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Similarities and differences in the pathophysiology of asthma and COPD

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1.1 Introduction

In the early 1960s, when pulmonary function testing was limited to spirometry, a hypothesis was put forward that pulmonary diseases with similar clinical symptoms and spirometry findings such as asthma, chronic bronchitis and emphysema might be different expressions of one disease entity, in which both endogenous (host) and exogenous (environmental) factors would play a role in the pathogenesis. More refined diagnostic tools such as bodyplethysmography or helium-based pulmonary function analysis, which can measure pulmonary hyperinflation, were not available at that time. Pathophysiological as well as immunological characteristics of asthma such as IgE, mast cells and their mediators, leukotrienes, T-cell subsets, cytokines and chemokines had not been discovered. Still, the proposal that asthma, chronic obstructive pulmonary disease (COPD) and chronic bronchitis or emphysema might have a common pathogenic background has been repeated, and even now there is some debate about whether asthma and COPD should be regarded as:

- two different diseases in one lung;
- two diseases with one common pathogenesis; or
- one disease with different clinical phenotypes.

These hypotheses reflect some of the clinical uncertainties that can arise when end-stage COPD and bronchial asthma have to be distinguished based on spirometry and clinical findings alone. This can be especially challenging in patients who smoke on top of an atopic background.
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Epidemiological, genetic and pathophysiological data collected in the past 50 years, however, allow a relatively clear separation of COPD and asthma into rather distinct entities. These findings, which will be summarized below, make a common pathogenic origin for bronchial asthma and COPD most unlikely.

Among the epidemiological features that can separate asthma from COPD are differences in the age of onset, different risk factors and comorbidities, differences in the genetic background and differences in prognosis. While asthma is generally associated with a normal life expectancy, this is significantly reduced in COPD. Furthermore, marked differences in inflammatory cells and mediators present in the airways and lungs result in different patterns of inflammation and their intrabronchial and intrapulmonary distribution. As a consequence of these there are distinctly different features in the respective impairment of pulmonary function, different responses to airway irritants in bronchoprovocation tests, as well as marked differences in response to treatment and a different prognosis. These will be discussed in more detail below:

The clinical hallmark of asthma is episodic symptoms related to airflow limitation, often in response to external specific (allergen) or non-specific (airway irritants) factors. The characteristic feature of COPD in industrialized countries (which is also its main risk factor) is the long-term exposure to inhaled tobacco smoke or biomass combustion (the latter being more relevant to developing countries).

Asthma and COPD can sometimes be difficult to separate due to similarities in reported symptoms, airflow limitation and response to treatment. While individual patients may occasionally evade a clear separation into either asthma or COPD these patients are more likely an exception than the rule. These are often patients with asthma who have a longstanding smoking history or patients with a smoking history who develop intrinsic asthma. However, they do not support the hypothesis of a common pathogenetic origin or common pathogenetic pathways. The fact that end-stage asthma and COPD can display a number of pathophysiological similarities rather reflects the fact that the lung and its airways have a limited spectrum of responses to endogenous or exogenously induced inflammation irrespective of the origin of the insult. It would be unscientific to understand this limited spectrum of reactions, however, as evidence for a common pathogenesis. In an analogy, while end-stage fibrosing lung disease can appear with similar symptoms and even histopathology, irrespective of the underlying interstitial lung disease and the causative agents, a common pathogenesis is not suspected.

Accordingly, the so-called Dutch hypothesis from 1961 has been refuted in the past decades due to increasing knowledge about the underlying inflammatory processes in asthma and more recently in COPD.

From a clinical perspective, early stages of asthma as well as COPD can be differentiated based on patients’ history and clinical, laboratory and pulmonary function findings (Table 1.1).

