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REVIEW

The definition and diagnosis of Asthma

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Summary

The diagnosis of asthma depends on what we mean by the word. Its definition continues to be controversial because there is no single genetic or environmental cause. Addressed from a descriptive point of view, the disease components include airway inflammation, symptoms, variable airflow limitation and chronic airflow limitation. The *essentialist* definition conveys the message that asthma is a separate disease entity, fails to identify a primary defining characteristic which separates it from other diseases and is long winded. These disadvantages are overcome by the *nominalist* definition of asthma in which the word 'asthma' *refers* to an abnormality of airway function, specifically to wide variations in airflow limitation over short periods of time. In patients with asthma the other components of airway disease need to be considered. These have separate *nominalist* definitions and especially include different types of bronchitis for airway inflammation and chronic obstructive pulmonary disease for chronic airflow limitation. What is present will vary between and within patients. The accurate diagnosis of asthma and of other components of disease all require objective measurements. Currently spirometry and airway responsiveness should be available to the general practitioner, who sees milder disease, and additional quantitative sputum cell counts in specialist practice, where moderate to severe disease is more prevalent. Such measurements characterize the patient, identify heterogeneity and allow treatment to be personalized.

Introduction

The diagnosis of asthma depends on how we define it. However, defining asthma has been controversial and confused. Controversial, because most recent guidance documents convey asthma as a disease entity or concept, while for almost 50 years it has been argued and widely accepted that this is inappropriate. Confused, because it has come to mean different things to different people. Some have even suggested that the name be abolished. With advances in knowledge about airway disease(s) in general, the time is right to reconsider what we mean by asthma, its diagnosis, and its assessment. Central to the discussion is the appreciation of the heterogeneity of components of airway disease(s), of the careful use of words, of whether we regard asthma as a disease entity or as an abnormality of one of its components, and of the importance of measurements for accurate diagnosis and the individualization (or personalization) of optimum treatment by specialists.

Components of airway disease(s)

In the past 50 years components of airway disease(s) have not changed [1–6]. They include airway inflammation, symptoms, variable airflow limitation [that includes airway hyperresponsiveness (AHR)] and chronic airflow limitation (that implies structural changes). Improved knowledge has however illustrated how these relate and interact (Fig. 1a) [7]. Specifically, airway inflammation is central to the other components. It is of different types as illustrated by sputum cell counts and these result from different causes (Fig. 2). As these causes can vary from patient to patient and from one time to another in the same patient, so will the type of inflammation [8] and the pattern of chemical mediator release. For example, the release of bronchoconstrictive mediators can stimulate bronchoconstriction and increase variable airflow limitation [9–11]. The release of tissue damaging mediators can lead to chronic airflow limitation [12]. The airway inflammation can result in symptoms without affecting the other components. The inflammatory reactions to inhaled allergens [13] or to occupational chemicals to which the patient has become hypersensitive [14], and the inflammatory results of viral infections [15], can heighten airway responsiveness. The latter can also be heightened in patients with chronic airflow limitation associated with cigarette smoking [16]. The magnitude of AHR is an important determinant of the bronchoconstrictor response

