

Revisiting the Dutch hypothesis

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3. To review specific clinical factors as guidance for treatment of asthma and COPD.

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The Dutch hypothesis was first articulated in 1961, when many novel and advanced scientific techniques were not available, such as genomics techniques for pinpointing genes, gene expression, lipid and protein profiles, and the microbiome. In addition, computed tomographic scans and advanced analysis techniques to dissect (small) airways disease and emphysema were not available. At that time, the group of researchers under the visionary guidance of Professor N. G. M. Orie put forward that both genetic and environmental factors can determine whether one would have airway obstructive diseases, such as asthma and chronic obstructive pulmonary disease (COPD). Moreover, they stipulated that the phenotype of obstructive airway disease could

be affected by sex and changes with aging. Orie and colleagues' call to carefully phenotype patients with obstructive airways diseases has been adopted by many current researchers in an attempt to determine the heterogeneity of both asthma and COPD to better define these diseases and optimize their treatment. The founders of the Dutch hypothesis were far ahead of their time, and we can learn from their insights. We should fully characterize all patients in our clinical practice and not just state that they have asthma, COPD, or asthma and COPD overlap syndrome. This detailed phenotyping can help in understanding these obstructive airway diseases and provide guidance for disease management. (J Allergy Clin Immunol 2015;136:521-9.)

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THE HISTORY OF THE DUTCH HYPOTHESIS

"...one must be impressed by the very long road medicine must travel before an understanding of disease is reached, even when its clinical symptomatology is relatively simple" (Bronchitis I, 1961, page 1).¹

In the beginning of the past century, tuberculosis was one of the most prominent causes of chronic cough and phlegm, yet this

Abbreviations used

ACOS:	Asthma and COPD overlap syndrome
BHR:	Bronchial hyperresponsiveness
COPD:	Chronic obstructive pulmonary disease
CT:	Computed tomography
GWAS:	Genome-wide association study
ICS:	Inhaled corticosteroid
RCT:	Randomized controlled trial
SNP:	Single nucleotide polymorphism

changed when appropriate treatment was developed. Still, many subjects presented with chronic cough and phlegm that were not related to bacterial infections. Thus the causes of these respiratory symptoms and their underlying mechanisms were unknown. Therefore in 1960, Professors Orie, Sluiter, and de Vries organized a multidisciplinary symposium in Groningen, The Netherlands, with the name “bronchitis” and published this in a book (Fig 1).¹ They brought together skilled researchers from all over the world with experience in bacteriology, physiology, epidemiology, or environmental and clinical science. In the “Opening Address” of the first bronchitis symposium, he said the following¹: “...we hope to contribute to mutual understanding in those cases where controversial points of view have arisen from differences due to terminology or from a clever but too limited approach to the bronchitis problem.” This series of bronchitis symposia continues, with the last occurring in 2014.

This article will describe the history of the “Dutch hypothesis,” which was the consequence of the bronchitis symposium in 1960. We will try to put the different elements of this hypothesis (risk factors, clinical expression, and implications for clinical practice) into perspective for clinicians.

The discussions on the topic of differences and similarities between (chronic) bronchitis, emphysema, and asthma resulted in novel views on obstructive airway diseases, views that were proposed by Orie and Sluiter,¹ suggesting that asthma and chronic obstructive pulmonary disease (COPD; at that time labeled bronchitis) had common origins and clinical expressions and were determined both by endogenous (heredity, age, and sex) and exogenous (environment: allergens, smoking, viruses, and air pollution) factors. These novel views raised much debate and opposition. There were other views about the origins of bronchitis, especially one by Fletcher and Pride,² who put forward the hypothesis that this disease was caused by respiratory tract infections. This led to Orie’s views being dubbed by Fletcher and Pride as the “Dutch hypothesis” in 1969. In subsequent years, there was much debate and rethinking of the Dutch hypothesis, with defendants and opponents sharpening their points of view, leading to subsequent reviews and revisions. One of the interpretations was that the Dutch hypothesis was “lumping” asthma and COPD together, regarding it as one disease with one treatment.³ This was later set off from the opposite view of totally differentiating these diseases from one another, the “splitting view,”³ a view known also as the British hypothesis, which suggested no common origin or relationship between asthma and COPD.⁴

Of importance and generally forgotten, Orie and Sluiter¹ strongly recommended not to place a single disease label on a patient (ie, asthma or chronic bronchitis) but rather phenotype patients according to a scheme (Table I).⁵ They proposed this to be an integral part of their approach to disease definition, as stated