It should be noted that none of the clinical features on its own clearly distinguishes asthma from COPD. Recent studies indicate that the forced expiratory
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Table 1.1  Typical clinical features of COPD.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>Childhood/adolescence</td>
<td>&gt;40 years</td>
</tr>
<tr>
<td>Smoking history prior to onset</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Nocturnal symptoms</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Variable</td>
<td>On exertion</td>
</tr>
<tr>
<td>Allergy</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Course</td>
<td>Variable</td>
<td>Progressive</td>
</tr>
<tr>
<td>Airflow obstruction</td>
<td>Variable</td>
<td>Fixed</td>
</tr>
<tr>
<td>FEV₁ reversibility</td>
<td>Good, &gt;20%</td>
<td>Limited, &lt;20%</td>
</tr>
<tr>
<td>Airway hyperresponsiveness</td>
<td>Characteristic feature</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Response to corticosteroids</td>
<td>+++</td>
<td>(+)</td>
</tr>
<tr>
<td>Sputum production</td>
<td>+</td>
<td>+ to +++</td>
</tr>
</tbody>
</table>

FEV₁, forced expiratory volume in 1 second.

volume in 1 second (FEV₁)-reversibility to large doses of bronchodilators in COPD can change over time,\textsuperscript{25} possibly to a degree indistinguishable from bronchial asthma. Nevertheless, in severe COPD pulmonary function abnormalities are usually not responsive to β₂-agonists and/or corticosteroids and the absolute magnitude of response still differs.

Therefore, with increasing

- smoking history
- irreversibility of the airflow obstruction
- age
- dyspnoea on exertion
- $P_{\text{a}}\text{CO}_2$
- comorbidities such as coronary heart disease, arteriosclerosis, depression, osteoporosis, etc.

there is a rise in the likelihood that the patient has COPD.

1.2  Pulmonary function abnormalities in asthma and COPD

Pulmonary function abnormalities in asthma and COPD can be very similar. Both are characterized by airflow obstruction but careful analysis can reveal noticeable differences in pulmonary function testing that help to differentiate asthma from COPD (Table 1.2).
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#### Table 1.2 Pulmonary function abnormalities in asthma and COPD.

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of airflow obstruction</td>
<td>Central Airways</td>
<td>Peripheral Airways</td>
</tr>
<tr>
<td>Reversibility</td>
<td>From +++ to +</td>
<td>From + to ++</td>
</tr>
<tr>
<td>Hyperinflation</td>
<td>From + to ++ (dynamic)</td>
<td>From +++ to ++ (largely fixed)</td>
</tr>
<tr>
<td>Airflow obstruction increases in response to hyperinflation</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Airway resistance</td>
<td>Inspiratory and expiratory ++</td>
<td>Expiratory $\gg$ than inspiratory (expiratory airway collapse)</td>
</tr>
<tr>
<td>Hypercapnic respiratory failure</td>
<td>Only in severe, acute asthma attacks</td>
<td>Chronic hypercapnic failure possible</td>
</tr>
<tr>
<td>Airway hyperresponsiveness</td>
<td>Characteristic – direct and indirect stimuli</td>
<td>Not uniformly present – only direct stimuli</td>
</tr>
<tr>
<td>Diffusion capacity</td>
<td>Not impaired</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

#### Site of airflow obstruction

In asthma the site of the predominant airflow obstruction is usually located in the central airways. During severe attacks or in severe cases peripheral airways are also affected. In asthma, airway wall thickening due to airway remodelling increases with asthma severity and contributes to fixed airflow obstruction. In asthma, airway wall thickening due to airway remodelling increases with asthma severity and contributes to fixed airflow obstruction.26

Airflow obstruction in COPD, however, especially when associated with emphysema, is usually located in the peripheral airways. One of the mechanisms responsible for airflow obstruction in COPD is a dynamic collapse of the small airways during expiration due to an increase in intrathoracic pressure.27 Central airway obstruction in COPD is also caused by airway collapse due to tracheobronchial instability.