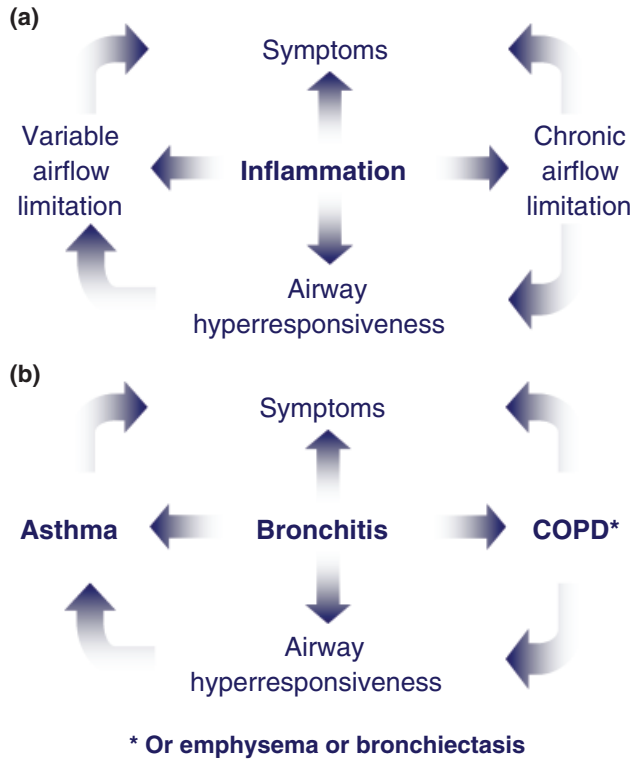

Fig. 1. (a) Relationships between symptoms, airway inflammation, and abnormalities of airway function. (b) How the components in (a) translate into how words are used to refer to disease. Asthma is synonymous with variable airflow limitation (see text) but the airway disease can include other components.

- **Neutrophilic**
  - Viral infections
  - Bacterial infections
  - Cigarette smoking
  - Occupational
  - Pollutants
  - Others
- **Eosinophilic**
  - Allergens
  - Chemical sensitizers
  - Steroid reduction
  - Unknown
- **Both** neutrophilic and eosinophilic
- **Neither** (paucigranulocytic)

Fig. 2. Types and causes of airway inflammation. These can vary between and within patients and more than one cause can be present at any one time.

to allergic [17] and non-allergic stimuli [18], to the bronchodilator effect of β-agonist and to the spontaneous diurnal variation of peak-expiratory flow (PEF) [9], i.e. to the degree of variable airflow limitation. This, as well as chronic airflow limitation, will contribute to symptoms. However, while these relationships between the components of disease are appreciated, the correlations between symptoms and abnormalities of function [19–21] or inflammation [22], and between inflammation and function [23, 24], are poor. This means that while the inflammation can affect the other components it does not always do so. Its effect will vary depending on the cell and molecular characteristics of the inflammation, on the degree of airway responsiveness and the pathological reasons for this, on lifestyle influences and on the patient's ability to recognize abnormalities. An appreciation of this is important with respect to the definition, diagnosis and assessment of airway disease(s) and their heterogeneity between and within individuals.

Asthma as a component of airway disease

The most detailed recent discourse on defining disease, and of asthma in particular, has been provided between 1959 and 1996 by Guy Scadding [2, 25–27], who was the founding Professor of Medicine of the Institute of Diseases of the Chest in London, now the National Heart and Lung Institute. In medical discourse, Scadding [26] advocates a *nominalist* approach to define diseases. This doctrine holds that abstract concepts, general terms, or universals have no independent existence but exist only as names. Thus he defines a disease as 'the sum of the abnormal phenomena displayed by a group of living organisms in association with a specific common characteristic by which they differ from the norm for their species in such a way to place them at a biological disadvantage'. The *sum of the abnormal phenomena* indicates that one or more components of disease can be present. However, the *specific common characteristic* is required to distinguish one disease from another [27]. Ideally it is based on a cause which might be environmental such as pulmonary tuberculosis or genetic as with cystic fibrosis or α 1 antitrypsin deficiency causing panacinar emphysema. When definition by cause is not possible, the word used might be based on symptoms and signs (which defines a syndrome), or an abnormality of function, or an aspect of pathology in ascending order as knowledge allows. Hence, the *nominalist* definition refers to a cause or component of the disease and is short.

Asthma can be defined better then a syndrome, except in young children (up to the age of about 5 or 6 years) or in underdeveloped or remote areas of a country or the world where objective measurements might not be available. In the early 1960s Scadding suggested that asthma should refer to an abnormality of function as 'a disease characterized by wide variations over short periods of time in resistance to flow in intrapulmonary airways'. This approach was also adopted by the American Thoracic Society [4]. The *wide variations over short periods* referred to improvement in spirometry after inhalation of a rapid-acting β-agonist, or to bronchoconstriction after a bronchoconstrictive stimulus such as methacholine or exercise (also know as AHR), or to the spontaneous daily

variation of PEF. This definition only considers the abnormality of smooth muscle function. It does not necessarily include the slower improvement in airway calibre after corticosteroid treatment. This involves inflammatory mechanisms, which although they can be associated with abnormalities of smooth muscle function, can also occur in their absence as indicated by lack of AHR [28, 29]. In smokers with chronic obstructive pulmonary disease (COPD) without improvement in forced-expiratory volume in 1 s (FEV_1) after β-agonist, the presence and treatment of an associated eosinophilic bronchitis with corticosteroid can improve the FEV_1 [30–32].