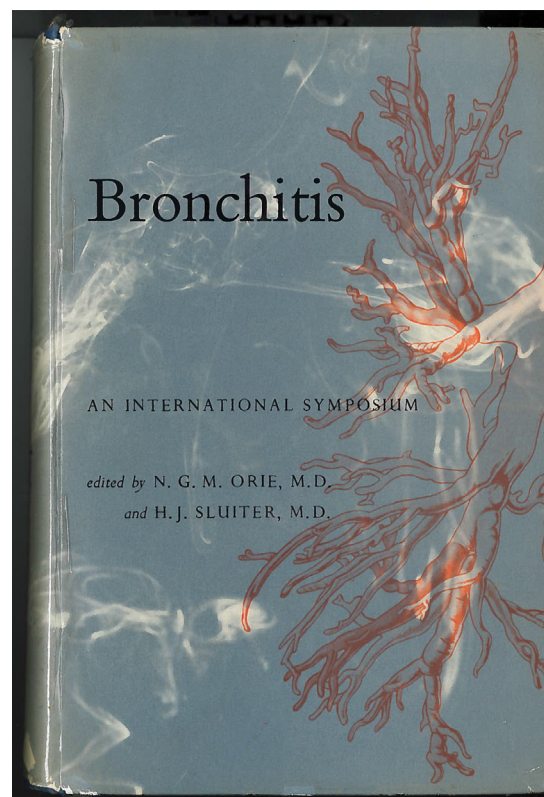


FIG 1. Cover of the first book on bronchitis, symposia on asthma and COPD, and their similarities and discrepancies held in Groningen as of 1960. This contained the foundation of the Dutch hypothesis.

during the same bronchitis meeting, where they put forward the commonalities of asthma and COPD.¹ This strongly stimulated clinicians to provide a detailed description of patients’ signs, symptoms, and clinical characteristics, which were collectively denoted as chronic nonspecific lung disease. Although far ahead of its time, the way that Orie¹ defined phenotypes in 1961 is slightly different from how phenotyping is understood today in which multiple characteristics are integrated to define one phenotype, such as “late-onset eosinophilic asthma.”

Asthma and COPD are both complex diseases for which the underlying pathophysiology remains largely unknown. The genetic part of the Dutch hypothesis has not been proved because no strong common genetic origins of asthma and COPD have been identified by using current genome-wide association studies (GWASs). However, the studies have provided many good ideas and stimulated in-depth research into obstructive airway diseases. Some ideas have led to new developments in insights and treatment of asthma and COPD. Orie and colleagues put forward several important views that are still of value: (1) asthma and bronchitis (currently COPD) have a hereditary component; (2) sex and age should be taken into account when defining symptoms and signs of disease (ie, a male preponderance of asthma in childhood) and an increase in respiratory symptoms and hyper-reactivity with aging, in which “mechanical influences probably considerably affect the clinical picture”; and (3) eosinophilia can be linked to allergy, and recent bacterial infections tend to decrease the number of circulating eosinophils.

What has become clear is that there is large phenotypic heterogeneity of both asthma and COPD. This brings us back to

TABLE I. Phenotypes necessary to define a patient with respiratory symptoms according to Orie and Sluiter in *Bronchitis*¹

1. Personal history of disease linked to asthmatic constitution (infantile eczema, hay fever, asthma, and bronchitis)
2. Family history of these diseases
3. Symptoms* (type, severity, and spontaneous variability in cough, sputum production, and dyspnea)
4. Clinical picture (physical examination)
5. Basic elements
Hyperreactivity
Allergy
6. Infections* (bacterial and viral)
7. Air pollution* (indoors and outdoors, smoking)*
8. Lung function
Spontaneous and induced changes
Level of FEV ₁
FEV ₁ reaction to bronchodilating drugs
FEV ₁ reaction to bronchoconstricting drugs
9. Blood and sputum eosinophilia

*These annotations are from another publication, also published in 1961.⁵

one of the final messages of the group that put forward the Dutch hypothesis: one should define patients by various characteristics.

From the first bronchitis symposia,^{1,6} the main focus has been on risk factors for disease development. Advanced techniques, such as genomics and computed tomographic (CT) scans, were not available, and hence physiology and clinical phenotyping were important determinants of the insights in asthma and COPD at that time. However, with great vision and foresight, the participants envisaged that genetics would be of importance in interaction with environmental factors. Moreover, viral and bacterial infections, as well as air pollution and eosinophils, were already mentioned as important drivers of these diseases.

In this article we look back at the Dutch hypothesis, discuss new insights into the development of the diseases involved, and provide an overview of the parameters that were proposed by Professor Orie and his colleagues as a prerogative for defining risk factors, clinical expression, and clinical management of respiratory disease (Table I).

