

The Dutch Hypothesis (chronic non-specific lung disease) revisited

H.J. Sluiter, G.H. Koëter, J.G.R. de Monchy*, D.S. Postma, K. de Vries*, N.G.M. Orie

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ABSTRACT: In 1961 the hypothesis (later referred to as the Dutch Hypothesis (DH)) was put forward that asthma, chronic bronchitis and emphysema should be considered as different expressions of one disease entity, in which both endogenous (host) and exogenous (environmental) factors play a role in the pathogenesis. A hereditary predisposition to develop allergy and bronchial hyperreactivity were considered to be important denominators of disease susceptibility. Complications and complicating diseases would also contribute to the ultimate phenotype of the patient. In the present paper we discuss the relevance of this hypothesis in 1990. Until now it has not been refuted; circumstantial evidence in its favour has accumulated, but formal proof is still lacking. Further research should pay more attention to the genetic aspects of the disease. Arguments are presented against the use of the terms asthma, chronic bronchitis, and emphysema as indicators of disease entities, and in favour of the use of an umbrella-term, *e.g.* chronic non-specific lung disease (CNSLD), provided that, in addition, every patient is characterized using so-called defining criteria.

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Depts of Pulmonology and *Allergology of the Dept of Internal Medicine, University Hospital, Groningen, The Netherlands.

Correspondence: H.J. Sluiter, Dept of Pulmonology, Dept of Internal Medicine, University Hospital, Groningen, The Netherlands.

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A major part of the clinical and scientific work of pulmonary specialists in the developed countries deals with aspects of diseases such as asthma, chronic bronchitis and emphysema. Both for research and clinical purposes it is important to be able to compare the results of studies from different centres; they also have a bearing on clinical practice. It is a pity, therefore, that confusion about the meaning and use of these terms has been present for many years, often leading to unprofitable discussions when trying to compare results or treatment policies. This has probably impeded scientific progress. Efforts by several international conferences and policy-making institutes such as the 1959 Ciba Guest Symposium [1] and two conferences of the American Thoracic Society (ATS) [2, 3] have only partly cleared up this confusion.

In 1961 the hypothesis was put forward that asthma, chronic bronchitis and emphysema should not be considered as separate diseases, but rather as expressions of one disease-entity "chronic non-specific lung disease" (CNSLD). Both endogenous (host) and exogenous (environmental) factors were thought to play a role in the pathogenesis [4, 5]. In particular, the predisposition to develop allergy and bronchial hyperreactivity (or

hyperresponsiveness) (BHR) was considered to be an important denominator of disease susceptibility. Diffuse airway obstruction was considered as the common pathophysiological characteristic. In 1969, FLETCHER *et al.* [6] suggested the name Dutch Hypothesis (DH) and it has often been referred to as such since [7-9].

The international discussion still continues. Nowadays many investigators agree that it is often impossible to discriminate between chronic bronchitis and emphysema in clinical medicine. Several names have, therefore, been suggested for this complex, *e.g.* chronic obstructive lung (pulmonary, airway) disease (COLD, COPD, COAD) and chronic airflow obstruction (CAO). Asthma is generally considered to be a separate and identifiable entity. Some investigators, however, disagree. In their opinion, it is not possible to distinguish between *e.g.* asthma and chronic bronchitis [10, 11], especially in children, and they stress occasional observations of repeated pronounced responses to inhaled bronchodilators in patients with classic COPD. The diverging opinions are sometimes expressed in evocative terms [12-16]. In the present discussion we reconsider briefly the terminology issue first.

The terminology of asthma, chronic bronchitis and emphysema

Lumping or splitting? What is the use?

When can a clinical syndrome be considered a disease? GROSS [13] summarizes: "We tend to think of a disease as having a single underlying cause, an agent or genetic defect or nutritional deficiency, and a more or less distinct pathophysiological mechanism. We give it a name which confers individuality and helps to reinforce our notion of it as a discrete biological entity". It is clear that the "diseases" asthma, chronic bronchitis and emphysema, in their usual meaning, do not meet these standards.