Asthma cannot be defined by a cause because there are many or by pathology because the commonly described pathologic features are not specific for asthma. Thus, different cellular types of airway inflammation are common to chronic airway disease in general [33–36]. Of other features seen in asthma, increased smooth muscle mass in the airway walls has been described in children with cystic fibrosis and non-cystic fibrosis bronchiectasis [37], subepithelial thickening is observed in allergic rhinitis without asthma [38] and in asymptomatic patients with AHR [39], and epithelial denudation seen in endobronchial biopsies may be an artifact and does not always correlate with the severity of symptoms, AHR or airflow obstruction [40].

This *nominalist* definition identifies asthma as just a component of the overall disease process (Figs 1a and b) [7]. At the same time as asthma was defined in this way, COPD was also primarily defined, and still is, as another specific abnormality of airway function as 'a disease characterized by airflow limitation that is not fully reversible' [41]. This is usually recognized from post-bronchodilator spirometry. However, as the airflow limitation could result from airway inflammation, it is important that this is reversed or minimized before COPD is diagnosed. Otherwise, what may appear to be COPD when, for example, steroid-responsive eosinophilic airway inflammation is present, might not be so when the inflammation has been optimally treated.

Nominalist definitions also apply to emphysema and bronchiectasis, which are based on pathological structural changes. It also applies to 'bronchitis', which can be referred to as 'inflammation in the airways' (Figs 1a and b) [7]. The airway inflammation can be objectively identified by inflammatory markers in sputum, bronchial wash, bronchoalveolar lavage or bronchial biopsy. Of these markers, refined methods of quantitative sputum cell counts are the most clinically applicable and discriminative at present [42]. They identify the type of bronchitis as eosinophilic, neutrophilic, both or neither [43], and these will vary from time to time depending on environmental factors or treatment. The use of the term 'eosinophilic bronchitis' in connection with asthma is not new. It was mentioned by Orie and Sluiter [3] in the first Bronchitis Symposium in Groningen. Gleich even suggested that asthma might be re-named 'eosinophilic bronchitis' [44] but this is inappropriate as asthma can occur without its presence [45] and eosinophilic bronchitis can occur without asthma [46]. It can also occur with rhinitis or COPD without asthma [30–32, 47]. Proof that bronchitis, hyperresponsiveness and symptoms can occur independent of each other are also provided by mathematical models. A factor analysis of various clinical characteristics of 99 patients with stable asthma demonstrated that FEV_1, FEV/VC and age loaded on factor I, PC_{20} methacholine and β-agonist response of FEV_1 loaded on factor II, and sputum eosinophilic cationic protein and eosinophils loaded on factor III [48]. Similar observations have been made in patients with a primary clinical diagnosis of COPD [49]. Hence, by using a *nominalist* approach to definitions, individual patients might have combinations of asthma, COPD, emphysema, bronchiectasis or bronchitis of different types.

Asthma as a disease entity/concept

A step back in defining asthma has resulted from recent guidance documents, which adopt an *essentialist* definition that uses words in an abstract fashion and implies that diseases can be classified into mutually exclusive categories. For example, the Global Initiative for Asthma (GINA) document defines asthma as 'a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness and coughing particularly at night or in the early morning. These episodes are usually associated with wide spread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment' [50]. Hence, it defines asthma by its clinical, physiological and pathological characteristics. It has a number of limitations. There is no primary defining characteristic which permits the diagnosis to be made and to distinguish it from other conditions. It implies that asthma is a separate disease entity or concept which differs from other disease entities like COPD; however, there is frequent overlap and, hence heterogeneity, of components in each disease entity [30, 31, 47]. The definition is long winded. It has no place in Science [27].

