A "splitting" look at chronic nonspecific lung disease (CNSLD): common features but diverse pathogenesis

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ABSTRACT: The term chronic nonspecific lung disease (CNSLD) was proposed by the Ciba Symposium in 1959 as an umbrella term grouping chronic bronchitis, asthma, emphysema and irreversible or persistent obstructive lung disease. However, it has only been widely used by proponents of the Dutch Hypothesis, which states that these diseases all result from a common genetic root and should be considered as one disease. A major reason for proposing this hypothesis in 1961 was that these different entities share some common features, especially airway hyperresponsiveness. Although not formally disproven, evidence is accumulating - and reviewed here - against this "one disease concept"; hence, common features should not necessarily imply a common pathogenesis.

Overlap features are sufficiently frequent in clinical practice to cause problems for labelling patients within the scope of CNSLD. The term could still be used as a starting point for a "splitting approach", identifying a small number of important basic features in order to allow a more systematic use of established labels for diseases within CNSLD. Our proposal for labelling emphasizes a consistent use of asthma, emphysema and chronic obstructive pulmonary disease (COPD), but restricts the use of chronic bronchitis to those patients with chronic bronchial hypersecretion without chronic airways obstruction.

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Overlap syndromes are common in many areas of medicine when pathogenesis is poorly defined; traditionally they are vigorously debated by proponents of a "lumping" or a "splitting" approach. In respiratory disease the debate about lumping asthma and chronic obstructive pulmonary disease (COPD) - or chronic bronchitis and emphysema - under one umbrella term, in contrast to a splitting approach, trying to improve distinctions between them, has been going on for many years [1]. In most countries, and especially in the UK and the USA, chest physicians may be portrayed as "splitters", regarding asthma and COPD as quite different conditions. This can be easily confirmed by examining the chapter headings in standard textbooks.

Only Dutch-speaking physicians in the Netherlands and the Flemish part of Belgium have preferred to lump these diseases of intrapulmonary airways obstruction under a general heading chronic nonspecific lung disease (CNSLD), in Dutch CARA, literally translated as chronic aspecific respiratory affection. CNSLD had been proposed in 1959 by the Ciba Symposium [2] as a convenient umbrella term, but has not been widely adopted. The Ciba Symposium had foreseen this when it stated that "this cumbersome phrase will seldom be used in clinical practice, for patients will usually be allocated to one of the classes", subsequently designated as chronic bronchitis, asthma and irreversible or persistent obstructive lung disease. The widespread Dutch use of CARA, however, results from a hypothesis formulated by Oud and co-workers of Groningen in 1961 [3, 4], later coined as the Dutch hypothesis (DH), that asthma, chronic bronchitis and emphysema all result from a common genetic root and should be considered as one disease. Elsewhere in this issue [5], the senior investigators of the Groningen group have revisited their hypothesis three decades later, and set out their current views on the need to reinforce the DH and to retain the term CNSLD instead of the other well-established terms. Their vigorous defence of the DH should generate interest in view of the frequent reference to the hypothesis in recent literature.

Although the long-standing arguments about lumping and splitting may not be very relevant to everyday clinical practice, they may be more important in influencing the directions of research into pathogenesis and interpretation of overlap features. Thus, airway
hyperresponsiveness (AHR), found in both asthma and COPD, may be attributed by a splitter to the limited ways in which the lungs can respond to a vast range of widely differing insults, whilst a Dutch physician might interpret such a shared feature as positive evidence of a common pathogenetic factor.

**Same pathogenesis for asthma and COPD?**

The DH proposes that the same genetic host factor(s) interact(s) with varying environmental factors in all patients with asthma or COPD [3, 5]. The common genetic root is considered to be an innate predisposition to AHR and to allergy. An important consequence would be that disease episodes occurring in different periods of life are recognized as part of that one disease, called CNSLD. Many diseases result from the interaction between a genetic endowment and environmental modification, but can one still accept that the same genetic factors account for asthma in a child and emphysema in an elderly smoker?

AHR is the clinical feature that has been most intensively investigated in recent years. There is general agreement that AHR is consistently found in COPD as well as in asthma, but since in COPD it appears to be strongly related to geometric factors, many investigators have suggested that it may be a consequence of airway disease rather than a genetically-endowed predisposing factor to COPD. This hypothesis can only be fully tested by long-term studies of the natural history of AHR, but recent work by James et al. in Vancouver [6], quantifying how inflammatory thickening of bronchial walls could lead to AHR, provides further support for the importance of geometric factors. Other studies of the response to different challenges, the detailed shape of the dose-response curve and the relationship to eosinophilia all suggest that there are subtle differences between AHR of asthma and COPD [7, 8].

