDE4 is the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels, which in turn downregulates the inflammatory response

by modulating the expression of pro-inflammatory and anti-inflammatory cytokines.

APS – see Antiphospholipid syndrome (APS).

ARA diagnostic criteria of SLE – see Systemic lupus erythematosus (SLE).

Arachidonic acid A polyunsarurated fatty acid found in the phospholipids of cell membranes from which it is released by the activity of phospholipases A_2 or C. The free arachidonic acid has a short half-life and rapidly metabolised by either cyclooxygenase or lipoxygenase. In the cyclooxygenase pathway, prostaglandins, prostacyclin and thromboxane occur, whilst the lipoxygenase pathway produces leukotrienes or lipoxins.

Arthritis associated with erythema nodosum in the course of infection Erythema nodosum (EN) is characterised by painful nodular subcutaneous infiltrates due to an inflammation of the subcutaneous adipose tissue. Its onset may be associated with the use of certain drugs (penicillin, sulphonamides, contraceptives, etc.), sarcoidosis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus or neoplasms, but most frequently it is associated with infection. Pathogenically it is most probably a hypersensitive reaction to a trigger factor.

► *Clinical picture*
The red nodules are 1–10 cm in size; they take the form of subcutaneous prominent infiltrates and are usually painful. They are localised most frequently on the lower extremities. They are generally of time-limited duration and often spontaneously resolve in 6–8 weeks. In approximately half of cases, joints (arthralgia, arthritis) are affected. Acute arthropathy in EN can be easily distinguished from chronic arthropathy in sarcoidosis with EN. In some cases the occurrence of EN can be regarded as the symptom of a clinically well-defined disease (e.g. post-Yersinia reactive arthritis).

Arthritis Impact Measurement Scale (AIMS) – see Instruments of assessing (health status measurements, outcome measurement).

Arthritis Impact Measurement Scales 2-Short Form (AIMS2-SF) The AIMS2-SF is a shortened version of the AIMS2. It is aimed at measuring health status in individuals with arthritis. The self-administered 26-item measure asks about physical functioning, pain, psychological status and social interactions. Items assessing health perceptions, demographics and treatment information from the AIMS2 were not included. The range of AIMS1-SF is 0–10. Higher values indicate poorer outcomes.

Arthritis induced by *Salmonella* or *Brucella* infection It occurs rarely, most often in stock breeders and veterinary doctors. Both infections may be accompanied by sacroiliitis and spondylitis. Specific serologic examinations are positive.

Arthritis in brucellosis Infectious arthritis caused by *Brucella* (B) *melitensis*, *B. abortus*, *B. suis* and *B. canis.*

► *Symptoms and signs*
Brucellosis can be accompanied by arthralgia at any stage of the disease. Besides other symptoms and signs, arthritis of peripheral joints can occur, and the sacroiliac joints and the spine can be affected. Rarely osteomyelitis develops.

Arthritis in chronic sarcoidosis In prolonged disease, a polyarthritis similar to rheumatoid arthritis (RA) develops in 30–40 % of afflicted people. The course of the disease is relapsing and remitting, and the most affected joints are the knees, ankles, wrists and (symmetrically) small joints of the hand (MCP, PIP). Dactylitis can occur.

► *Laboratory diagnostics*
Attention should be drawn to a high erythrocyte sedimentation rate, eosinophilia, positive latex-fixation test (that's why this disease could be confused with RA), hypergammaglobulinaemia and negative tuberculin test (Kveim test is no longer performed due to risk of transmitting viruses such as Creutzfeldt disease). A histological picture is also characteristic (noncaseating granulomas).

Arthritis of viral origin

Rubella arthritis

It occurs in 15–20 % of infections overcome in adult age. It may be mono-, oligo or polyarthritis.

Signs: muscle pain and suboccipital lymphadenopathy. Presence of rash is not inevitable.

Laboratory tests. Differential blood count reveals a characteristic prevalence of mononuclear cells, which are also detected in the synovial fluid. Increased antibody titre against rubella may be proven serologically.

Therapy. The disease resolves spontaneously, or a symptomatic therapy is applied.

Infectious mononucleosis

It causes arthritis which is similar to rubella arthritis; other symptoms help to determine the diagnosis. Paul–Bunnell reaction is positive.

Transient coxitis

It occurs in children and during puberty following upper respiratory tract infections. It is likely to be caused by virosis. Laboratory tests are not pathognomic.

Radiological signs. X-ray scan is negative; accumulation of fluid in the joint may be proven by ultrasound examination.

Therapy. The disease resolves spontaneously; it is possible to administer non-steroidal antirheumatic agents.