RISK FACTORS

Genetics

Twin and family studies indicate that both asthma and COPD have a strong genetic contribution. Over the past 10 years, GWASs have shown that multiple prevalent single nucleotide polymorphisms (SNPs) explain a limited proportion of asthma and COPD. Candidate gene studies for asthma and COPD have suggested that there are shared genetic origins for asthma and COPD, such as matrix metalloproteinase 9 (*MMP9*) and *TGFBI*.⁷ However, SNPs identified by using GWASs for asthma and COPD separately show no clear overlap. Some of the SNPs associated with lung function in general populations are also associated with lung function in asthmatic populations.⁸

Recently, 2 GWASs specifically investigated the shared genetic origins of asthma and COPD.^{9,10} A Dutch combined meta-analysis of 2 different populations of asthmatic patients and patients with COPD indicated the involvement of 3 potential loci for both diseases: chromosomes 2p24.3, 5q23.1 and 13q14.2,

containing DEAD-box polypeptide 1 (DDX1), COMM domain containing 10 (*COMM10*; both of which participate in the nuclear factor κ B pathway), and guanine nucleotide binding protein gamma 5 pseudogene 5 (*GNG5P5*, a pseudogene), respectively.⁹ The replication analysis in 7 additional populations was nonsignificant, suggesting that there is no strong common genetic component in asthma and COPD. Alternative explanations for these findings include the effects of rare genetic variants not captured by GWASs and involvement of population-specific environmental factors in different countries and continents, which is compatible with the Dutch hypothesis that genetic and environmental risk factors determine the clinical phenotypic outcome, such as lifestyle and occupation.

The second article¹⁰ analyzed patients with COPD with a doctor's diagnosis of asthma before the age of 40 years, so-called asthma and COPD overlap syndrome (ACOS), and set this population off against patients with COPD without a doctor's diagnosis of asthma. In addition, they investigated associations between ACOS and SNPs previously associated with asthma or COPD. Again, no genome-wide significant hits were found in the 450 patients with ACOS and 3120 patients with COPD, and no significant association with known asthma or COPD genes were found. Some top hits were of interest, such as the lung developmental gene Sry-related HMG-BOX gene 5 (*SOX5*) and G protein-coupled receptor 65 (*GPR65*), which neared genome-wide significance in a meta-analysis of African American and non-Hispanic white subjects and is a gene involved in eosinophil activation. In summary, although candidate studies appeared to confirm the idea of a shared genetic origin of asthma and COPD, thus far, this has not been confirmed in large-scale GWASs.

Allergy

Allergy refers to type 1 hypersensitivity to an environmental antigen. Atopy is defined by immediate wheal-and-flare skin reactions to common environmental antigens and familial aggregation or heritability of the trait in families. At the time of formulation of the Dutch hypothesis, IgE had just been discovered, and most allergy evaluation was through skin tests, which are not reliable in older subjects. Increased total serum IgE levels can occur as a result of allergy but are also associated with cigarette smoke exposure, either *in utero* or through active smoking. Thus not all increases in total serum IgE levels result from immediate-type hypersensitivity to environmental antigen.¹¹

In healthy subjects IgE levels increase with increasing age until the mid-30s and then decrease progressively in later adult life. There have been secular increases in IgE levels over time that parallel the increase in immediate-type skin test reactivity. Roughly 50% of the US young adult population will have increased total and specific IgE levels.¹² Serum increases in cord blood or early-life total and specific IgE levels are among the earliest predictors of childhood asthma and are clear determinants of asthma severity and persistence in childhood. However, the relationship of increased IgE levels to reduced growth in lung function in nonasthmatic children, early decrease in lung function in asthmatic or nonasthmatic adults, and development of COPD is negative or nonexistent. In addition, although total IgE levels are increased in smokers and patients with COPD, there is no evidence that this increase has any effect on the clinical course of COPD or on COPD-related mortality.¹¹

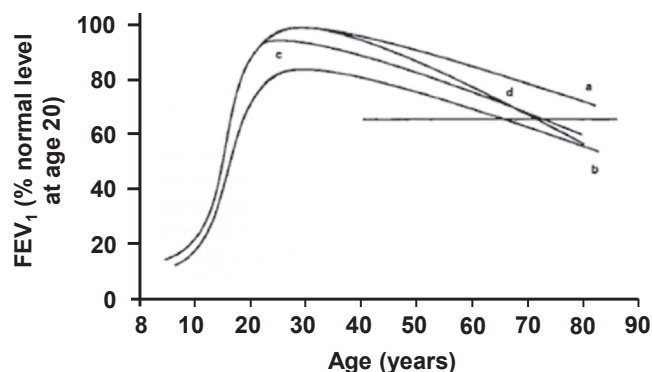


FIG 2. Hypothetical tracking curves of FEV₁ for a patient through life. The normal pattern of growth and decrease with age is shown by curve *a*. Significantly reduced FEV₁ can develop through a normal rate of decrease after a reduced growth phase (curve *b*), through an early initiation of decrease after normal growth (curve *c*), or through an accelerated decrease after normal growth (curve *d*). Reproduced with permission from Rijcken.³⁵