Since the original proposal of the DH in 1961, the genetics of two conditions which regularly lead to death from chronic airways obstruction, alpha,-protease inhibitor (alpha,-PI) deficiency [9] and cystic fibrosis [10], have been identified. The genetic abnormalities in these two diseases are quite different, although their clinical features would permit them to be included into the category of CNSLD or CARA. Furthermore, identification of the major forms of these defects has allowed numerous studies to be made of heterozygotes for cystic fibrosis [11] or for some of the major alleles of alpha,-PI deficiency [9]; overall these studies have had great difficulty in demonstrating any increased risk of airway obstruction or other chronic respiratory disease in heterozygotes. The genetics of atopy and AHR are much less advanced but we suspect that the abnormality responsible for alpha,-PI deficiency and cystic fibrosis is irrelevant to the great mass of patients with CNSLD even though both diseases are also associated with AHR.

Despite the common core of airway pathology in asthma and COPD there appear to be differences in the nature of airway inflammation in the two conditions, notably the importance of eosinophils in the former but not the latter, which are compatible with a lesser role for allergy in COPD. But the British or American physician is struck by how little the DH has to say on the importance of smoking and the pathogenesis of emphysema. He has been educated to believe that emphysema is not an inevitable consequence of every form of severe intrapulmonary airways obstruction, e.g. it is not anticipated in chronic asthma, cystic fibrosis or, indeed, in other forms of obstructive bronchiolitis not related to smoking. Burrows and co-workers [12, 13] claim to have provided rather strong epidemiological evidence against the “one disease concept” of the DH in distinguishing at least two types of chronic airways obstruction in older subjects, one type in which the presence of an asthmatic predisposition seemed to conform with the DH, while in the other type the chronic airways obstruction, occurring insidiously after many years of heavy smoking, with frequent functional and radiological evidence of emphysema, did not seem to bear any relationship to an asthmatic constitution.

How can such different groups be explained by the unifying DH? Could older patients with emphysematous COPD have had an innate predisposition to CNSLD, but have lost their allergy and part of their asthmatic-type AHR and recollection of their juvenile asthma also, and as a result of that not have been prevented from smoking heavily for many years [14]? When only a minority of heavy smokers appear to have either a protease-antiprotease imbalance or susceptible small airways, can this be accounted for by the same genetic factors as those predisposing to asthma? The great strength of the DH is the emphasis that it places on the genetic and childhood factors influencing the expression of the disease. Its weakness is that it may inhibit the investigation of diverse pathogenetic factors in special sub-groups. Progress will indeed depend on such investigations, on more well-conducted, long-term follow-up studies and also on a better insight into the genetics of CNSLD. Meanwhile, we leave it to the reader to judge whether the hypothesis resists a careful revisit in 1991.

**Lumping or splitting at the clinical level**

At the clinical level there is a vast common ground between the Groningen approach and that of the other respiratory physicians. We can all agree that overlap patients are sufficiently frequent to cause problems for labelling in practice, expressed in such widely used terms as chronic asthmatic bronchitis. We can all agree that discrimination between chronic airways obstruction due to intrinsic disease of the airways and due to emphysema is often impossible in clinical medicine. We may have difficulty in defining chronic bronchitis, in distinguishing between asthma and bronchitis, in deciding whether AHR is of genetic or environmental origin, and in deciding how much reversibility is required to make a diagnosis of asthma or exclude a diagnosis of COPD. We may be unhappy about including patients without
airways obstruction under the general heading of CNSLD, although this aims to include "simple" chronic bronchitis.

A recent study of model case histories [15] demonstrated that it is easy to add new labels, but difficult to displace old ones as long established as asthma, chronic bronchitis and emphysema. We suspect that an attempt to establish the general use of CNSLD would be difficult. The proposal of the Groningen workers to describe more adequately each patient by adding a (long) list of precise defining criteria does not seem to us to take sufficiently into account the need for practical or well-established short-hand labels for communication within the medical profession or with the lay public.

Because of uncertainties about pathogenesis and subdivision of patients, however, we would have less difficulty in using the term CNSLD as a common starting point for any patient within its scope, as originally proposed by the Ciba symposium(*). From there a small number of important basic features, on which one could agree without great difficulty, could be identified and graded, leading to a more systematic use of the available short-hand labels for diseases within CNSLD.