Trauma-associated arthritis

Traumatic arthritis

May be caused by a stroke, sprain or pulling.

Joint exudates may be bloodily, which however does not necessarily mean an injury to an intra-joint formation (e.g. the meniscus). Most frequently, it means that cruciate ligaments or (also) the joint capsule has been pulled or torn.

It occurs more often in hypermobile, a so-called excessively lax joint.

Therapy. Indication of bed rest, compressions, non-steroid antirheumatic agents, puncture as necessary, glucocorticoids (administered intra-articularly), later mobilisation and physiotherapy.

Arthrogryposis multiplex congenita A syndrome of multiple congenital, non-progressing joint contractures caused by fibrotic changes in periarticular tissue and muscles. It is caused by a mutation in genes encoding proteins inevitable for muscle contractions. The incidence of the disease is 1/3–10,000 live-born infants. It affects all of the extremities in a symmetrical manner with deformities having both flexion and extension nature (most often in upper extremities). Skin folds are pronounced with the onset of pterygia. Fine motor skills, sensation and mental development are usually normal. Arthrogryposis is usually associated with neurogenic disorders (structural brain damage, myelodysplasia), myopathies (congenital muscle dystrophy), connective tissue disorders (e.g. Ehlers–Danlos syndrome) and bone dyplasias (e.g. diastrophic dysplasia, campomelic dysplasia, etc.). The treatment goal (rehabilitation, orthosis, surgical interventions) is to ensure as much self-sufficiency of the patient as possible.

Arthropathy in the course of inflammatory bowel diseases Arthropathy can be a systemic complication of regional enteritis (Crohn's disease) or ulcerative colitis. Most frequently it is a peripheral arthritis, with sacroiliitis occurring less often. The incidence of arthropathy in the course of inflammatory bowel disease is estimated at about 7.5–21 %. The occurrence of sacroiliitis is associated predominantly with the presence of HLA-B27 antigen; there is no known association of HLA with peripheral joint involvement.

► *Symptoms and signs*
Erythema nodosum, but also pyoderma gangrenosum, can be important extra-articular manifestations. The course of the peripheral arthritis mirrors the severity of underlying bowel disease but has no influence on the progression of changes in the axial skeleton

Arthropathy in ochronosis This is principally a degenerative process of known aetiology with a profound tendency to disability. The core of clinical signs and symptoms in ochronotic arthropathy affects the spine. Symptoms begin at the end of the 3rd decade of life. The male to female ratio is 2:1.

Objective signs include flattening of the thoracic kyphosis and lumbar lordosis and a mild rigidity with a tendency to worsening. Gradually in the advanced stages, an unevenness of the contours of the spine appears with irregular prominence of spinous processes and complete ankylosis of the whole lumbar and thoracic spine. The cervical part of the spine preserves its mobility for quite a long time despite considerable radiographic changes. In the advanced stages, extension and rotation movements are limited, with the head in a flexed position. Due to the degenerative changes in the intervertebral discs, the intervertebral spaces narrow down causing a marked decrease in body height over 20 years.

Radiographic examination of the spine shows characteristic calcification of the intervertebral discs. Osteolytic and hyperplastic changes and secondary new bone formation occur on the vertebral bodies. Osteophytes and sporadically massive bone bridging of the ankylosing hyperostosis type are formed.

Arthropathy in thyroid disease Autoimmune thyroid diseases include Hashimoto's thyroiditis and Graves' disease. These diseases can be associated with other rheumatic disorders, such as rheumatoid arthritis, Sjögren's syndrome, systemic sclerosis, polymyalgia rheumatica, giant cell arteritis and relapsing polychondritis. These disorders are often interconnected and have a close relation to HLA-B8 and HLA-DR3 haplotypes. The presence of rheumatoid factor and anti-dsDNA antibodies is often seen in autoimmune thyroiditis. Autoimmune diseases of the thyroid gland develop in patients with systemic lupus erythematosus (SLE), which is often accompanied by the occurrence of antibodies against the thyroid gland. Autoimmune thyroiditis has been reported in Sjögren's syndrome. Polymyalgia rheumatica or giant cell arteritis can be related to the development of autoimmune disease of the thyroid gland. The occurrence of Hashimoto's thyroiditis with rheumatoid arthritis, SLE or other connective tissue diseases has also been reported. On the other hand, Hashimoto's thyroiditis alone can be characterised by a clinical picture of inflammatory polyarthritis not responding to thyroid hormone replacement, which can be erosive with the development of nodules.