#### Bronchodilator response

In addition, the responses to bronchodilators in COPD and asthma differ, although this has been partially challenged by recent data.25 Asthma is usually associated with a good response to bronchodilators, which can cause a complete reversibility to normal values of airflow obstruction. This is limited, however, in severe and/or longstanding cases. In COPD the administration of high doses of bronchodilators has been associated with an unpredictable variability in airflow obstruction.25 However, this variability less pronounced than in asthma and more closely related to pulmonary hyperinflation. Airway resistance, as measured by bodyplethysmography, is usually evenly distributed between inspiration and expiration in asthma while in COPD airway resistance is usually more pronounced during expiration, due to hyperinflation and expiratory airway collapse.

#### Arterial CO$_2$ tension ($P_{a\,CO_2}$)

Patients with asthma, even during episodes of symptomatic airway obstruction, rarely display hypercapnic respiratory failure. Instead, low to hypocapnic $P_{a\,CO_2}$ values are
SIMILARITIES AND DIFFERENCES IN THE PATHOPHYSIOLOGY OF ASTHMA AND COPD

Table 1.3  Asthma or COPD?

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Episodic</td>
<td>Little variability in symptoms</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Childhood/adolescence</td>
<td>&gt;40 years of age</td>
</tr>
<tr>
<td>First episode</td>
<td>Usually dramatic</td>
<td>Slowly progressive/unnnoticed</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Good; usually little or no progress</td>
<td>Limited – chronic progressive</td>
</tr>
<tr>
<td>Treatment</td>
<td>Good response to glucocorticosteroids</td>
<td>Little response</td>
</tr>
</tbody>
</table>

classic for asthma. Elevated $P_aCO_2$ levels during symptomatic asthma attacks are indicators of impending respiratory arrest. In contrast, in COPD elevated $P_aCO_2$ levels and chronic hypercapnic respiratory failure are common in more severe cases due to chronic fatigue of the respiratory pump.

**Diffusion capacity**

Diffusion capacity for carbon monoxide (DLCO) is rarely if ever impaired in asthma. In COPD, however, a reduction in the diffusion capacity is a typical finding and useful to separate COPD from asthma.

**Overlap between asthma and COPD**

There is little doubt that asthma can present with features of COPD such as poorly reversible airflow obstruction, and COPD can display a marked reversibility in airflow obstruction. Yet, asthma and COPD are unlikely to represent different ends of a spectrum of similar diseases just because of similar pulmonary function abnormalities that are shared with other acute or chronic lung diseases such as cystic fibrosis, post-tuberculosis-syndromes, end-stage sarcoidosis or bronchiolitis. Neither the fact that some patients with asthma can have a progressive course nor the observation that some patients with COPD can have a marked reversibility of their airflow obstruction are suggestive of pathogenic similarities. It appears likely, however, that patients with asthma who smoke can develop features of COPD in addition to their asthma. Their asthma is usually more severe and responds less well to corticosteroids. These patients have not been studied in detail, and a clinical separation into asthmatic and COPD-related contributions to individual cases’ symptoms is difficult.

**1.3  Risk factors for asthma and COPD**

**Genetic**

A large number of loci and genes with polymorphisms have been identified as possible susceptibility genes for asthma or special features of asthma such as bronchial
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hyperresponsiveness. Many of these include genes for mediators and/or receptors associated with atopy such as interleukin-4 (IL-4), IL-13 and others.

In contrast, one of the models for COPD that is associated with a single-gene background is the hereditary alpha-1-antiproteinase deficiency. Whether genetic polymorphisms in other genes encoding for antiproteases or proteases are also linked to COPD pathogenesis is currently under investigation.

However, there is little concordance between genetic risk factors for asthma and COPD, again suggesting that a common underlying pathogenesis is unlikely.