Basic features in CNSLD

Review of the current literature suggests that the clinician is concerned to identify only a few basic features [16, 17], which are believed to help to distinguish important differences within the whole spectrum of CNSLD. These appear to be the presence or absence of: 1) chronic bronchial hypersecretion; 2) alveolar destruction; 3) airways obstruction.

Each of these features develops insidiously; in the following comments we include criteria for deciding that a feature is sufficiently developed to justify inclusion in a clinical label. These boundaries are clearly arbitrary.

1) Chronic bronchial hypersecretion

This has received much emphasis in the past when chronic cough and sputum production were thought to be the first symptoms heralding the subsequent development of airways obstruction. The work of Fletcher et al. [18] has since popularized the idea that the hypersecretory and the obstructive disorders were relatively distinct, although both were associated with cigarette smoking, but continued attention to the presence of hypersecretion can be justified by its relationship to the tendency to recurrent bronchial infection.

Mucosal inflammation and bronchial gland hyperplasia in central airways are the best morphological correlates to the clinical features of chronic cough and production of phlegm. The precise original Medical Research Council (MRC) criteria for diagnosing chronic bronchial mucus hypersecretion [19] are based on history and require cough and sputum production to be present for most days during at least three months a year for at least two subsequent years.

2) Alveolar destruction (emphysema)

For many years emphysema was regarded as being the direct cause of breathlessness in patients with chronic bronchitis and emphysema; thus a smoker with simple chronic bronchitis who became persistently breathless was thought to have developed emphysema. Nowadays, the precise role of emphysema in contributing to airways obstruction and disordered gas exchange is more controversial, because much of the pathophysiology could equally well be explained by disease of the airways. In vivo, decreased vascular markings on chest radiograph or computerized tomographic (CT) scan, a reduced diffusing capacity of the lungs for carbon monoxide (Tlco) with a low Tlco/alveolar volume (VA) value or decreased elastic recoil indicate alveolar destruction. This can be diagnosed with a fair degree of confidence if CT markings and density are markedly reduced and if Tlco is decreased below 60% of predicted, not attributable to any other cause.

3) Airways obstruction

The features that the clinician is usually trying to distinguish are related to the severity of the airways obstruction, the underlying pathophysiological process and the response to bronchodilator or to bronchoconstrictor stimuli. The overlap between these aims is obvious.

The characteristic asthmatic features are variability usually associated with enhanced bronchoconstrictor and bronchodilator responses. In general few details are known about the sites of airway narrowing in asthma or of changes induced by bronchoconstrictor and bronchodilator stimuli.

Airway hyperresponsiveness (AHR). This refers to exaggerated airway narrowing responses to stimuli of different kinds. Precise mechanisms are still unclear but probably AHR can be induced or increased by airway inflammation. As mentioned previously, a component
can be attributed to the effect of airway geometry, and this might even be the sole cause for AHR found in heavy cigarette smokers. Diagnosis can be suspected from history, but confirmation requires an abnormal standardized bronchial challenge test or any other objective evidence for bronchial lability.

**Reversible airways obstruction.** This is the reversible component of airflow limitation, likely to be due to excessive smooth muscle tone and hypertrophy, as well as mucosal oedema. The diagnosis is confirmed by demonstrating significant improvement of airway function in response to inhaled, oral or parenteral bronchodilators or steroids. Unfortunately there are no generally accepted criteria for defining and grading reversibility; one proposal could be to grade it as manifest if the maximal increase over baseline in forced expiratory volume in one second (FEV₁) following drug trial is at least 20%, when the baseline FEV₁ is ≤1.5 l, and 15% if baseline FEV₁ is >1.5 l.

**Chronic obstructive bronchiolitis.** Alveolar destruction and chronic obstructive bronchiolitis largely account for the irreversible component of chronic airflow limitation, which can be diagnosed when despite maximal treatment FEV₁ has not been shown to exceed 80% of lower confidence limits of normal values predicted on at least three occasions during one year.

Chronic obstructive bronchiolitis is meant to represent the non-emphysematous component of irreversible airflow limitation, resulting from narrowing of small peripheral airways, essentially the membranous and respiratory bronchioles, due to goblet cell metaplasia, inflammatory exude and mucus plugging, and leading to distortion and even total obliteration. Most studies suggest that static narrowing of larger conducting airways is unusual in COPD, although enhanced dynamic collapse of these airways on expiration is common.