Although increased IgE levels can contribute to eosinophilic airway inflammation, eosinophilic inflammation can be activated by non-IgE-related mechanisms. There are clearly data suggesting that, independent of other allergy and lung function phenotypes, peripheral blood eosinophils are a risk factor for reduced maximal level of lung function,¹³ development of COPD,¹⁴ and death from COPD.¹⁵ Of the 3 factors of skin test response positivity, total serum IgE levels, and eosinophilia, eosinophilia also best predicts bronchial hyperresponsiveness (BHR).¹⁶ Data from the Childhood Asthma Management Program study suggested that lung growth in childhood asthma was not influenced by IgE.¹⁷ In longitudinal data from the Vlagtwedde-Vlaardingen study BHR, eosinophil counts, smoking, and respiratory symptoms were important predictors of COPD, but total IgE was not.¹³

However, total IgE cannot be dismissed altogether: it is a predictor of which adults with asthma/COPD respond to inhaled corticosteroids (ICSs).^{18,19}

In summary, total serum IgE levels are increased either by smoking or allergen exposure. Total (and specific) IgE levels are good predictors of childhood allergic asthma and of response to ICSs but not of the development or course of COPD.

BHR

Hyperreactivity was defined in *Bronchitis 1* as “an increased reactivity of the bronchial tree as found in asthmatic individuals demonstrated by the administration of histamine and acetylcholine.”¹ Because the threshold of hyperreactivity (now called hyperresponsiveness) is defined by a 20% decrease in FEV₁, it is clear that the severity of BHR is dependent on baseline FEV₁. Hyperresponsiveness is a hallmark of asthma, although not present in all asthmatic patients, and is present in some 60% of patients with COPD, even those with mild disease, when FEV₁ does not affect its outcome.²⁰ It is a risk factor for respiratory symptom development in the general population^{14,21} and additionally for reduced lung function,^{11,22} accelerated lung function decrease,^{23,24} and mortality caused by COPD.²⁵ Moreover, more severe BHR associates with a smaller chance of symptom remission.²⁶ Finally, hyperresponsiveness is a risk factor for asthma as well²⁶⁻²⁸ from 1 month of age²⁸ onward. Thus BHR is a risk factor for both asthma and COPD, as well as for their severity.

CLINICAL EXPRESSION

Lung function

The classic dichotomy of asthma as a disease of variable lung function reverting to normal between symptomatic episodes and COPD as a disease of fixed airways obstruction that never reverts to normal and is relentlessly progressive is no longer tenable. A subset of asthmatic patients has increased lung function decrease and low lung function,^{23,29} with an at best incomplete response to therapy (ie, persistent obstruction). Greater lung function decrease over time seems to occur especially with longer disease duration.³⁰ FEV₁ values might be driven by obstruction in the large and small airways, which can be present in both asthmatic patients and patients with COPD.^{31,32} Hogg et al³³ showed that a higher percentage of small airways containing inflammatory cells is associated with lower FEV₁ in patients with COPD. CT scans showed narrowing and loss of airways in patients with COPD versus healthy control subjects,^{24,25} changes already present in patients with mild COPD, even in lung regions without signs of emphysematous destruction. This suggests that small-airway obstruction precedes emphysema. These emphysematous changes are not overtly present in asthmatic patients; hence this might seem to signify that the Dutch hypothesis is at least partially invalid. However, Orie and Sluiter¹ already stipulated that changes in clinical expression are driven by environmental factors. It has now become quite clear that small-airway disease can be present in asthmatic patients as well, apart from smoking behavior.³¹ Whether it requires smoking in addition to the small-airways dysfunction to progress to frank emphysema is currently unknown.

The initially used American Thoracic Society definition of COPD as a relentlessly progressive disease has been shown to be invalid,³⁴ with some patients showing hardly any decrease in lung function over time, even though they have less than normal FEV₁ values. This can be explained by epidemiologic studies showing that some patients do not reach a normal plateau in lung function between ages 20 and 30 years (Fig 2)³⁵ and hence always remain at a lung function level of less than the normal value, even when this cannot be attributed to personal smoking.³⁶ Additionally, quitting smoking reverts these decreased values back to normal or near-normal values in patients with COPD.³⁷