Environmental

Atopy has been identified as a major risk factor for asthma, and a large proportion of patients with asthma experience asthmatic symptoms after inhalation and/or ingestion of allergens. The direct effects of allergens on pulmonary function and symptoms can be demonstrated in challenge models such as inhaled or segmental allergen challenge (Figure 1.1). Accordingly, the prevalence for atopy is significantly increased in asthma (with the exception of intrinsic asthma) while there is no evidence for such an association in patients with COPD. Yet, the precise role of IgE-mediated allergic reactions in the pathogenesis of chronic asthma remains unclear. In contrast, there is no challenge model for COPD. The identified risk factor in the vast majority of cases in the Western world is the chronic inhalation of cigarette smoke.

Figure 1.1  Endobronchial changes following segmental allergen challenge. Anterobasal segment of the right lower lobe. Left: Before allergen deposition; right: 5 minutes following allergen challenge. Mucosal oedema, bronchoconstriction and airway secretions can be seen within minutes following endobronchial allergen deposition. This is a feature specific for allergic asthma. Reproduced with permission from Virchow JC Jr, Walker C, Hafner D, Kortsik C, Werner P, Matthys H, and Kroegel C. T cells and cytokines in bronchoalveolar lavage fluid after segmental allergen provocation in atopic asthma, Am. J. Respir. Crit. Care Med. 1995;151:960–968, © American Thoracic Society.
Comorbidities for asthma and COPD

A positive family history for atopy or allergic diseases is a strong risk factor for asthma. Children with a positive family history for asthma who have atopic dermatitis have a high risk of developing asthma themselves. Typically, comorbidities in asthma are also risk factors and they often precede the onset of asthma in individual cases. Allergic rhinitis, atopic dermatitis and sinus disease frequently develop prior to the onset on asthma. A specific subset of patients with asthma, of which about two-thirds are of the intrinsic phenotype, also have an acquired sensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, indometacin and others. The common mode of action of these drugs is the inhibition of cyclooxygenase I. In these patients ingestion, local application or inhalation of these drugs will result in severe asthma attacks. This acquired syndrome of intolerance against NSAIDs occurs on top of a persistent and progressive asthma. This syndrome, formerly termed aspirin-sensitive asthma, or AIA, has therefore been labelled as aspirin-exacerbated respiratory disease (EARD). Intolerance to NSAIDs is not associated with COPD.

In contrast, in COPD comorbidities such as coronary heart disease, arteriosclerosis, depression and osteoporosis are also consequences of the main risk factor for COPD, namely smoking. There is still debate about whether or not they represent true comorbidities or rather concomitant diseases caused by the same risk factor. True comorbidities of COPD might be differences in risk-taking behaviour and factors associated with social status, both of which have been associated with smoking prevalence. In contrast to asthma there is no association with family history for COPD; the noteworthy exception is that the likelihood for smoking is increased in the offspring of parents who smoke. Whether this is merely a behavioural trait or evidence for a genetic transmission is still debated. Small birthweight (and possibly other susceptibility parameters) have also been associated with COPD. Involvement of the upper airways in COPD has not been studied in detail but appears to be substantially less compared to asthma. The reasons why only a proportion of smoking individuals will eventually develop COPD is still unclear. However, the proportion appears to be substantially higher than previously expected. The prevalence of atopy in patients with COPD is not increased.

Atopy as a risk factor for asthma: intrinsic asthma

Allergic asthma has been associated with the atopic phenotype. It is now clear that not all asthma is allergic, but many patients, especially of early onset, have elevated IgE concentrations and increased levels of specific IgE. While allergic mechanisms play an important role in acute asthma exacerbations following allergen exposure their role in the pathogenesis of chronic asthma is still unclear. In particular, in intrinsic asthma elevated IgE concentrations cannot be documented, and atopic mechanisms are not involved in the clinical picture of intrinsic asthma, which usually starts in adulthood and includes chronic nasal and sinus polyposis.
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1.4 Cellular inflammation in asthma and COPD