The 1987 ATS statement [3] on "the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma" defines COPD as "a disorder characterized by abnormal tests of expiratory flow that do not change markedly over periods of several months of observation". No guidelines are provided as to the interpretation of the term "markedly". Many patients who fit into the ATS criteria for asthma (see below) also have persistent expiratory airflow obstruction over many years. The disorders emphysema, peripheral airways disease and chronic bronchitis are incorporated in COPD: "any individual patient may have *one or all* (our italics) of these features". Emphysema is defined morphologically. It is stressed that bronchial hyperreactivity "may be present in patients with COPD as measured by an improvement in airflow following the inhalation of beta-adrenergic agents or worsening after inhalation of methacholine or histamine". According to the ATS, the latter is also present in many patients with "asthma": "a clinical syndrome characterized by increased responsiveness of the tracheobronchial tree to a variety of stimuli". The ATS working group noted that the diagnoses of COPD and asthma may overlap: "Patients with COPD may have significant reversibility after treatment and patients with asthma may develop airflow obstruction with little or no reversibility". The statement continues: "The separation of these overlap patients is often arbitrary and difficult, and from a clinical standpoint probably not important unless the diagnosis has therapeutic implications, *i.e.* the bronchospasm results from a specific and identifiable agent". We disagree with the ATS statement where it states the "the diagnosis of asthma can *occasionally* (our italics) be confusing because of its overlap with COPD". In our experience these overlap patients constitute a fair percentage of the total number of patients. This becomes even more apparent when the patients are observed over several years. Today's patient may in a few years' time present himself as a patient with a different obstructive airways "disease" [17, 18], probably as the result of combined changes in host and environment (see later).

Is a diagnostic label required for treatment of the patient or for scientific work? Provided everyone agrees about its meaning and its contents a label can certainly be useful, but it is not an absolute requirement. We cannot, however, get along without precise defining criteria

[19, 20], by which the individual patient is characterized, clearly and beyond any doubt. Defining criteria include age and gender, data from the history (both personal and family) and physical examination, lung function (including reversibility studies), data on allergy and bronchial hyperreactivity (including the modulating influence of age and gender), complications and potential coexistent disease (see below).

It has been objected that lumping everything together under one heading, *e.g.* CNSLD (= COPD + asthma), may lead to loss of important information, resulting in a poor description of the patient, incomparability of patient groups, and thus inhibition of research progress. If no defining criteria had been added we would agree. At present our knowledge is simply insufficient and does not allow a division of the obstructive airways disease-complex into discrete disease-entities in a way that will satisfy most investigators. Although future research may allow us to single out one or more distinct entities - as has already been done for hereditary alpha₁-antitrypsin-deficiency-caused emphysema, there will probably always remain a (vast?) group of patients that cannot be allocated to one distinct disease. This is inherent in a disease complex in which host and environmental factors express themselves in various ways and intensities.

The use of defining criteria in patients of the asthma-COPD complex makes it possible to compare the results of scientific studies and treatment trials from different centres all over the world.

This plea for the use of defining criteria instead of diagnostic labels does not imply that this rather cumbersome way of expression also applies to the everyday communication between doctor and patient. As long as the message gets across to the patient, any label will be adequate.

The Dutch Hypothesis in 1990

Traditionally, environmental factors (especially smoking, occupational exposures and air pollution) have been considered to be the main factors in the pathogenesis of "chronic bronchitis" and "emphysema". Asthma, on the other hand, is generally looked upon as a disease in its own right, allergic sensitization being the main pathogenetic factor. In 1961, we postulated that the three "diseases" were in fact expressions of one basic disease in which the combined endogenous (host) and exogenous (environmental) factors shaped the patient's profile [4]. At that time several aspects were considered to be important:

- 1) the probably hereditary nature of the disease;
- 2) some basic factors: allergic sensitization and bronchial hyperreactivity (BHR);
- 3) diffuse airway obstruction as the common pathophysiological characteristic;
- 4) the modulating influence of age and gender on the expression of the essential elements, and thus on the clinical picture;
- 5) the contribution of complicating factors, *e.g.* bacterial inflammation, anatomical changes (*e.g.* bronchiectasis)

and acute viral respiratory infections to the clinical picture;

6) the influence of the disease on both the clinical picture and on the course of other, coexistent bronchopulmonary diseases, e.g. sarcoidosis, tuberculosis, or pneumoconiosis;

7) the advantage of using the umbrella term "chronic non-specific lung disease" (CNSLD) and the necessity of adding defining terms, both for the sake of adequate treatment and scientific communication.

In the course of the subsequent years a truly enormous amount of research on many different aspects of the disease-complex has been and is being carried out. We will now consider where we stand in 1990 as to the pathogenesis and definition of the disease which will be referred to as CNSLD (= asthma + COPD).

Natural history

The DH regards the phenotype of the patient as the result of the combined action of genetic and environmental factors, of the presence and intensity of complications, and of the presence and adequacy of treatment. We know very little about the genetic factors (see later); we know that the load of the environmental factors will show strong variations between patients and countries. CNSLD is a lifelong disease, which makes prospective, longitudinal studies on the natural history, encompassing all life-stages, virtually impossible: there will be important changes with time in e.g. environmental load or medical intervention. Long-term epidemiological studies such as the Vlagtwedde-Vlaardingen surveys [21] have nevertheless made a substantial contribution to our knowledge; as have cross-sectional and short-term cohort-studies carried out in childhood and repeated in adolescence [22].

