of bullous emphysema. As the disease progresses hypoxaemia and pulmonary hypertension develop. Cor pulmonale appears in all patients. The therapy is symptomatic and the prognosis obscure.

1.9 Interstitial lung diseases

Interstitial lung diseases are defined as a group of conditions with a common sign of diffuse inflammatory alterations in the terminal parts of lungs and airways. The term of interstitial lung diseases refers especially to the fact, that the **interstitium of alveolar walls is thickened in consequence of fibrotic changes**. Changes of the epithelial cells in alveoli and terminal bronchioles are present, as well as alterations of the capillary endothelial cells in the alveolar walls, and in the lung parenchyma. Interstitial diseases can progress slowly, as long as the alveolar-capillary units become gradually destroyed and *irreversibly lost*. The condition can lead to respiratory failure which ends lethally. Interstitial lung diseases have an inexpressive clinical symptomatology. Dyspnoea during physical effort and an unproductive cough can occur. An expressive clinical manifestation does not occur usually before the respiratory surface of lungs becomes really reduced.

Disorders appearing during interstitial lung diseases are caused by the inflammatory reaction which is induced by activation of *inflammatory cells*, accumulated in alveolar walls.

Terminal bronchioles and alveoli with the capillaries and venules form together mutually cooperating functional pulmonary untis. The walls of alveoli consist of a single layer of epithelial cells situated on a thin basement membrane. 95 per cent of these cells are epithelial cells of type I. The remaining 5 per cent are the cells of type II, producing surfactant – a complex substance which prevents the collapse of alveoli by reducing the surface tension. Under the thin basement membrane there is the interstitium which contains mesenchymal cells and the supporting tissue consisting of collagen, elastic fibres, proteoglycans and several glycoproteins. The pulmonary capillaries are in very close contact to alveoli. The basement membrane of capillaries is very often in immediate vicinity to the basement membrane of the alveolar walls which is lined on its other side with epithelial cells of type I. Here are the sites where the gas exchange takes place. In intact lungs the thickness of alveolar walls is 5–10 μm. **In interstitial diseases the wall of alveoli is several times thicker** at the expense of the alveolar space. In the first type, the alveolar walls can deform in consequence of *inflammatory cell* accumulation in interstitium. This condition results in the derangement of alveolar wall *architecture*. These changes are reversible. They can be repaired after elimination of material participating in the inflammatory process In the second type there are fibrotic changes. This type ocurs in idiopathic pulmonary fibrosis or frequently when the pathogenic factor is present in the inhaled air. The epithelial cells of type I are destroyed and they are replaced by cuboid cells being, in fact, the proliferated cells of type II. The cells from terminal bronchioli also migrate into the alveoli. Simulteneously, the capillary endothelial cells are destroyed. In the interstitium oedema and proliferation of mesenchymal cells producing collagen occur. The interstitium undergoes fibrotic changes. A very aggressive form develops when the accumulated material from interstitium enters the alveoli through their destroyed alveolar basement membranes. This material is connected with the alveolar walls and forms a picture of intraalveolar fibrosis. Such type of alterations has an especially bad prognosis.

According to the etiologic factor, two groups of interstitial lung diseases can be distinguished. The first one includes diseases where the etiologic factor is not exactly defined, or it is complex. The second group includes interstitial lung diseases where the etiologic factor is represented by pathogenic particles or noxious gases present in the inhaled air.

Inflammatory changes that are the cause of destroyed alveolar walls are mediated by inflammatory – immunity cells accumulated in the lung parenchyma. The inflammatory process is localized especially in the alveoli (therefore it is called alveolitis), but also in the alveolar walls, in small bronchioles and sometimes also in the pulmonary vessels. The troubles of patients result from the disturbed gas exchange and from the destroyed alveolar-capillary units of the lungs. It is not always clear, how the inflammatory reaction in the alveoli is initiated. In the

idiopathic fibrosis of lungs, alveolar macrophages are activated by means of immune complexes. Activated macrophages release chemotactic factors, which *attract* in particular the neutrophils. In sarcoidosis activated T cells release the chemotactic factor which attracts monocytes. In these cases the activation of the inflammatory process is evident. Sometimes, several substances damage directly the alveolar wall and initiate the onset of the inflammatory reaction, e.g. several types of drugs, especially cytostatics and antibiotics.

Under physiological conditions, in healthy people each alveolus contains about 80 potential *inflammatory cells*. Of this number 65–70 are alveolar macrophages, the rest are T cells. There are few B cells in the alveoli. Polymorphonuclear leucocytes occur rarely. An exception is in smokers, in whom polymorphonuclear leucocytes occur in alveoli. As a rule, the alveolar macrophages, T cells and B cells are not activated in normal lungs.

The distal parts of lungs contains immunoglobulins. The majority of them are IgG, to a lesser extent IgA and the least are IgM. Also some components of the complement are present. Moreover, there are macromolecules protecting the tissue from damage caused by the inflammatory reaction. They include, above all, the antiproteases and antioxidases.

