8.1 Summary

This thesis focuses on two aspects of human pulmonary emphysema. The first part (chapters 2-4) describes the studies we performed to investigate the pathogenesis of this disorder. The second part (chapters 5-7) deals with the effects of corticosteroid treatment in emphysema.

The study population of this thesis consisted of a group of 58 male non-allergic patients with COPD and a clinical diagnosis of emphysema. All patients were smokers or ex-smokers. All had normal alpha_{1}-antitrypsin serum levels.

The pathogenesis of emphysema is largely unknown. Chronic inflammation of the peripheral airways is thought to play an important role. For many years, it has been hypothesized that an imbalance between proteolytic, especially elastolytic, and antiproteolytic activity in the lungs underlies the destructive changes that are found in the pulmonary parenchyma in emphysema. In patients with normal alpha_{1}-antitrypsin serum levels, the cause of this imbalance has not yet been elucidated. The major risk factor for emphysema is cigarette smoking. Since only about 15% of smokers develop COPD, however, it has to be presumed that other factors in addition to smoking contribute to the proposed protease-antiprotease imbalance and the development of emphysema.

In order to investigate the presence and nature of inflammatory processes in the peripheral airways of patients with emphysema, we performed bronchoalveolar lavage (BAL) in patients with emphysema and healthy controls (chapter 2). BAL appeared to be a safe and well-tolerated procedure in patients as well as controls. Recovery of BAL fluid and cells was higher in controls than in patients. Differential cell counts were not significantly different in controls and patients. Patients underwent a second BAL after treatment with a short course of oral prednisolone. Treatment with prednisolone did not induce major changes in BAL findings. Taken together, these results are not suggestive of an active inflammatory process in the peripheral airways of patients with emphysema.

In contrast, increased numbers of cells and significant differences in differential cell counts were found in smokers as compared to ex-smokers. This was observed in both
controls and patients, reflecting an increased inflammatory burden in the lungs of smoking subjects. This finding does not explain, however, why some smokers develop emphysema whereas others do not.

Polymorphonuclear leukocytes (PMN) are the major human source of elastase. In addition, these cells can produce reactive oxygen metabolites that have been shown to be capable of inactivating antiproteases. The studies described in the chapters 3 and 4 are based on the hypothesis that an increased "activity", i.e. an increased tendency to release lysosomal enzymes and/or to generate reactive oxygen species, of PMN might underlie the proposed protease-antiprotease imbalance in emphysema and the increased susceptibility of some smokers to develop emphysema. Polymorphonuclear leukocytes (PMN) were isolated from peripheral blood of patients with emphysema and healthy controls. Neither the in vitro release of elastase, β-glucuronidase, and myeloperoxidase, nor the total cellular content of these lysosomal enzymes was significantly different in patients with emphysema and healthy subjects. Within both groups, no significant differences were found between smokers and ex-smokers (chapter 3). On the basis of these results it is unlikely that an abnormality in PMN lysosomal enzyme release or content is a pathogenetic factor in emphysema. Our results, however, do not exclude the possibility that PMN behave differently in the local environment of the lungs.

In contrast to lysosomal enzyme release, the in vitro generation of superoxide anion \( \left( O_2^- \right) \) by PMN was significantly higher in patients with emphysema than in healthy controls. Moreover, the increased in vitro generation of \( O_2^- \) in the patient group significantly decreased after in vivo treatment with oral prednisolone (chapter 4). These observations suggest an abnormality in the oxidative metabolism of PMN that may predispose an individual for the development of emphysema, since an increased oxidative metabolism may disturb the protease-antiprotease balance through oxidative inactivation of antiproteases. This abnormality may at least partially be reversed by treatment with corticosteroids. In patients as well as controls, \( O_2^- \) generation by PMN was not significantly different between smoking and ex-smoking individuals, indicating that the observed abnormality in \( O_2^- \) generation is not related to actual smoking habits.

Chapter 5 gives an overview of the effects of treatment with corticosteroids that have been reported in COPD. Short-term studies with oral as well as inhaled corticosteroids show little or no benefit. Long-term studies are scarce and their interpretation is hampered by methodological problems (retrospective studies) and patient selection (inclusion of allergic individuals or patients with rapidly deteriorating lung
ture of emphysema and the possibility that treatment effects manifest themselves only after prolonged treatment periods.