In 1976, FLETCHER *et al.* [23] discussed the natural history of COPD. They distinguished an obstructive disorder from a hypersecretive disorder. Whereas the first, *via* progressive impairment of expiratory airflow, ultimately leads to severe disability, this impairment was less evident in the second disorder. Smoking was considered to be the predominant cause of both. They often occurred together and developed particularly in persons with a constitutional susceptibility. (In later years the authors acknowledged that this classification could not be upheld).

In 1987, BURROWS *et al.* [24] distinguished in their COPD patients an emphysematous subgroup and an asthmatic-bronchitic subgroup. The latter group had a higher survival rate and a lower rate of decline of lung function than the former. They suggested that a more adequate control of the progression of asthmatic bronchitis by therapy might explain its more favourable prognosis. They later stated [25] that the Dutch hypothesis appeared to be only relevant to their "chronic asthmatic bronchitis" group. The patients in this group were predominantly older women diagnosed as asthmatic on the basis of an affirmative answer to the question: "Have you ever had asthma?", many of them having positive allergy skin tests. Although we agree with the therapeu-

tic and prognostic conclusions, we are not convinced that these patients constitute a special subgroup. In trying to extrapolate Burrows' findings to our population, we would undoubtedly have the same problem as we had when trying to separate other subgroups from the CNSLD-population: the large number of overlap patients.

Burrows suggests that the asthmatic-bronchitic type of disorder appears to depend on an "asthmatic predisposition", whereas the "emphysematous disorder" has no obvious relationship to such asthmatic characteristics, but appears to be directly related to cigarette smoking. However, this provides, no explanation as to why only a minority of smokers develop this disease. This is a central issue in the Dutch Hypothesis.

Many studies deal with the influence of smoking on the occurrence and progression of CNSLD. Most of these studies discuss patients with abnormal symptoms, signs, or functional characteristics, who were smokers, ex-smokers, or lifelong nonsmokers. Many smokers, however, have neither symptoms nor signs of airways disease.

The defining characteristics of CNSLD

Symptoms and signs. It is impossible to discuss the symptoms and signs of CNSLD without referring to their "natural history". The variability of the clinical picture in a patient's life is often impressive; it may range from an occasional, minor illness to a severe, life-threatening or disabling disease. The wheezy infant may become the child with attacks of dyspnoea and may either outgrow the disease at puberty (often only temporarily!), or maintain the complaints in adult life. In later years a more continuous dyspnoea, with exacerbations, will often replace the attacks [18]. The importance of childhood history is becoming increasingly clear, as the link between childhood and adult disease is taking shape [26]. Diseases in children may help in the diagnosis of older relatives [27].

There is still much work to be done on the standardization of the information obtained by history-taking, especially on the grading of dyspnoea [28] (kind, intensity), cough, and sputum. The same applies to the physical examination.

Diffuse airway obstruction. Diffuse airway obstruction, in varying degrees, is not exclusive to "asthma"; its presence has been demonstrated unambiguously in COPD. It may vary from fully reversible (spontaneously or as a result of treatment) to almost totally irreversible, or to the combination of a reversible and an irreversible component. Careful observation over extended periods of time and repeated examinations, using different lung function tests and different drugs, may be necessary to detect signs of reversibility [29-31].

Irreversible airway obstruction may be caused in at least two ways: loss of elasticity (e.g. in anatomical emphysema) and (post-)inflammatory changes. Inflammatory airway changes play an important role in the late allergic reaction. Post-inflammatory changes in

the small airways have been demonstrated in smokers, but also in young people with chronic pulmonary disease [32, 33]. In recent years, the small airways have come to be considered as a potentially important site of airways pathology and obstruction in obstructive airways disease [34–37]. Inhalation corticosteroids have been shown to cause a gradual decrease in chronic post-inflammatory changes, although complete disappearance of these changes seems to be rare [38]. Oral corticosteroids have been shown [39, 40] to stop the progressive deterioration in lung function in some patients with moderate and severe chronic progressive obstruction. This effect only became apparent after administration of the drug for several months. This may suggest that this beneficial effect is due to the anti-inflammatory action on the chronic inflammatory changes. Whatever the explanation may be, this observation presents a strong argument against the conclusion, based only on the results of short-term observations or interventions, that the condition is untreatable.

Allergic sensitization. Allergic sensitization has always played a key-role in discussions about "asthma". It also figures prominently in the Dutch Hypothesis. Patient history, in combination with skin tests and eosinophilia of blood (and sputum), and also inhalation-challenge tests and the level of serum immunoglobulin E (IgE) and radio-allergosorbent test (RAST) are the basic elements of a diagnosis of sensitization.

Unexplained eosinophilia may stimulate the search for an unknown allergen. It has been stated [41] that the fact that a specific allergen cannot be demonstrated, does not plead against a diagnosis of allergic disease; the classification into extrinsic (allergic) and intrinsic (non-allergic) disease is therefore meaningless. A positive challenge test is not only the result of allergic factors, but also of non-allergic factors [42, 43], especially bronchial hyperreactivity.