Hyperthyroidism The following rheumatic syndromes occur in hyperthyroidism:

- Thyroid acropachy
- Proximal myopathy
- Osteoporosis

Hypothyroidism In hypothyroidism, we often see an arthropathy resembling rheumatoid arthritis, articular chondrocalcinosis or synovitis of the flexors of the hand. There may be carpal tunnel syndrome and a proximal myopathy with muscle hypertrophy.

The following rheumatic syndromes occur in hypothyroidism:

- Arthropathies
- Carpal tunnel syndrome
- Myopathies

Arthroscopic joint washout and cartilage Arthroscopic washout of a joint helps to remove small fragments of cartilage that irritate synovia. The washout can also be combined with arthroscopic debridement of the cartilage ('shaving'). There is evidence that this combined approach provides pain relief and improves the joint function, but does not improve cartilage turnover.

A number of microsurgical arthroscopic techniques have been developed in an attempt to improve cartilage turnover, e.g. small holes are drilled into the subchondral circulation to stimulate the growth of fibrocartilaginous tissue into subchondral bone. Spongialisation, which is resection of the whole subchondral bone disc in chondromalacia patellae, also improves outcomes.

The other method of improving cartilage turnover is to use cartilaginous auto- or allotransplants. This technique is particularly used in young individuals after intra-articular trauma. The area of damage is covered by numerous autologous small transplants (mosaicplasty) or by precisely turned and closely inserted osteochondral transplants to the area of the damaged cartilage.

Frozen allogenic transplants are also used, but they are associated with the risk of immunological rejection. Periosteal and perichondral tissue is also used to cover defects of the cartilage. The main problem with these techniques is the fixation of the transplants to the area of the defect and their frequent calcification. More recently, as part of tissue engineering, autologous cells, which are obtained by small biopsy, e.g. from nasal cartilage, are implanted directly into the subchondral bone.

Articular cartilage – see Hyaline cartilage.

Aseptic necrosis of the navicular bone – see Köhler's disease.

Atopic reactions Anaphylactic reactions occurring in atopic individuals (atopy). Atopic individuals have a genetic predisposition to the development of allergic diseases of hypersensitivity, such as bronchial asthma, allergic rhinitis, urticaria, eczema, certain gastrointestinal disorders, etc. Atopy is a genetically conditioned feature, whereas anaphylaxis is a reaction that occurs more frequently in atopic individuals than in common individuals.

Atrophy A decrease in cell volume and restriction of cell functioning. Atrophy is often seen in regions with insufficient vascular supply or chronic inflammation. It can be a consequence of decreased skeletal muscle activity and can be regarded as an adaptive response to stress, whereby the cells decrease their volume, restrict different functions which leads to a decrease in energy consumption. As soon as the conditions in the affected region normalise, the atrophied cells restore their function and increase their volume. Their specific functions, such as protein synthesis or contractile muscle strength, also normalise.

Inactivity-induced atrophy This most common atrophy is subsequent to decreased requirements for a function, e.g. immobilisation of the limb after a fracture or in long-term confinement. Atrophy of muscle cells and decrease in muscle strength

occur. Restoring the activity leads to normalisation of the volume, function and strength of the muscle.

Insufficient oxygen supply A disturbance of blood supply to the tissues ends with ischaemia. Total ischaemia with interruption of oxygen supply to tissues leads to cell death. A partial ischaemia or incomplete occlusion of the vessel or places with inadequately formed collateral circulation leads to chronic restriction of oxygen supply, and as a consequence the life expectancy of the cells is shortened. This process can be seen in regions of borderline ischaemia, e.g. necrosis (infarction) of heart, brain and kidneys.

Malnutrition Starvation or malnutrition associated with a chronic disease leads to cell atrophy, mainly in skeletal muscles. It is presumed that the cell atrophy is caused by a partial ischaemia leading to under nutrition of the tissues.

Interruption of trophic signalling The function of a number of cells depends on a signal transmitted by chemical mediators (e.g. endocrine system or neuromuscular transmission). Elimination of the sources of signalling (hormonal, transmission, etc.) decreases the requirements of cells of certain organs like adrenal glands, thyroid gland, skeletal muscles and so on. This can happen in the case of endocrine gland removal or muscle denervation.

Persistent cell damage This is caused most often by a chronic inflammation associated with prolonged viral or bacterial infection. It's not clear whether an irritant agent, inflammatory process or both cause the cell damage. In any case, the cells at the place of chronic inflammation often atrophy. Physical damage, e.g. permanent pressure in an unsuitable locality, also induces atrophy.