The issues with the GINA definition has lead to confusion of what asthma is and how it should be diagnosed. This is reflected in the British Guideline [51], which states that there are 'no standardized findings on investigation' and that 'it is not possible to make clear evidence based recommendations on how to make the diagnosis'. In spite of this, the guideline recommends what is evident from the *nominalist* definition of Scadding and others. It appropriately states that one should try to obtain objective support, that spirometry is preferred to PEF and that when the diagnosis is uncertain and there is no airflow limitation, airway responsiveness should be measured. The

- **Causal or exacerbating factors**
  - Atopy
  - Occupational
  - NSAID intolerance
  - Infections
  - Smoking
- **Inflammatory or structural abnormalities**
  - Eosinophilic/neutrophilic/both/neither
  - Emphysema
  - Bronchiectasis
- **Clinical or physiological features**
  - Age of onset
  - Episodic or persistent
  - Minimum corticosteroid treatment for control
  - COPD

Fig. 3. Phenotypes in patients with asthma.

guideline also states that 'more recent descriptions include AHR and inflammation and how these relate and are best measured is unclear'. In fact, AHR has been part of the definition since the early 1960s and, while the importance of airway inflammation has been emphasized more recently, its occurrence was also recognized at that time. We do know how they relate (Fig. 1a) and can be best measured at this time.

The confusion in the *essentialist* GINA definition is highlighted by the heterogeneity of components and causes of disease between individuals and from time to time in the same individual, and by the recent emphasis on different phenotypes of disease (Fig. 3) [52]. Phenotype refers to 'a set of observable characteristics of an individual or group resulting from the interaction of its genotype with its environment' [53]. The phenotypes, a term that is often loosely employed, might be classified into clinical or physiological, inflammatory or pathological, or possible causes or exacerbating factors [52]. They suggest that asthma and COPD are not single disease entities. As a result, the Lancet has recently suggested that asthma be abandoned as a disease concept and that it might be best to abolish the name altogether [54]. Abandoning asthma as a disease entity is also a reason for abolishing separate advisory groups on asthma or COPD in favour of combining the two. We agree with abandoning the *essentialist* definition of asthma as a disease concept. However, we advocate maintaining the *nominalist* definition of asthma which logically fits with *nominalist* definitions of other components of chronic airway disease such as COPD, bronchitis, emphysema and bronchiectasis. We support what was stated by Orie and Sluiter at the Bronchitis II Symposium [5] that the details of the individual patient should be exactly described. Also, as advocated by Gross (1980) [55], that this would provide a more precise picture and would force us to concentrate on the facts. The facts require measurements to be available and the measurements guide consideration of causes and specific treatment.

Focus on measurements

The importance of measurements was clearly stated by Lord Kelvin in 1891 [56]. 'When you can measure what you are speaking about and express it in numbers, you know something about it; but when you can not measure it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind'. Measurements are critical to understanding and individually treating airway disease which includes asthma. Symptoms are non-specific. They can result from variable airflow limitation, inflammation, chronic airflow limitation when this is moderate to severe, or other respiratory and non-respiratory conditions. Furthermore, at best, there are poor correlations between symptoms and airway function or airway inflammation and between airway function and inflammation. Hence, reliance on symptoms commonly leads to misdiagnosis, both under- or overdiagnosis, and mistreatment [21, 57, 58].

Variable airflow limitation of asthma is recognized objectively by the presence of β-agonist reversibility of FEV_1 or PEF, or of AHR, or of an increase in the diurnal variation of PEF [51]. Spirometry with FEV_1 and VC values is an initial requirement and is better then PEF because it is more sensitive and is discriminative between obstructive and no-obstructive ventilatory defects. Measurement of airway responsiveness is more sensitive to identify variable airflow limitation than β-agonist reversibility of FEV_1 and is needed to validate the diagnosis of asthma when symptoms raise the possibility and spirometry is normal [9, 59]. In general, airway responsiveness to histamine or methacholine by the tidal breathing method is more sensitive in demonstrating AHR than indirect stimuli such as exercise, eucapnic hyperventilation of dry air, mannitol or adenosine monophosphate [60]. However, there can be exceptions which means that responsiveness to an appropriate indirect stimulus might be needed to validate asthma when histamine or methacholine responsiveness is normal. An example is when current exercise symptoms are associated with current normal methacholine airway responsiveness [60]. The use of PEF to identify an increase in diurnal variation of the measurements has a disadvantage of being more open to performance error and to compliance [61]. Also, when measuring daily variation between early morning and late afternoon, the difference between the lowest PEF pre-rapid-acting β-agonist and the highest post-β-agonist values in relation to the mean is more sensitive then without adding the β-agonist effect [9].

