1.3 Pneumonia

Pneumonia is an inflammatory process affecting the pulmonary parenchyma. It afflicts the terminal parts of airways, the respiratory bronchioles and the alveolar units. Histological examination reveals alveolitis associated with accumulation of exudate. In majority of cases it is caused by infection. It spreads to the interstitium surrounding the alveoli. Therefore impaired gas exchange occurs in the involved region of the lungs. **Microorganisms can enter the lungs**:

- by direct inhalation of microbes from the air
- from the mouth and nasopharynx
- by the haematogenous spread from another part of organism
- by penetration from the surroundings

Most often the microbes reach the lungs by **inhalation from the mouth** or nasopharynx. The upper airways are colonized by a microbial flora consisting of aerobic bacteria like Streptococci, Neisseria, Staphylococci, Haemophilus. Aerobic gram-negative bacilli like Pseudomonas aeruginosa, Klebsiella pneumoniae or Escherichia coli only rarely occur in healthy people. Numerous anaerobic bacteria occur in gingival fissures and on the teeth with carious lesions. Under physiological conditions, balance between the microbes and the nasopharyngeal mucous membrane is maintained.

Pneumonia does not usually occur in otherwise healthy persons. It can arise due to the disturbances of several mechanisms of the defence system consisting of a complex of anatomical barriers, cleansing activitity of airways, cellular and humoral mechanisms in the alveoli. The normal lungs are sterile already below their first bronchial branching.

The upper airways represent **anatomical barriers** of mechanical type. The airflow is directed in such a way, that it is actually filtered. The mucous membrane uptakes the particles entering the airways and the mucociliary system removes them. The cough also participates in the clearing process.

The antibacterial capacity of normal secretion in airways was intensively examined in the past. The greatest attention was concentrated on lysosyme, complement and immunoglobulins. The biological importance of these factors can be demonstrated experimentally, however they are of uncertain and probably very little importance for the organism as a whole. The factor of adhesion of microbes to the surface of mucous membrane is of greater importance. The cells of the mucous membrane of airways contain several surface receptors for different species of microbes. Some of the microbes are binding to fibronectin, which is not an integral part of the cell membrane. Its presence can be detected after exposing the mucous membrane to the effect of respiratory secretion. Other microbes, on the contrary, adhere to the cell surface only when fibronectin is removed.

The anatomical barrier can be surmounted very probably during sleep. **During sleep** aspiration of oropharyngeal secretion probably occurs. Pneumonia may develop due to aspiration of as little as 0.0001 ml of secretion. The aspired secretion can be removed by the mucociliary system of airways with participation of mucus secreting cells in submucousal glands and the goblet cells of the mucous membrane. The secretion, together with the pathogens, are moved towards the mouth by the cilia. The speed of ciliar movement is very high (1200 per minute). It is not quite cleare what a role can be ascribed to the possible resorption of a part of secretion by the mucous membrane of the airways. The change in the secretion viscosity or in the mucociliary system *activity* evidently participate in successful elimination of pathogens.

Nevertheless, when undesired particles and infectious agents reach the terminal respiratory units, another group of defense mechanisms begin to operate. The terminal respiratory units contain neither the mucociliary system, nor the goblet cells. The undesired particles cannot be eliminated from these regions, not even by cough. *The clearence of these regions* is dependent on phagocytic cells and humoral factors.

When the bacteria or dust particles reach the alveolar surface, they are very rapidly phagocytized. Phagocytosis differs according to the phagocytized substrate. The inert particles are phagocytized very rapidly by **alveolar macrophages**. The undamaged bacteria are phagocytized slowly. The opsonization

of bacteria enhances phagocytosis by ten times.

The nonimmune opsonines are present in a thin layer *lining* the alveoli. It consists of a lipoprotein surfactant from pneumocytes of type II, and fragments of glycoprotein fibronectin, produced by alveolar macrophages or delivered from intravascular space.

The immune opsonines in the alveoli are IgG antibodies and the complement factor C3b, which potentiates the bond to the membrane receptors. IgG and its subgroups are present in the bronchioalveolar lavage fluid of healthy people in an approximately identical amount as in serum. IgG2 contains antibodies to capsular saccharides of the pathogens, namely Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus and to the lipopolysacharides of the gram-negative bacteria. IgG1 and IgG4 adhere to the membranes of alveolar macrophages. The Fc-gamma receptors of macrophages are responsible especially for IgG3 and to lesser extent for IgG1 binding. The complement system can be activated in the airways. It functions as a barrier against the pathogenic factors.

1.3.1 Alveolar macrophages and lymphocytes

Alveolar macrophages can survive in alveoli months to years. They are capable to phagocytize and kill the microorganisms repeatedly. Besides, they are able to migrate. They pass through the pores to the adjoining alveoli and migrate to the more proximal parts of the respiratory tract. Macrophages are capable to destroy *the antigenic material* and engage also the alveolar lymphocytes to participate in this process. In addition, macrophages can enter the lymphatic system and are transported to the regional lymph-nodes, which also participate in humoral and cellular immunity responses in the lungs.

The alveoli contain about 10 % of all lymphocytes which occur in the airways. Two thirds of these lymphocytes are T lymphocytes. One part of the helper T lymphocytes are HLA-DR positive lymphocytes which produce interleukin 2. This is involved especially in viral diseases. Several important cytokines produced by T lymphocytes activate the alveolar macrophages. The killer T cells can be activated by gamma-interferon and can affect pathogenic germs directly.