Reversibility

Older textbooks provided a clear clinical decision tool that held asthma to be (fully) reversible to bronchodilators, whereas COPD was an irreversible disease. The latter has been mistaken by some to signify the absence of significant response to bronchodilators in patients with COPD. This is untrue in many patients with COPD and of interest because bronchodilators are the first line of therapy in patients with COPD. Several studies have shown that up to 50% of patients with COPD have significant reversibility at some point in time.^{37,38} Of note, the bronchodilator response of asthma needs to be seen in perspective as well. As detailed earlier, some older and even younger patients with asthma might have an irreversible component to their obstruction, which sometimes disappears after rigid steroid treatment (ie, lack of bronchodilator FEV₁ during massive obstruction followed by a bigger response once the disease ameliorates). Additionally, the use of a bronchodilator test in patients with (near) normal lung function is rather useless because of the ceiling effect (ie, one cannot improve in FEV₁ any further when this value is already at ≥100% of predicted

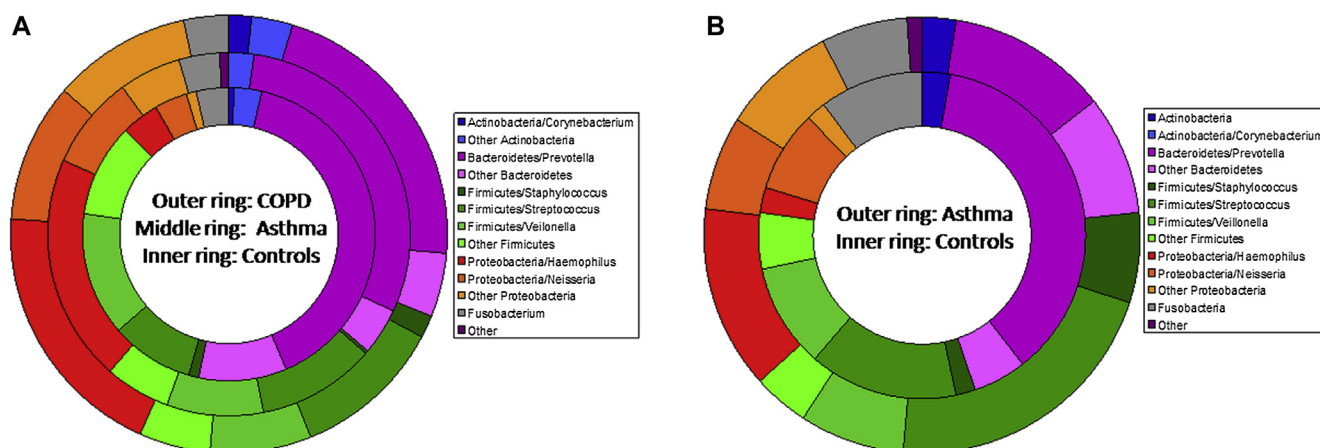


FIG 3. Distribution of common phyla and genera in diseased and normal bronchi. **A**, Distribution of the phyla from sheathed bronchoscopic brushings of the left upper lobe for patients with asthma and COPD and healthy subjects subdivided into the 7 most frequent genera (*Corynebacterium*, *Prevotella*, *Staphylococcus*, *Streptococcus*, *Veillonella*, *Haemophilus*, and *Neisseria*). **B**, Distribution of the phyla from bronchoalveolar lavage fluid in children with difficult asthma and controls. Reproduced with permission from Hilty et al.⁵⁴

value). Among others, for this latter reason, bronchodilator reversibility commonly decreases as lung function increases across a broad spectrum of disease characteristics and age.³⁹

If not a good tool to disentangle asthma from COPD, reversibility could be a prognostic sign. However, the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points study showed that patients with consistently reversible COPD ($n = 227$) did not differ in mortality, hospitalization, or exacerbation frequency from patients with irreversible disease after adjustment for baseline FEV₁.³¹ Thus although reversibility is present, it is not a prognostic sign in patients with COPD.

BHR

BHR is bothersome to patients because it inflicts attacks of breathlessness and cough. Although it is unknown how BHR develops, both genetic and environmental factors, such as *in utero* and postnatal cigarette smoke and allergen exposure, as well as effects of sex and aging, are likely to play a role.⁴⁰ BHR consists of a variable and a fixed component.³² The variable components largely derive from the acute release of proinflammatory mediators as a result of ongoing airway inflammation.³⁶ The fixed component of BHR results from structural changes in the airways, such as epithelial desquamation, goblet cell metaplasia, fibrosis, increased smooth muscle mass, angiogenesis, and extracellular matrix changes. This can take place in both the large and small airways.⁴¹

Over the past decades, BHR has been shown to be an important phenotypic characteristic of asthma associated with asthma morbidity, exacerbations, and increased airway inflammation (eosinophils and mast cells).³⁶

In patients with COPD, BHR has been shown to occur in up to 60% to 90% of patients.^{20,42,43} Some authors have argued that BHR in patients with COPD merely reflects a lower prechallenge FEV₁ and is not of pathophysiologic importance.^{32,44} However, this does not appear to be the case, both because it also occurs in patients with mild obstruction⁴⁵ and because we recently showed that the severity of BHR in patients with COPD is independently associated with both markers of small-airways disease (residual volume/total lung capacity percentage) and airway

inflammation (neutrophils, lymphocytes, and macrophages).⁴² Thus BHR is an independent trait that provides information on phenotype and disease activity both in asthmatic patients and those with COPD.