Asthma

The pathogenesis of asthma has been associated with a number of inflammatory cells and mediators. The cells that are usually increased in peripheral blood, in sputum and in airway biopsies and that have been associated with asthma severity as well as response to corticosteroid treatment are eosinophils. These cells appear to be causally related to asthmatic inflammation and subsequent symptoms. Therapeutic approaches to reduce eosinophil numbers and/or function have been associated with improvements in asthma of different severity.43–45

Other cells present in increased numbers and increased activation status are cells associated with the atopic-allergic phenotype such as mast cells and basophils. Upon interaction of cell-bound allergen-specific IgE and allergen, mast cells and basophils release histamine and other bronchoactive mediators such as leukotrienes. Dendritic cells of the myeloid as well as the plasmacytoid phenotype46 infiltrate the airways following allergen challenge to orchestrate an immune response. Allergic as well as intrinsic asthma has been associated with an accumulation of activated T-cells of the T-helper cell phenotype, which can release a number of cytokines involved in asthmatic inflammation.33 In atopic patients there are increased concentrations of cytokines such as IL-4, IL-13 and IL-5. All have been shown to increase eosinophil survival but IL-5 appears to be the most potent cytokine to attract and activate eosinophils. IL-4 and IL-13 are released in response to allergen exposure and are involved in initiating and maintaining an IgE response. Interleukin-5 is crucial for eosinophil activation and survival and can be found in elevated concentrations in allergic as well as in intrinsic asthma.41 Recent studies suggest that effective blockade of IL-5 in asthma can result in improvement of clinically relevant outcomes such as a reduction in asthma exacerbations.44,45 Other mediators of relevance to the eosinophilia in asthma are CCL5 and eotaxin, and the leukotrienes C4, D4 and E4, which are released by a number of cells including mast cells and eosinophils. They are chemotactic for eosinophils and induce a long-lasting contraction of airway smooth muscle. Their pathogenetic role in asthma has been demonstrated by specific leukotriene receptor antagonists that block the CysLT1 receptor and reduce asthma-related symptoms such as airflow obstruction and asthma exacerbations.47,48

COPD

The cellular inflammation in COPD in contrast, is characterized by an increase in macrophages, neutrophils and dendritic cells, especially of the myeloid DC phenotype, which have a reduced expression of chemokine receptors required for the migration to regional lymph nodes.49

In addition, there appear to be increased numbers or percentages of CD8+ T-lymphocytes, termed Tc1-type cells. Their precise role has not been established and an exact phenotypic characterization of these cells and their precise function is
still lacking. The increase in endobronchial neutrophils seen in a majority of patients with COPD has also been associated with COPD pathogenesis. Neutrophils can release elastase and other proteases that can irreversibly damage pulmonary structures leading to tissue degradation and pulmonary emphysema.

Mediators relatively uniquely expressed in COPD are leukotriene B\textsubscript{4} (LTB\textsubscript{4}) and the chemokine CXCL-8 (interleukin-8) while bronchoconstrictory mediators such as histamine or cysteinyl-leukotrienes, which play a role in asthma pathophysiology, are not elevated in COPD.\textsuperscript{22} Eosinophils have been recovered mainly during COPD exacerbations but their responsiveness to corticosteroids differs. In stable COPD eosinophil numbers are usually not elevated.

1.5 Distribution and consequences of inflammation in asthma and COPD

Despite some crude similarities between asthma and COPD, the distribution of inflammation and its consequences are markedly different (Table 1.4).\textsuperscript{50} In asthma, histopathological examination of endobronchial biopsies reveals epithelial shedding, to which a number of mechanisms contribute. Collagen and myofibroblast deposition below the epithelium, which results in basement membrane thickening, has been described as a feature specific to asthmatic airways.\textsuperscript{51} In addition a marked hypertrophy of the smooth muscle layer of the airways can be observed in asthma, which has been related to the degree of airflow obstruction in asthma.\textsuperscript{52} Recently, neoangiogenesis in asthmatic airways has been described.\textsuperscript{53} Destruction of lung parenchyma and the development of emphysema is not a typical feature of asthma. In contrast to COPD, where mortality has been associated with COPD exacerbations,\textsuperscript{54} mortality in asthma has not been linked to the number of exacerbations but rather to the severity of asthma attacks.