1.3.2 Inflammatory reaction

At the beginning the alveolar macrophages are activated. After their contact with the pathogen they initiate the inflammatory reaction of the organism in several ways. First of all, it is the production of chemotactic factors, particularly leukotriene B4. This factor acts chemotactically on polymorphonuclear leucocytes and affects the permeability of the pulmonary capillaries and venules. The polymorphonuclear leucocytes pass through the capillary endothelium into the alveoli. Also C3a and C5a components of the complement and the components of the kinin system can induce change in the capillary permeability. By combination of these factors **an abundant supply of polymorphonuclear leukocytes to the alveoli** is ensured. These changes lead usually to infiltration detectable by radiography. The production of interleukin 1 and tumour necrosis factor-α by alveolar macrophages cause systemic effects as chills, fever, myalgia and malaise. **The polymorphonuclear leucocytes** *are useful* in the destruction of pathogens. Yet during this process **proteolytic enzymes are released**, being capable to damage the lung tissue. Through the damaged endothelial cells the fluid permeates into the interstitial space. Proteolytic enzymes are neutralized by protein inhibitors, alpha 1 antitrypsin and alpha 2 macroglobulin. They are present in serum and in the secretion of the airways. In this way the inflammatory reaction is accelerated on one hand, and depressed on the other. It is not clear, in what way the reparative arrangements leading to recovery *are initiated*.

The state is complicated when interstitial or alveolar oedema develop. Phagocytosis,which has an important role in the development of pneumonia and especially in the elimination of pathogens, can be affected. In the past when antibiotics were not used, a dramatic improvement on the 7th day of pneumonia was often observed. The improvement has been associated with a rapid fall of body temperature. This state was called crisis or *"the breaking of fever"*. It was due to antibody production and to change in the phagocytosis. Nowadays, due to antibiotic treatment, *the crisis* is usually not observed. Several antibiotics participate in the killing of pathogenic microbes.

The major symptoms of pneumonia are the cough, fever, production of sputum, chest pain and dyspnoea (tachypnoea). A typical pneumonia usually de-

velops subsequently to a systemic viral disease. The pathogenic microorganism is Streptococcus pneumoniae. In this case high number of neutrophil leukocytes and a excessive number of Pneumococci can be found in the sputum.

Pneumonia can be complicated by development of pulmonary abscess. The pulmonary abscess is a condition, when the destroyed area of lungs containing pus and the necrotic tissue is covered by so called pyogenic membrane. The necrotic and purulent material cannot be eliminated due to bronchial obturation. Pulmonary abscess can arise also during a neoplastic process in the lungs. Yet, it can be induced by septic thrombi, e.g. in staphylococcal endocarditis localized on the tricuspid valve. More often it occurs during aspiration pneumonia. Anaerobic pulmonary abscess occurs due to purulent processes in the oral cavity. More often it occurs in alcoholics and in patients suffering from certain neurologic diseases. An abscess can become clinically apparent as a chest pain with fever, intermittent haemoptysis and dyspnoea. The manifestations of chronic abscess are less dramatic. Usually the clinical pattern includes productive cough, foul-smelling breath and sputum, dyspnoea, intermittent fever, weight loss, anorexia, chest pain. This clinical manifestation resembles that of the lung gangrene.

1.4 Hypersensitive pneumonitis

Hypersensitive pneumonitis or exogenous allergic alveolitis is an inflammatory process with the participation of the immunity system. It affects the pulmonary parenchyma, especially the alveolar wall and the terminal bronchioles. The confirmation of the diagnosis requires the concordance of the clinical state and radiographic findings, together with pathophysiological changes and the immunologic criteria. **The etiologic agents include several substances occuring in the external environment**. Often it is organic dust of various origin or the components of agricultural production. In one third of cases the underlying cause are fungi.

The contact with pathogenic substance very soon evokes immediate reaction of organism, characterized by an increase in polymorphonuclear leukocytes in alveoli and terminal bronchioles which is immediatly followed by an increase in the mononuclear leucocyte number. Later, changes characteristic for the repeated contact whit the antigen (reactions of type II, or of type IV) occur. In the bronchioalveolar lavage fluid T lymphocytes can be observed, or polymorphonuclear leucocytes, especially in patients exposed for a long time to the effect of antigen. The findings include also the rise in the numbre of mast cells. During asymptomatic period T lymphocytes (CD4) can be found in the bronchioalveolar lavage fluid.

The major clinical symptoms are cough, fever and dyspnoea. In severe cases cyanosis develops. Chronic forms are progressing and lead to involvement of interstitium. All forms are usually acompanied with increase in erythrocyte sedimentation rate, C-reactive protein and serum immunoglobulins. In acute states neutrophilia and lymphopenia are usually present.

In long lasting process discrete nodular infiltration of the lungs appear which can develop into diffuse reticulonodular infiltration.

During the hypersensitive pneumonitis the lung volumes decrease, the diffusing capacity is impaired, compliance decreases and during physical effort hypoxaemia arises. In advanced states hypoxaemia is present already at rest. Biopsy examination of the lung tissue does not provide any unambiguous picture which could enable to establish the diagnosis precisely. In the active phase of the disease an interstitial infiltration can be observed. The infiltration contains plasma cells, lymphocytes, sometimes eosinophils and neutrophils. In advanced stages interstitial fibrosis occurs. Chronic forms can be hardly distinguished from other interstitial disorders and from idiopathic lung fibrosis. The spirometric and radiographic examinations, identification of the potential antigen and detection of antibodies are very important for determination of the clinical stage of the disease. The therapy is based on glucocorticoids, however the elimination of the causative antigen from environment or entire alteration of the living and working environment of the patient are the most effective therapeutical measures.