To determine the effectiveness of corticosteroids in emphysema, we performed a long-term, randomized, double-blind, placebo-controlled, parallel intervention study in our group of non-allergic emphysema patients. Patients were treated with either:
1) inhaled budesonide 1600 μg per day plus placebo tablet, or
2) inhaled budesonide 1600 μg per day plus oral prednisolone 5 mg per day, or
3) placebo inhalations plus placebo tablet.

Treatment was given during two years. In that period, clinical assessment, consisting of history, physical examination, and spirometry, took place every two months. \( PC_{20} \) histamine was measured every four months.

In chapter 6, the effects of corticosteroid treatment on withdrawal from the study, pulmonary symptoms, lung function decline, and frequency and duration of exacerbations are described.

Withdrawal due to pulmonary problems, such as frequent exacerbations or rapid deterioration of lung function, was significantly higher in the placebo group than in the actively treated groups, suggesting a favourable influence of corticosteroids on pulmonary "stability" in patients with emphysema. Treatment with corticosteroids significantly reduced pulmonary symptoms. Median annual decline of FEV₁ was smaller in both actively treated groups (-30 ml/yr in the budesonide group and -40 ml/yr in the budesonide plus prednisolone group, respectively) than in the placebo group (-60 ml/yr), but variation was large and differences were not statistically significant. No effect was found on frequency or duration of exacerbations in patients who completed the whole study. Treatment with an inhaled corticosteroid in combination with oral prednisolone was not more effective than treatment with an inhaled corticosteroid alone. Finally, our observations reflected the deleterious effect of smoking: FEV₁ declined more rapidly in smokers than in ex-smokers, whether they were treated with corticosteroids or not.

In chapter 7 we describe the effect of corticosteroid treatment on airways hyperresponsiveness (AHR) in patients with emphysema. In this study we also investigated which factors modulate level and longitudinal change in AHR in these patients.

During the two years of follow-up, \( PC_{20} \) histamine decreased in the whole group, and this decrease was not influenced by corticosteroid treatment. \( PC_{20} \) tended to decrease faster in smokers than in ex-smokers. \( PC_{20} \) was significantly associated with
prechallenge FEV₁ at each time point. This association has been found in other studies as well. We observed, however, that not only prechallenge FEV₁ determines the level and decline of AHR in patients with emphysema. Total serum IgE level at the beginning of the study was significantly and inversely associated with PC₂₀ histamine. Moreover, a higher initial serum IgE level was associated with a smaller annual decrease of PC₂₀. No significant associations were found between the number of blood eosinophils at the start of the study and level or decline of PC₂₀. The observed relationships between serum IgE and level and decline of AHR are remarkable since we included only non-allergic patients with serum IgE levels within the normal range. Our findings suggest an important role for IgE in the course of emphysema.

8.2 Discussion and implications for future research

The aim of the studies described in this thesis was:
- to improve the understanding of the pathogenesis of emphysema and especially of the role of polymorphonuclear leukocytes in the proposed protease-antiprotease imbalance;
- to determine the efficacy of long-term treatment with corticosteroids in emphysema.

To achieve this goal, we studied a group of carefully selected patients with COPD and clinical manifestations of emphysema. Emphysema was diagnosed on the basis of history, physical examination, lung function tests, and chest X-ray. Because emphysema can be diagnosed with certainty only by means of pathologic-anatomical examination of biopsy specimens, we had no definite proof of the presence and extent of emphysema in our patient population. In clinical practice, however, clinical criteria are considered sufficient and it is no routine to confirm the diagnosis by means of a biopsy, which requires an invasive procedure that can have potentially dangerous complications. By the time we selected our patient population (in the middle eighties) the value of computed tomography (CT) in diagnosing emphysema had not yet been established. Nowadays, this technique may be of additional value in assessing the presence and severity of emphysema during life, especially for research purposes.

Our BAL findings (chapter 2) do not confirm the presence of an active inflammatory process in the peripheral airways of patients with emphysema. This is remarkable, since a chronic inflammatory process is thought to be present in both developing and established COPD. Several factors have to be considered when interpreting this finding. Although BAL can be performed safely in patients with emphysema, the