The activated interstitial inflammation is characterized by a marked increase in numbre of *inflammatory cells* in the alveolar walls, but also on the alveolar epithelial surface. Sometimes neutrophils and macrophages preponderate. This condition is called neutrophil-macrophage alveolitis. In alveolitis eosinophils play an important role. However, their number usually does not prevail.

The inflammatory process with the participation of different cells can be improved by treatment to such extent that the original structure of alveoli is almost restored. However, if during the inflammatory process the proliferation of mesenchymal cells and accumulation of collagen appear, the original structure of alveoli can never be restored. Providing a sufficient number of lymphocytes and macrophages participate in the infammatory process and activated CD4 + T helper cells accumulate, granulomas develop. In fibrosis the damage of parenchyma and accumulation of mesenchymal cells are present. Neutrophils are the most damage-causing cells, namely by production of high reactive metabolites of oxygen, which destroy the parenchymal cells. In addition, they produce specific proteases, degrading the interstitial collagen and basement membranes. Eosinophils are also able to damage the parenchymal cells of lungs, yet they are not as aggressive as neutrophils. Activated alveolar macrophages release toxic oxidants which have a cytotoxic effect on the parenchymal cells of the lungs. They influence also the accumulation of mesenchymal cells by releasing the platelet-growth factor, fibronectin, and the insulin like growth factor. The platelet factor attracts the mesenchymal cells, fibronectin conects the mesenchymal cells with the extracellular matrix. The insulin-like growth factor influences the proliferation of mesenchymal cells. As a result, the alveolar walls thicken and their architecture is deranged.

The damage and the thickening of the alveolar walls lead to a disturbance of oxygen transport. The clinical manifestation of the disease results from hypoxia of the tissues and organs. The patients complain of fatigue and dyspnoea during effort. Along with the progression of the disease dyspnoea deteriorates. The delivery of oxygen to the tissues is simultaneously limited by the number of the existing alveolar-capillary units. Their number determines also the pressure relations in the pulmonary blood flow. After their destruction the hypertension develops, which has no tendency to lead to the right heart failure with its typical clinical manifestation. The fatal end is usually caused by the deficiency of oxygen and not by the right heart failure. Cyanosis occurs very late. Analysis of blood gases reveals a moderate hypoxaemia without hypercapnia. It is caused by the fact, that the patients with interstitial fibrosis tend to hyperventilate mainly because of their subjective feeling of dyspnoea and not because of hypoxia, which is moderate. During physical exercise the pO_2 decreases, but pCO_2 does not change. The measurements of ventilatory function reveal a decreased vital capacity and normal value of forced expiratory volume per second (because the airways are free, without obstruction). The chest roentgenogram is usually not typical. Only when the reticulonodular form develops the roentenography shows a honeycomb resembling alterations. The clubbing belongs to the regular clinical findings.

The interstitial fibrosis is hardly responsive to the therapy. A certain stabilization can be reached by glucocorticoid therapy.

1.9.1 Interstitial diseases of lungs of unknown etiology

In general the interstitial lung diseases are prevalently of unknown etiology. The most typical are the idiopathic fibrosis of lungs and sarcoidosis.

Idiopathic fibrosis of lungs. It is *a classic prototype* of an interstitial lung disease. It represents a neutrophil-macrophage alveolitis leading progressively to destruction of the alveolar-capillary units. In patients with idiopathic fibrosis of lungs viral infections occur more frequently and in their blood circulating immune complexes are present. In bronchoalveolar lavage fluid neutrophils and macrophages preponderate. It is assumed that the circulating immune complexes activate alveolar macrophages which release neutrophilic chemotactic factors. Neutrophils release toxic oxygen radicals and proteases. Macrophages increase their own production of the platelet-activating factor, the insulin-like growth factor (IGF) and fibronectin leading to fibrosis of alveolar walls and to increase in number of mesenchymal cells.

Sarcoidosis. It is a chronic multisystem disorder of unknown etiology, where the organs are damaged by inflammatory process. The inflammatory process takes place in the alveolar and bronchiolar walls. Alveolar macrophages are activated by an unknown antigen. Interleukin 1 released by macrophages induces an accumulation of the T helper lymphocytes. The process continues as further components of inflammatory process are activated.

Fibrosis of the lungs in systemic diseases. Alterations in lungs are found in about 25 per cent of patients with rheumatoid arthritis. Interstitial fibrosis can be caused also by the therapy of rheumatoid arthritis. It occurs most frequently during methotrexate treatment.

The systemic lupus erythematosus is usually associated with lymphocyte alveolitis caused probably by deposition of circulating immune complexes within the alveolar wall.

Antibodies to alveolar basement membrane can be detected in Goodpasture's syndrome. This disease is characterized by pulmonary haemorrhage, interstitial disease of the lungs, glomerulonephritis with circulating antibodies to basememt membrane of glomeruli and the antibodies to alveolar basement membrane. It is assumed that the antibodies to both types of basement membranes are identical.