Table 1 estimates the usual combination of these basic features in patients corresponding to commonly used clinical labels. When we compare these features to the use of the three classic labels, asthma, chronic bronchitis and emphysema, two comments can be made. First, there is no commonly used term to describe Airways obstruction due to intrinsic abnormality of the airways themselves or to describe its location. To some extent this lack is concealed by the term COPD which describes the presence of irreversible airways obstruction, but does not attempt to distinguish whether this is due to emphysema or intrinsic airway narrowing, or to indicate the site of any disease of the airways. This is excellent for clinical practice, but inconvenient for discussion of pathogenesis and has led to the suggested use of chronic obstructive bronchiolitis [16]. Secondly, although each of the basic features is characteristically most pronounced in one of the clinical subgroups, overlap features are common in asthma, chronic bronchitis and emphysema and even more obvious when the label is COPD.

Since these basic features are actually determining clinical presentation, prognosis and treatment, they are identified and graded at every diagnostic work-up. Names given to these features may be improved and other features may be taken into account, e.g. the presence of allergy and an atopic background, or of respiratory failure. More work may be needed to reach a wider agreement on the identification and the gradation of such features.

Information as to which labels can be expected to be used in various types of CNSLD is provided by the recent study of four model case histories [15]. Table 2, drawn from the data of this study, gives for each case: 1) age, as well as baseline and maximal FEV₁ values; 2) intensity of four basic features as described in the case presentations; 3) labels used, either alone or in combination, by 121 respondents from 11 countries, mostly teachers of respiratory medicine. It indicates that asthma and emphysema are well accepted, that chronic bronchitis is the label used to refer to chronic bronchial hypersecretion, but half the respondents qualified the term specifically to indicate the absence of airways obstruction. In non-asthmatic poorly reversible chronic airways obstruction the term COPD appears to be best accepted.
Table 2. — Use of labels in chronic nonspecific lung disease

<table>
<thead>
<tr>
<th>Model cases</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>50</td>
<td>55</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>FEV₁ % pred</td>
<td>Baseline</td>
<td>After oral steroids (3 wks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>98</td>
<td>65</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>101</td>
<td>92</td>
<td>42</td>
<td>50</td>
</tr>
</tbody>
</table>

Intensity of basic features

- Bronchial hypersecretion
- Alveolar destruction
- Reversible obstruction
- Obstructive bronchiolitis

<table>
<thead>
<tr>
<th>Labels used</th>
<th>% (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>71</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>46</td>
</tr>
<tr>
<td>Non-obstructive, etc.</td>
<td>48</td>
</tr>
<tr>
<td>Obstructive</td>
<td>-</td>
</tr>
<tr>
<td>Asthmatic</td>
<td>-</td>
</tr>
<tr>
<td>Emphysema</td>
<td>2</td>
</tr>
<tr>
<td>COPD</td>
<td>2</td>
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</tbody>
</table>

See also Pride et al. [15]: °; all model patients are or were cigarette smokers. Patient B had suffered mild childhood asthma. Patient D had marked hypoxaemia and mild hypercapnia.

*: degree of intensity: - = absent, + = mild, ++ = moderate, +++ = severe.

Proposals for labelling within CNSLD (table 3)

From this experience we believe the major requirement is a more consistent use of available labels. An improvement would be the more general use of chronic obstructive pulmonary disease (COPD) - or its equivalents in French (maladie pulmonaire chronique obstructive), German (chronische obstructive lungenkrankheit), Dutch (chronische obstructieve longziekte), rather than its near-synonyms chronic obstructive airways disease (COAD), chronic airways obstruction (CAO), chronic airflow limitation (CAL). In view of the now popular distinction between hypersecretory and obstructive disease in smokers, COPD alone would not imply accompanying hypersecretion. The use of COPD is also emphasized in the new International Classification of Diseases (ICD-10). Undoubtedly chronic bronchitis is a confusing term, as shown by the response to model cases A and D (table 2), which exactly reflects the ambiguity in the new ICD-10 classification where “chronic bronchitis unspecified” is included under chronic obstructive disease. Attempts to redefine asthma as “chronic eosinophilic bronchitis” [20] would increase these ambiguities. The more descriptive label, chronic bronchial hypersecretion, is self-explanatory and is already familiar.