Cell ageing A process, which is independent of disease. The main cause of ageing of cells, especially those not replicating (heart, brain), is atrophy of such cells. The volume of all parenchymal organs in the body decreases with age. The volume of important organs decreases in old age, and in the very elderly a decrease in volume of the heart can also be seen – senile atrophy.

Atypical mycobacteria-induced synovitis Mycobacteria cause in particular synovitis of the wrist, small joints of the hand, chronic tenosynovitis and less frequently spondylitis.

The diagnosis is confirmed by biopsy which can prove changes caused by tuberculosis. Ziehl–Neelseen staining and cultivations are positive, but animal tests are always negative.

Therapy. Indication of tuberculostatic drugs and synovectomy.

Auranofin – see Gold salts.

Autoantibodies Antibodies whose formation is induced by autoantigens.

Autoantibodies assessed in systemic lupus erythematosus (SLE) – other In approximately 30 % of patients with SLE, there are antibodies against the hnRNP

(heterogenic nuclear) A1 protein. Clinically, it correlates with the occurrence of Raynaud's phenomenon and disturbance of oesophagus motility. The antibodies against the RA-33 antigen (hnRNP-A2) were originally regarded as specific to rheumatoid arthritis. They have been observed also in patients with mixed connective tissue disease (MCTD) and SLE. In these cases they often appear together with anti-snRNP antibodies. The nuclear membrane contains laminins A, B and C, serving partly as a structural component of the membrane and partly as a foot holding of the chromosomes in the cells during interphase. The antibodies against these structures induce a peripheral or marginal fluorescence on the nucleus of Hep-2 cells; it was presumed that anti-dsDNA antibodies were the main cause. Anti-laminin antibodies were reported in systemic connective tissue diseases including SLE, where they are likely to be associated with the presence of lupoid or chronic active hepatitis.

There were antibodies against heat shock proteins hsp90 (5–50 % of SLE patients), ribonuclease P (25 %), ubiquitine (80 %), RNA polymerase II (9–14 %) or interferon gamma-inducible protein p16 (29 %) found in SLE. The diagnostic and clinical importance of all the mentioned antibodies is still not clear. In 30 % of SLE patients, the antibodies belonging to p-ANCA, i.e. antibodies against neutrophil cytoplasm, were demonstrated. To be specific, there are antibodies against elastase that occur most frequently in drug-induced lupus.

Autoimmune diseases They occur as a consequence of the overproduction of antibodies or autoreactive T lymphocytes inducing a state of autoaggression, i.e. harm to one's own tissue and its structure. The presence of a small number of antibodies doesn't necessarily mean it is a pathological process. To prove this, it should be demonstrated that: (1) certain antibodies are formed regularly only in the case of one specific disease, (2) the autoantigen inducing their formation can, after immunisation, provoke the development of the same pathological process in an experimental animal model, and (3) this experimental disease can be transmitted via the serum or lymphocytes to a non-immunised animal (Witebsky's criteria). The autoimmune disorders may impair several organs (systemic) or only one specific organ (organ specific).

Systemic autoimmune disorders include, for example, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome and systemic sclerosis.

Organ-specific autoimmune disorders may impair the following:

- *Endocrine system*: Addison's disease, Graves' disease, Hashimoto's disease and juvenile diabetes mellitus
- *Haematopoetic system*: autoimmune haemolytic anaemia, autoimmune neutropenia and paroxysmal cold haemoglobinuria
- *Gastrointestinal organs*: ulcerative colitis, Crohn's disease, chronic active hepatitis and primary biliary cirrhosis
- *Neuromuscular system*: myasthenia gravis and multiple sclerosis
- *Skin*: pemphigus vulgaris
- *Cardiopulmonary system*: rheumatic fever
- *Genitourinary system*: IgA nephropathy and idiopathic membrane nephropathy

Autoimmune haemolytic anaemia It is caused by antibodies against erythrocyte antigens that after binding to a corresponding antigen activate complement and thereby cause haemolysis. Most of these anaemias can be divided into warm and cold antibody anaemia. Warm antibody haemolytic anaemia is caused by IgG antibodies against Rh antigens, and the optimal reaction temperature is 37 °C. Cold antibodies are aimed at antigens H and I, belonging to the IgM isotype, and an optimal interaction with erythrocytes occurs at 4 °C, but it is positive also at 25 and 31 °C.