Eosinophilic airway inflammation

Eosinophilic airway inflammation is present in the majority of patients with asthma, especially when they are not treated with inhaled or oral corticosteroids.³⁶ Although the level of eosinophilic inflammation is associated with symptoms and exacerbations, as well as severity of airflow obstruction and BHR, the strength of the association has generally been found to be relatively weak.^{46,47} It has been suggested that chronic eosinophilic inflammation can contribute to airway remodeling and development of fixed airflow obstruction when left untreated in the long-term.⁴⁸

An increased percentage of sputum eosinophils is present in up to 40% of patients with COPD as well, especially with more severe airflow obstruction.^{49,50} The number of eosinophils in sputum and peripheral blood increases during COPD exacerbations.⁵¹ Liesker et al⁵² demonstrated that patients with COPD with sputum eosinophilia ($\geq 3\%$) have an increased risk of an exacerbation during subsequent ICS withdrawal when compared with their noneosinophilic counterparts. Thus eosinophilic inflammation contributes to phenotypic heterogeneity in both asthmatic patients and those with COPD.

Interestingly, new data show that not only might eosinophils have distinct and overlapping meanings in asthmatic patients and those with COPD but also sputum inflammatory mediators are of importance. Ghebre et al⁵³ performed cluster and factor analysis on sputum inflammatory mediators and determined distinct and overlapping groups of patients with asthma and COPD. An asthma-predominant cluster with eosinophilic inflammation and increased T_H2 inflammatory mediators was distinct from a COPD-predominant group with mixed eosinophilic and neutrophilic cells and increased proinflammatory cytokine levels. A third group had overlap and clinically chronic bronchitis, neutrophilic predominance, bacterial colonization, and increased IL-1 β and TNF- α levels. Results suggested that the Dutch

hypothesis might have value in this respect. However, this was a cross-sectional study in which asthmatic patients used prednisone in 59% of cases, whereas percentages in the COPD and overlap groups were 15% and 41%, which might have affected the results, just as differences in smoking habits and other characteristics might affect inflammatory cells and mediators. Longitudinal studies incorporating genetic, environmental, and sex influences might further help in this respect.

Bacterial infections

For Orie and Sluiter,¹ bacterial and viral infections were important contributors to obstructive airway diseases associating with exacerbations and perpetuation of the disease. As detailed in the introduction, chronic cough and phlegm were very common in 1961, and a considerably higher proportion of patients with any lung disease had bronchiectases, either comorbid or primary in origin. Analysis of the role of chronic low-grade inflammation was at its infancy, and most of the interest focused on eosinophils in blood and newly in sputum (see below).

COPD has always been associated with colonization, yet its role has not been elucidated. For asthmatic airways, as for normal airways, the lower airways were traditionally regarded as a germ-free environment. However, recent insights into the airway microbiome using culture-independent detection techniques that include sequencing suggest that the lower airways are all colonized with airway microbiota and that the airway microbiome in asthmatic patients and patients with COPD differs from that in healthy control subjects (Fig 3).⁵⁴ Although it is unknown whether this is the cause or consequence of their disease or treatment, these observations illustrate that novel techniques can provide further insights into the role of bacteria in the shared origins of obstructive airway disease.

The differences between asthmatic patients and healthy subjects appear to start early in life. One-month-old neonates colonized in the hypopharyngeal region with *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycobacterium catarrhalis*, or their combination have an increased risk for recurrent wheeze and asthma early in life.⁵⁵ Whereas viral infections, such as rhinovirus and respiratory syncytial virus infections, have been related to asthma onset and asthma exacerbations, bacterial infections are not viewed as an important cause of exacerbations in asthmatic patients to date. In contrast, bacterial (next to viral) infections have been regarded as important causes of COPD exacerbations. In fact, the majority of COPD exacerbations are triggered by bacterial and/or viral infections, and antibiotics remain the therapy of choice for bacteria-induced exacerbations, including *H influenzae*, *Pseudomonas aeruginosa*, and others. With techniques improving, including PCR on nasal or throat swabs with short detection times, the percentage of proved virus-induced COPD exacerbations is increasing also in day-to-day clinical work. The role of bacterial colonization and its relation to low-grade inflammation remain a fascinating area of research, even if only for the increased risk of exacerbations and accelerated loss of lung function.⁵⁶