The airway epithelium in COPD is characterized by squamous cell metaplasia of the bronchial epithelium and a bronchiolar fibrosis,\textsuperscript{55} and the development of emphysema. Smooth muscle constriction or hypertrophy is not a feature of COPD. The inflammation in COPD is arranged in lymphocyte-containing follicles suggesting an adaptive immune response in the airways.\textsuperscript{56,57}

| **Table 1.4** Epithelial injury in asthma and COPD. |
|---------------------------------|---------------------------------|
| **Asthma**                      | **COPD**                        |
| Epithelial fragility/shedding   | Squamous cell metaplasia        |
| Collagen deposition/basement membrane thickening | Bronchiolar fibrosis |
| Hypertrophy/hyperplasia of the airway smooth muscle layer | |
| Glandular hypertrophy           | |
| Angiogenesis                    | |
Table 1.5  Distribution of airway inflammation in asthma and COPD.

<table>
<thead>
<tr>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central airways</td>
<td>Small airways</td>
</tr>
<tr>
<td>Involvement of peripheral airways</td>
<td>Destruction of lung parenchyma, emphysema</td>
</tr>
</tbody>
</table>

Both asthma and COPD are characterized by submucosal gland hypertrophy, which can contribute to mucus production and airflow obstruction. The precise contribution of submucosal glands to the pathophysiology of asthma and COPD might be considerable but has been insufficiently studied.

1.6 Patterns of epithelial injury in asthma and COPD

Most of the changes described above in asthma can be observed predominantly in the more central airways, from where they can spread to more peripheral airways as observed in more severe asthma. However, COPD is located predominantly in the small airways, where destruction of lung parenchyma leading to pulmonary emphysema occurs (Table 1.5).

1.7 Airway hyperresponsiveness

Airway hyperresponsiveness (AHR) to direct (e.g. histamine, methacholine) as well as indirect (adenosine, cold air, exercise) stimuli is a characteristic pathophysiological feature of asthma. Its pathogenesis in asthma is most likely multifactorial. Several features of asthma pathophysiology contribute to this hyperresponsiveness. These include structural changes to the airways, such as airway remodelling, which result in fixed airflow obstruction, but also inflammatory changes. Recently, the role of neurotrophins and their effects on neurogenic remodelling of the airways has been added to the mechanisms contributing to AHR. While inflammatory contributions to AHR can be reversible following treatment a complete loss of airway hyperresponsiveness in asthma is an uncommon event suggesting that the pathogenesis of AHR cannot be explained by inflammation alone. Airway hyperresponsiveness in asthma does not show a plateau effect to increasing doses of the respective stimulus. Thus, with increasing dose of stimulus the asthmatic airway will constrict further, which is characteristic neither for normal airways nor for airways in COPD.

In contrast to asthma, airway hyperresponsiveness in COPD is typically limited to direct stimuli such as histamine suggesting that the airway response in COPD is largely determined by airway calibre rather than an inflammatory bronchoconstriction.

1.8 Beta-receptor blockers

Asthmatic airways have a peculiar sensitivity to beta-receptor blockers. Exposure of patients with asthma even to low doses or even topical application can result in
deterioration of asthma control and severe and long-lasting bronchospasm. The precise mechanisms responsible for this unique pathophysiological feature of asthma are incompletely understood but may be associated with postsynaptic regulation of neurotransmitter release in the airways. While bronchial asthma is a contraindication for beta-blockers their use in COPD is not associated with any deterioration of pulmonary function, again suggesting fundamental differences in asthma and COPD.