Despite the difficulties in precisely defining asthma and differentiating asthma from overlap patients with COPD, we believe the term will prove impossible to displace. Several studies in children [21] and adults [22] have suggested labelling as chronic bronchitis (and presumably also as COPD) leads to less treatment being applied than if the label is asthma. But hopefully there should be no difference in the treatment applied to “COPD with reversibility” [23] and “asthma with incomplete reversibility”, at least not while treatments for the reversible components of airways obstruction remain identical. Depending, thus, on the manifest presence of reversibility, alveolar destruction or hypersecretion, one can add to the main term labels referring to them, e.g. COPD with reversibility and emphysema. Alternatively qualifying adjectives before the term COPD could be used, e.g. asthmatic, hypersecretory or emphysematous. This may be controversial but would at least refer more explicitly to chronic airways obstruction as the most important feature. Such composite labels should be self-explanatory and complete to avoid introducing further confusion. Some composite labels in current use are ambiguous; thus, asthmatic bronchitis presumably implies variability in airways obstruction but it is uncertain whether bronchitis implies incomplete reversibility, bronchial hypersecretion, or both! When neither chronic airways obstruction nor an asthma pattern are present, only the features that are present are labelled, e.g. chronic bronchitis (or preferably chronic bronchial hypersecretion) and emphysema (or possibly pure emphysema).

Concluding remarks

The Dutch Hypothesis and its consequent unifying view on CNSLD undoubtedly remains an intellectual challenge in 1991. The Groningen view has been complemented with the practical proposal not to use CNSLD or CARA as the only diagnostic label in daily practice, but to add to it a number of defining criteria, including...
Table 3. – Proposals for labelling in CNSLD

1. Chronic airways obstruction:
   - FEV₁ and/or FEV₁/VC below lower confidence limits of normal values in the absence of a restrictive pattern
   - found to be present more than three times in one year despite adequate treatment
   Proposed label = Chronic obstructive pulmonary disease (COPD)

   1.1 With reversibility:
      - maximal FEV₁ increase from basal value after bronchodilators and/or corticosteroids: ≥15% from FEV₁ >1.5 l
      ≥20% from FEV₁ ≤1.5 l
   Proposed label = COPD with reversibility (or asthmatic COPD?)

   1.2 With chronic bronchial hypersecretion:
      - sputum on most days during at least 3 months for at least two years
   Proposed label = COPD with bronchial hypersecretion (or hypersecretory COPD?)

   1.3 With alveolar destruction:
      - markedly decreased vascular markings on CT-scan
      - TLco below 60% predicted and not attributable to any other cause
   Proposed label = COPD with emphysema (or emphysematous COPD?)

2. Asthma pattern:
   - current or previous history of attacks of dyspnoea and wheezing
   - rapid and/or total reversibility of airway obstruction
   - circadian variability of peak flow rate exceeding 15%
   - marked airway hyperresponsiveness or with specific pattern [7, 8]
   - atopy, blood or sputum eosinophilia, or increased total serum IgE
   Proposed label = Asthma

   2.1 With incomplete reversibility:
      Proposed label = Asthma with incomplete reversibility

   2.2 With chronic bronchial hypersecretion:
      Proposed label = Asthma with bronchial hypersecretion

3. No chronic airways obstruction, no asthma pattern:

   3.1 Chronic bronchial hypersecretion:
      Proposed label = (Simple) Chronic bronchitis (or chronic bronchial hypersecretion?)

   3.2 Alveolar destruction:
      Proposed label = (Pure) Emphysema

   For abbreviations see text.

previous history, age, sex, symptoms, allergic status, complications, hyperresponsiveness and reversibility. Our alternative approach emphasizing a wider range of pathogenetic factors lacks this ambitious overview, but puts more emphasis on the development of specific preventive and therapeutic measures beyond the current use of bronchodilators, anti-inflammatory agents and antibiotics. Such specific therapy or prevention is already relevant for some specific allergens causing asthma, for alpha₁-PI deficiency and hypogammaglobulinaemia and may soon be available for cystic fibrosis.

Despite our sceptic view on the DH as a model of pathogenesis, from a clinical viewpoint we do not reject an initial lumping of patients with intrapulmonary airways obstruction under the umbrella term CNSLD, because it would reduce the risk of too swiftly allocating patients to either asthma or COPD. Even if the type of treatment does not seem to be greatly affected by labelling, its intensity and duration might be [24]. However, from CNSLD a careful splitting approach should be undertaken through a precise identification and gradation of basic features, followed by systematic use of some well-accepted labels. Such further standardization of terminology is not a futile exercise. It should facilitate teaching and also scientific communication especially in epidemiology. Even if we seem able to improve the use of terminology in communications between physicians, designing adequate labels for communicating with patients and the general public remains a major challenge.
References