IMPLICATIONS FOR CLINICAL MANAGEMENT BHR

At least 3 different clinical trials have investigated algorithms to use BHR as a disease marker guiding asthma treatment. The

first study was a 2-year randomized controlled trial (RCT) performed in 75 adults with mild-to-moderate asthma with 3-month BHR assessments. In the control group treatment level was based on clinical symptoms, β -agonist use, and peak expiratory flow variation, and in the BHR arm the level was based additionally on BHR severity. Patients treated with ICS doses according to BHR severity had fewer exacerbations, higher FEV₁ improvement, and greater reduction in airway wall basement membrane thickness. These patients used, on average, 400 μ g of ICSs more than the reference group. Thus adding BHR to titrate ICS doses could improve patient outcomes at the cost of higher ICS doses.⁵⁷

The second study was a 40-week RCT of 466 children older than 12 years and adults with asthma. The treatment algorithm was based on severity classes (symptom score, puffs of albuterol, mean peak expiratory flow variability, and FEV₁) with or without adding BHR to the treatment algorithm. Three groups were compared: fluticasone/salmeterol combination in the BHR strategy, fluticasone in the BHR strategy, and fluticasone in regular care. The primary hypothesis was that titrating asthma treatment with long-acting β -agonists could provide optimal asthma control (with or without BHR) at lower steroid doses. The main results of this study were negative: there were no significant differences in the primary outcome (dose of ICS needed) or any of the secondary outcome parameters (lung function or rescue medication).⁵⁸

Finally, a third study in 210 children with moderate atopic asthma aimed to assess whether a treatment algorithm incorporating BHR could improve asthma control, which was expressed as the number of symptom-free days. In a 2-year RCT treatment was adapted every 3 months based on symptoms (reference strategy) or on symptoms and BHR (BHR strategy). No difference was found in the percentage of symptom-free days between treatment strategies. As a secondary outcome, prebronchodilator FEV₁ was higher in the BHR strategy (2.3% of predicted value) compared with the reference strategy.⁵⁹ Although BHR is a feature of COPD in approximately two thirds of patients with COPD, studies aiming at reducing BHR or using BHR to guide therapy in patients with COPD have thus far been nonrewarding.^{60,61}

In conclusion, the published data thus far do not strongly support using BHR in guiding asthma or COPD treatment.

Eosinophils

It is well known that ICSs are highly effectively in modifying eosinophilic airway inflammation in asthmatic patients. It has been shown in asthmatic patients that ICS therapy aimed at normalizing the number of sputum eosinophils is more effective than standard treatment based on symptoms and lung function.⁶² This leads to better improvement in asthma control and lung function and markedly reduces the number of asthma exacerbations.

The role of ICS treatment is less clear in patients with COPD. Although ICSs improve symptoms and quality of life and reduce the number of exacerbations, most studies did not find positive effects on the long-term decrease in FEV₁.⁶³⁻⁶⁶ However, there might be a subgroup of patients with COPD with a favorable response to corticosteroids. Several studies have shown that eosinophilic inflammation predicted better improvement in FEV₁ after short-term (2- to 6-week) treatment with ICSs.^{49,67}

Moreover, a treatment regimen with ICSs aimed to reduce the percentage of sputum eosinophils more effectively reduces the number of COPD exacerbations than standard treatment and at a similar total ICS dose.⁵⁰ In addition, blood eosinophilia of 2% or greater during a COPD exacerbation predicted a favorable response to a course of oral corticosteroids (ie, more rapid improvement in lung function and health status compared with placebo).⁶⁸ In contrast, in patients with COPD with less than 2% blood eosinophils, treatment with oral corticosteroids was associated with a worse outcome.⁶⁸

Finally, we evaluated genes previously reported to be associated with T_H2-high asthma in 2 independent cohorts of patients with COPD.⁶⁹ A higher T_H2 composite score, a metric induced in patients with T_H2-high asthma, was found to be associated with more severe airflow obstruction in patients with COPD and asthmatic features, such as increased eosinophil counts in bronchial biopsy specimens and peripheral blood, bronchodilator reversibility, and improvement in hyperinflation after long-term (30-month) corticosteroid treatment.⁶⁹ These findings are compatible with the Dutch hypothesis because the phenotypic feature of T_H2-driven eosinophilic inflammation predicts favorable ICS treatment responsiveness both in asthmatic patients and those with COPD, at least with respect to short-term improvement in lung function and health status. Whether this predicts a better long-term outcome in patients with COPD remains to be elucidated in future studies.

Bacterial infections

The implications of bacterial infections and/or colonization for clinical management are still not fully understood. It is widely accepted that early and aggressive therapy for infections and especially pneumonias reduced the occurrence of bronchiectases. However, also, attempts to eradicate bacteria in airways with their open access was seldom long-lasting and therefore usually nonrewarding. These views have started to change.