Autoimmune hepatitis This is referred to as chronic active hepatitis. It affects mostly young women who present with fever, arthralgia, jaundice and skin eruptions. The inflammatory changes can be seen predominantly in the periportal region where the infiltrating T_H1 lymphocytes and other cells damage the hepatocytes. The disease is associated with HLA-A1, HLA-B8, HLA-DR3 and HLA-DR4 antigens, and a familial predisposition has been observed. There are antibodies against the smooth muscles, actin and hepatocyte membranes. Autoantibodies against hepatocytes do not have a pathogenic role. A polyclonal hypergammaglobulinaemia is present, mostly of the IgG class and to a lesser extent the IgM and IgA class. The disorder is associated with other immunopathological conditions such as systemic lupus erythematosus, Sjögren's syndrome, autoimmune thyroiditis, insulin-dependent diabetes mellitus, etc.

Autoimmune neutropenia This is caused by increased destruction of neutrophils or by suppression of myeloid cell growth by autoantibodies not always detectable in the serum. It occurs as a primary condition or secondary to other autoimmune disorders. Patients suffer from recurrent infections or can be asymptomatic.

Autoimmunity Usually an immunopathological process with dysregulated immune response to autoantigens (self-antigens). This response is inhibited in physiological states or has only a regulatory purpose, so its products cause no harm to one's own tissue and cells containing relevant autoantigens on their surface. The harmful autoimmune reactions appear in an overreaction of the immune system caused by disturbances in immune homeostasis (the balance between stimulating and inhibiting factors), and then they are referred to as autoaggressive reactions. They induce autoimmune diseases.

Autoinflammatory diseases A set of disorders also called autoinflammatory (fever) syndromes or periodic fever syndromes characterised by recurrent episodes of fever as result of systemic and organ-specific inflammation caused by errors in the innate immune system. Unlike autoimmune disorders patients with autoinflammatory diseases do not produce autoantibodies. Most autoinflammatory diseases are monogenic and present during childhood. Autoinflammatory diseases include familial Mediterranean fever (FMF; the most common periodic fever syndrome), mevalonate kinase deficiency (MKD), tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS), cryopyrin-associated periodic syndromes

(CAPS), Muckle–Wells syndrome and periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome.

Autonomic nervous system (ANS) The autonomic part of the nervous system which maintains homeostasis in the body and harmonises activity of the visceral organs, mostly without the conscious participation of the individual. It is divided into the sympathetic and parasympathetic nervous system.

Autotolerance The ability of the body not to stimulate immunocompetent cells into an immune response to potential antigens that are components of one's own tissues and cells.

Avascular necrosis of the lunate bone – see Kienbock disease.

Axon The prolonged sprout of the nerve cell transmitting impulses from the cell body. It can vary between 1 mm long or longer than 1 m in length.

Azathioprine A nitroimidazole derivative of 6-mercaptopurine, a purine antagonist. It inhibits DNA synthesis and so is used in the treatment of acute leukaemia and as an immunosuppressant for B-cell and T-cell response. It decreases the number of circulating NK cells, neutrophils and monocytes. It is used in the treatment of various autoimmune disorders (systemic lupus erythematosus, Sjögren's syndrome and rheumatoid arthritis).

Azathioprine and 6-mercaptopurine belong to purine analogues. Currently, neither azathioprine nor 6-mercaptopurine is the drug of first choice in the treatment of rheumatoid arthritis (RA), but they both remain a valuable therapeutic option for RA when complicated by vasculitis, glomerulonephritis or when other DMARDs are not tolerated.

► *Dosage*
Azathioprine in RA is administered orally in a daily dose from 1.5 to 2.5 mg/kg (75–200 mg daily). Its full effects take a couple of months. It is necessary to monitor the blood count and liver function tests during treatment: every 14 days for the first 2 months and subsequently every 6–8 weeks. The occurrence of leucopenia is an indication for withdrawal of treatment.

► *Clinical efficiency*
Several clinical trials show the comparable clinical efficiency of azathioprine with antimalarials, penicillamine, parenteral gold, cyclophosphamide and cyclosporin, but less when compared to methotrexate in RA.
The therapeutic efficiency and toxicity of azathioprine are dose dependent increase proportionally to the administered dose. However, patients with a genetic deficiency of thiopurine methyltransferase (TPMT) are at increased risk of severe myelosuppression and liver toxicity, so studies are looking at the efficacy of measuring the TMPT genotype and/or enzyme activity in patients prior to treatment. Azathioprine is well tolerated in pregnancy and is not associated

with congenital malformations in humans. In spite of data showing that only very small amounts transfer into breast milk, its administration during breast-feeding is not recommended.

► *Adverse effects*

Gastrointestinal symptoms such as nausea and vomiting, leucopenia and increased liver transaminases. Clinical symptoms resolve after withdrawal of treatment. Long-term treatment with azathioprine is associated with a higher risk of malignancies, particularly haematopoietic and lymphoreticular malignancies.