In idiopathic pulmonary haemosiderosis alveolar haemorrhage anaemia due to iron deficiency, and a transitory parenchymal infiltration of lungs is found. The histological examination reveals focal haemorrhage, alveolitis with dominating macrophages, or haemosiderin-positive macrophages.

The chronic eosinophilic pneumonia is characterized by cough, dyspnoea, fatigue, fever, nocturnal perspiration, weight loss and eosinophilia in peripheral blood. The histological analysis shows alveolitis with the preponderance of eosinophils and macrophages. The stimulus for the accumulation of eosinophils is not well known. Eosinophils can destroy the alveolar walls by production of toxic oxygen radicals and peptides with a high electric charge.

Interstitial pneumonitis arises as a result of infiltration of the alveolar structures with lymphocytes. The same picture occurs also in HIV infection. In alveolar proteinosis the alveoli are periodically filled with proteinic-lipidic material. This is usually associated with mononuclear alveolitis and fibrosis.

1.9.2 Interstitial diseases of lungs of known etiology

There are many known factors which cause interstitial lung diseases. Different particles and infections may act as pathogenic factors. In addition, useful substances having undesirable effect on pulmonary tissue can be also involved.

Inhalation of anorganic dusts. It is a group of diseases termed pneumoconioses. At the beginning the particles of anorganic dusts always damage the pulmonary parenchyma evoking an inflammatory reaction which can result in destruction of the alveolar-capillary units. (Pneumoconioses are described in a particular chapter).

Inhalation of organic dusts. If effect of organic dusts is involved the hypersensitivity pneumonia or allergic alveolitis occur. If the episodes are repeated, in a part of the involved people the interstitial pulmonary disease may develop. At the beginning a macrophage-lymphocytic alveolitis occurs with the participation of neutrophils which can later lead to pulmonary fibrosis.

1.9.3 Interstitial lung diseases induced by drugs

The effects of drugs can be very different. They can lead in some cases to fatal end. The biopsy shows damage of parenchymal cells and oedema of alveolar walls. Macrophage-lymphocytic alveolitis with neutrophils, but also with eosinophils can be found in alveoli. The chronic form of impairment induced by drugs is very difficult to prove. In the majority of cases there is macrophage-lymphocytic alveolitis with polymorphonuclear leucocytes of the mixed type.

Antineoplastic drugs cause in 2–3 per cent of patients interstitial fibrosis. Similarly antibiotics, salts of gold and other drugs can initiate the arise of interstitial fibrosis. A close correlation between effects of some herbicides and arise of interstitial fibrosis has been found. Radiotherapy can also act as the initiating mechanism.

Infection caused by Mycoplasma, Legionella pneumoniae, and HIV infections associated with parasitic infection caused by Pneumocystis carinii, progress into the form of interstitial lung disease.

It is very important to bear in mind that also the inhalation of oxygen in high concentration for several days causes a damage of the pulmonary parenchyma. The toxicity of oxygen can be very dangerous to patients with respiratory failure. The respiratory failure breaks down as chronic pulmonary fibrosis begins to develop.

1.10 Respiratory failure

1.10.1 Acute and chronic respiratory failure

The respiratory organs procure the necessary *supply* of O_2 and elimination of CO_2 in all physiological situations, in order to maintain the optimal pO_2 and pCO_2 in the arterial blood. **Respiratory failure represents a condition with impaired exchange of gases between the alveolar space and pulmonary capillaries. It is manifested by changes of the $pO_2$and pCO_2 in arterial blood; when pO_2 falls below normal values (excluding the right to left shunt in the heart) and pCO_2 rises above the physiological value (excluding the respiratory compensation of metabolic alkalosis)**. The definition of the respiratory failure has results from laboratory findings, completed by clinical symptoms. Respiratory failure is not a disease, it is a state, developing during various disorders. Sometimes the lungs can be intact. E.g. after an overdose of sedatives, hypnotics the respiratory failure may develop because of the respiratory centre depression.

pO_2	10,0 – 13,3 kPa (75–100 mm Hg)
pCO_2	4,8 – 6,1 kPa (36–46 mm Hg)

Table 1.1: Normal values of blood gases

pO_2	< 8 kPa (60 mm Hg)
pCO_2	> 7 kPa (55 mm Hg)

Table 1.2: Values of blood gases in respiratory failure

Respiratory failure is traditionally distinguished as being acute or chronic. It is an artificial classification which is more traditional than logical. A rapid deterioration in chronic respiratory failure should be considered as an acute respiratory failure which does not agree with our conception of the acute state being changed to a chronic one. Nevertheless, this classification is important from the etiologic point of view and from that of the possibilities of treatment.

Respiration includes four processes: ventilation, diffusion, perfusion, the governing and control of respiration. Disturbance of any of these four activities can cause the respiratory failure.

During **hypoventilation** the changes in pO_2 and pCO_2 in the arterial blood are parallel. The simple, uncomplicated hypoventilation leads to decrease in pO_2 and to increase in pCO_2 by identical value. However, this is not an universal principle.

Disorder of diffusion during normal activity is usually not manifested by marked changes in pO_2 and