Some 10 to 15 years ago, it emerged that less readily detectable bacteria, such as *Mycoplasma pneumoniae* and chlamydia, occur more often in patients with asthma, both children and adults, and that its treatment as an extended course of, for example, 2 to 4 weeks could bring about lasting improvements. More complicated is the usefulness of long-term treatment with macrolides in patients with noneosinophilic asthma apart from the presence of bacteria.⁷⁰ More recently, there has been an upsurge in COPD in the chronic use of especially macrolides,⁷¹ which have proved to reduce the exacerbation frequency. Whether this is due to their bacteriostatic or anti-inflammatory effect is as yet unresolved.

SUMMARY AND FUTURE PERSPECTIVES

The Dutch hypothesis was first articulated in 1961,¹ when many novel and advanced scientific techniques were not available, such as genomics techniques for pinpointing genes, gene expression, lipid and protein profiles, and the microbiome. In addition, CT scans and advanced analysis techniques used to dissect small-airways disease and emphysema were unavailable.^{24,25,72} At that time, a group of researchers under the visionary guidance of Professor N. G. M. Orie put forward that both genetic and environmental factors can determine

whether one would have airway obstructive diseases, such as asthma and COPD. This insight was only substantiated after the turn of the century, when it was discovered that *in utero* smoking interacts with genes to increase the risk of asthma in childhood.

Orie and colleague's call to carefully phenotype patients with obstructive airways diseases has been adopted by many current researchers in an attempt to determine the heterogeneity of both asthma and COPD to better define these diseases and optimize their treatment strategies. Next to improved characterization of asthma and COPD, this renews attention for patients with ACOS. Only quite recently, guidelines have been put forward that specifically focus on patients with ACOS.^{73,74} This renewed interest in these overlap patients is important because they have been systematically excluded from RCTs, and hence we do not know their optimal management strategies. This dichotomous splitting of disease labels in trials has simplified views on asthma and COPD. Many patients with ACOS were left out of trials, and therefore this large group of patients was excluded from our reference world for clinical practice. Orie and Sluiter¹ also put forward that age influences the clinical phenotypes of patients with obstructive airway disease, as exemplified by progression from reversible to irreversible asthma and from atopic to nonatopic asthma. Additionally, they put forward that sex and environmental factors affect the phenotype, such as smoking in asthmatic patients, which is associated with accelerated lung function loss or irreversible airway obstruction, and air pollution, which can affect respiratory markers differently in male and female patients, and the observation that female patients are more susceptible to cigarette smoking than male patients.

Thus the founders of the Dutch hypothesis were far ahead of their time, and we can learn from their insights. We should fully characterize all patients in our clinical practice and not only state that they have asthma, COPD, or ACOS. This detailed phenotyping can help in understanding these obstructive airway diseases and provide guidance for disease management.

Future studies are needed to better develop markers for disease-specific treatments based on phenotypes. A recent example is that T_H2-driven eosinophilic inflammation predicts favorable ICS treatment responsiveness both in asthmatic patients and those with COPD. Although ICS treatment might be better at improving FEV₁ in asthmatic patients with this T_H2 airway wall profile, the same airway wall profile might have beneficial effects in patients with COPD, yet here it does not associate with FEV₁ response but residual volume/total lung capacity response. Hence we need to be careful not to be biased toward FEV₁ as the first and prime outcome parameter yet search for phenotype-specific outcome parameters in the subgroups of asthmatic patients and those with COPD. Also, pharmacogenomics has identified that some SNPs in the β -receptor might signify worsened disease outcome, especially in nonwhite patients with asthma who do not use ICSs.⁷⁵ Future studies have to refine and expand these results toward other genes that might signify responders to well-known and novel treatments.

In summary, we like to put forward that full clinical characterization, as developed by Orie and Sluiter (Table I),¹ can still be used, adapted, and expanded with novel insights to apply in clinical practice, and by focusing on the clinical outcome, this might help us better choose treatments for our patients with obstructive airway disease.

What do we know?

- The Dutch hypothesis suggested that asthma and COPD have common origins and clinical expressions and are determined both by endogenous (heredity, age and, sex) and exogenous (environment: allergens, smoking, viruses, and air pollution) factors.
- Some risk factors are shared in asthmatic patients and those with COPD (eosinophilia and BHR), and others are disease specific (IgE).
- A binary dissection of asthma and COPD is insufficient for researchers and clinicians.

What is still unknown?

- Whether the definition of sufficient phenotypes (eg, eosinophilic asthma) and subphenotypes will help to elucidate the spectrum of obstructive airways diseases
- Whether careful measurement of individual patient's characteristics without attaching distinct splitting disease labels helps in the management of obstructive airways diseases
- Whether rare genetic variants or prevalent genetic variants in interaction with the environment constitute shared genetic origins of asthma and COPD

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