The introduction of spirometry into general practice is often problematic, either because it is not readily available or it uses up time in a busy practice. Histamine or

methacholine tests have not been readily available in general practice. Both of these measurements should be made widely availably to general practitioners and, as the calibration of equipment and correct performance or the physiological measurements is crucial for accurate results, more consideration should be given to make them available to them through hospital or other pulmonary function laboratories. The availability of methacholine inhalation tests in general practice is particularly needed because this is where milder disease occurs (with symptoms and normal spirometry when the patient is seen), and where misdiagnosis is common. When interpreting results which are normal it is important to appreciate that these only reflect the current status of the patient. Such results do not exclude past asthma which might have been reversed completely by allergen or occupational sensitizer avoidance, the clearing of infection or by corticosteroid treatment. In this situation, current symptoms should be absent: if present, they are of another cause then asthma.

Understanding asthma in practice and research also requires measurement of airway inflammation, at least in specialist practice and when disease is moderate to severe [42, 62, 63]. The only clinical comprehensive measurement currently available is quantitative sputum cell counts [42]. Ways to introduce this into specialist practice need to be pursued because at present comprehensive alternatives are lacking. However, it is important to recognize that identification of eosinophils or neutrophils in the airway does not diagnose asthma. They help to predict the response to anti-inflammatory treatment. This is confirmed in clinical trials and in mathematical models [64].

Nominalist definitions and treatment

Nominalists definitions draw attention to the heterogeneity of airway disease in terms of causes and components, and to the treatment that is or is not required. They help to personalize treatment and prevent mistreatment.

At one end of the spectrum is asthma without bronchitis. This does not mean that treatment with a β-agonist is needed everyday. Its need will depend on the degree of AHR, the recognition by the patient of variable airflow limitation, and lifestyle. The presence of asthma does not mean that corticosteroid treatment is always needed. Exacerbations of asthma are particularly a result of eosinophilic bronchitis or infective (particularly viral) neutrophilic bronchitis [65]. The former requires causes to be identified and treatment by avoidance of these. An eosinophilic bronchitis predicts benefit from steroid treatment [66, 67]. When eosinophilic bronchitis is controlled with the smallest dose of corticosteroid possible, eosinophilic exacerbations are reduced. On the other hand, non-eosinophilic exacerbations, commonly neutrophilic and associated with an increase in total cell count (presumed to be infective in cause), are unresponsive to steroid treatment unless there is an associated eosinophilia [63]. Hence not all exacerbations of asthma will benefit from the addition of corticosteroid treatment. Furthermore not all exacerbations are equally responsive to bronchodilator treatment; steroid-responsive exacerbations (presumably eosinophilic) respond better to β-agonists than viral exacerbations (presumably non-eosinophilic) [68, 69].

At the other end of the spectrum of disease is the patient with asthma, COPD, eosinophilic bronchitis which requires a certain minimal dose of corticosteroid to control and occasional exacerbations of infective neutrophilic bronchitis. In some patients, emphysema or bronchiectasis may also be present. Some patients with COPD will be non-smokers. While COPD in cigarette smokers is usually not associated with eosinophilic bronchitis, some are and it is these that respond to corticosteroid treatment whether or not there is associated asthma [29]. The recognition of COPD in patients with asthma is important to identify. On the one hand, the presence of eosinophilic bronchitis needs to be controlled. On the other, the absence of eosinophilic bronchitis or the presence of infective bronchitis is important to identify so that over treatment with corticosteroid does not happen or appropriate antibiotic treatment is considered.

Conclusion

All of the common chronic lung diseases that affect the airways have *nominalist* definitions. Each refers to a component of the disease because none of them have a single cause. Different causes influence the pathology or abnormalities of airway function leading to heterogeneity of disease between and within individual patients. Asthma refers to 'wide variations over short periods of time in resistance to flow in intrapulmonary airways'. COPD refers to a different physiologic abnormality, bronchitis to airway inflammation and emphysema or bronchiectasis to pathology. While asthma, at one moment of time, can be present without evidence of bronchitis, it frequently occurs with eosinophilic or noneosinophilic bronchitis, or with COPD, or sometimes with bronchiectasis or emphysema. Because symptoms of airway disease are nonspecific, measurements are needed for accurate diagnosis. With these, the recognition of current asthma is easy. However, the other components of disease also need consideration, including the presence, type and severity of bronchitis. When this is done, diagnosis is accurate and complete, and the minimum treatment required for control and the treatment of exacerbations, by avoidance strategies and appropriate medications, can be personalized.

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