Furthermore, the chronic, unbalanced use of $\beta_2$-agonists in asthma has been associated with a tachyphylaxis to the bronchoprotective effects of $\beta_2$-agonists and possibly a loss in asthma control and an increase in asthma deaths.\textsuperscript{59} This has not been observed for COPD, where the bronchodilator response to $\beta_2$-agonists is in general lower than in asthma but where chronic use of $\beta_2$-agonists has not been associated with a loss of effect or a loss of control of COPD.

1.9 **Differential diagnosis of asthma and COPD**

The differential diagnosis of asthma and COPD include a large number of diseases such as:

- gastro-oesophageal reflux disease;
- vocal-cord dysfunction syndrome;
- hyperventilation syndrome;
- pulmonary oedema;
- congestive heart failure;
- carcinoid syndrome;
- tumours that obstruct central airways;
- pneumothorax;
- tracheomalacia;
- bronchiolitis obliterans;
- recurrent pulmonary emboli;
- pulmonary vasculitis;
- collagen vascular diseases;
- Swyer-James syndrome, etc.

All of these can, however, also occur together with asthma or COPD, which can further complicate diagnostic accuracy.

However, the fact that end-stage lung disease in severe asthma or COPD can at times be clinically indistinguishable is determined by the possible pattern of response of the affected organ. Whether so-called neutrophilic asthma (in which neutrophils are the predominant inflammatory cell in the airways) represents a ‘burned out’ variant of chronic (severe) asthma where the asthma-specific cellular inflammation is replaced by a
non-specific, neutrophil-dominated pathology is unclear and requires further studies. Similarly, the precise role of neutrophils in the 'neutrophil-dominated' pathology of COPD is uncertain. While neutrophils can contribute to parenchymal destruction with elastin-degrading enzymes their contribution to a COPD-specific inflammation is still unclear.

1.10 Overlap syndrome

It has been emphasized for a long time that there are a number of patients who are not reflected in clinical studies and who present with features of both COPD and asthma. This condition has been referred to as 'overlap syndrome', and it has been proposed that it can be recognized by the coexistence of increased variability of airflow in a patient with incompletely reversible airway obstruction. These patients may have either mild allergic asthma with a smoking history, or a longstanding asthma with progressive decline in pulmonary function, or have developed adult-onset, intrinsic asthma coexistent with a prior smoking history. Although inflammatory (neutrophils) and physiological features (smoking history, decline in pulmonary function, increasing age, recurrent exacerbations) in these patients can resemble classical COPD a prior history of asthma clearly contributes to their pathogenesis. Due to the fact that these patients are generally excluded from clinical trials, mainly based on their incomplete response to bronchodilators, the generalisibility from such trials to the general asthma (and COPD) population is limited. Whether the pathogenetic features of asthma and COPD actually converge in this population or whether different pathologies result in similar outcomes remains a controversial issue and will require future research. Increased attention to the course of bronchial asthma in relation to other chronic obstructive airway disease, especially in older people, is needed to improve care and subsequently prognosis with improved health outcomes.

1.11 Conclusion

Despite the fact that asthma and COPD can at times present with similar symptoms and similar changes in pulmonary function there is little evidence suggesting a common pathogenesis. In some, usually those asthma patients who smoke or who have been smoking, the individual contribution of asthma and smoking to the signs and symptoms of the disease can be difficult to separate. Especially in older patients with longstanding asthma and loss of reversibility, separation from COPD can be difficult. This patient group has usually been omitted from clinical studies. Despite the fact that a considerable number of patients are affected by this condition it is not well represented in guidelines and the general physician's perception. One of the main differences between asthma and COPD today remains that asthma can be treated while COPD can be prevented. However, at present there is little evidence that asthma can be prevented, while the response of COPD to currently available therapy is limited. This calls for future research
to address the long-term consequences of either disease in order to develop specific therapies with improved health outcomes for asthma as well as COPD.

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