IgE is the basis of the atopy concept. Atopy is defined as an inherited complex of symptoms consisting of allergic rhinitis, asthma and "atopic" dermatitis, and a raised level of antibodies of the IgE-class which are specific for a particular antigen. Specific IgE-mediated allergy has been transferred *via* B-cells with allergen-specific memory into a patient receiving a donor organ, causing attacks of asthmatic dyspnoea [44]. At present atopy is considered to have a multifactorial inheritance [45]: genetic and environmental factors contribute to its expression. At least two different genes are held to be responsible for the presence of atopy: one gene is associated with the histocompatibility system, controlling a specific immune response, and one controlling the level of serum IgE [46, 47].

Family studies have revealed a strong family concordance of IgE, atopy, and disease [48]; twin studies [49, 50] point in the same direction. The risk of atopy for children born from atopic parents [51] may be as high as 80% (two atopic parents) or 50–60% (one atopic parent) [52]. On the basis of studies of nuclear and extended families with atopy, an autosomal-dominant inheritance has been postulated [53], but this issue has not yet been

settled [45]. Environmental factors play an important role in the expression of atopic diseases [54, 55]. Maternal smoking increases the cord IgE-level and the incidence of the subsequent infant allergy [56]. Serum IgE-levels are higher in smokers than in nonsmokers [57, 58].

There is hardly room for doubt about the role of allergic sensitization in CNSLD patients with features of atopy, but what about the many others without these characteristics? Although sensitization may occasionally be demonstrated in older patients with CNSLD, this is not the case in many of these patients. In the latter category, attacks of dyspnoea are less prominent whereas a more chronic dyspnoeic state, showing both sudden and long-term variations, is often present. Before eliminating allergic sensitization as an essential factor in the development of disease in these patients, the following points should be considered:

- 1) the technique of diagnosing allergy may have been inadequate;
- 2) a new or as yet unknown allergen may be present;
- 3) information derived from total serum IgE yields only about half the amount of information from specific IgE [53];
- 4) a negative history of allergy in an older patient does not exclude allergic episodes in childhood.

Age has an effect on the manifestation of allergic disease [59–61]. The incidence of *e.g.* pollen-associated hay fever sharply declines after middle age [62]. The incidence of positive skin tests [63–65], degree of blood eosinophilia [66, 67], and level of serum-specific IgE [68] diminish markedly in older age, without any apparent change in the intensity of exposure to the allergen(s). On the other hand, serum IgE levels have been found to be significantly increased after challenge with a primary antigen even in older "bronchitic" patients who were considered to be "non-allergic" compared with matched "non-bronchitic" controls [69]. The exact cause(s) of these phenomena remain(s) unclear.

These considerations may be sufficient explanation for the failure to diagnose allergic sensitization in some patients with COPD. There is, of course, the possibility that sensitization, even when we cannot find any indices of it in a patient, was initially present and affected the pathogenesis of disease, in combination with BHR and environmental factors. In a later phase the disease machinery, once started by the combined efforts, might then be kept running without the influence of allergic factors. Such a procedure contrasts with the natural history of hay fever, in which both clinical disease and indices of sensitization gradually disappear towards middle age. The answer to the question about the role of allergy in presumably non-allergic patients will have to wait until we know more about the genetics of subjects with and without demonstrable allergic factors.

Bronchial hyperreactivity. Bronchial hyperreactivity (or hyperresponsiveness) (BHR) is defined as an increased responsiveness of the tracheobronchial tree to a variety of stimuli in low dosages that do not cause a similar reaction in normals [70–76]. According to the ATS

statement [3], BHR is the hallmark of asthma and may be present in COPD. In the Dutch Hypothesis, BHR, next to allergic sensitization, plays a central role in the pathogenesis of CNSLD. In recent years the number of studies dealing with BHR and our knowledge about this phenomenon have increased sharply, and several thorough reviews [77–80] have been published. We will confine ourselves to a few, general remarks.

The triggers that can provoke BHR have been categorized into inciters and inducers [81, 82]. Dependence on the degree of underlying BHR, inciters may cause varying degrees of acute reversible airflow obstruction, probably mainly by bronchospasm; this is *e.g.* the case with pharmacological agents, and inhalation of cigarette smoke or cold air. Inducers lead to increased BHR *via* inflammatory processes; they include viral infections of the airways, inhalant allergens, low molecular weight sensitizers and ozone. Other factors that may be of importance for the degree of BHR include the dietary sodium intake, extra intake leading to an increase in BHR [83]. BHR may vary or even disappear within relatively short periods. This has been called “transient” BHR as opposed to “persistent” BHR which may remain almost unchanged over long periods.

Epidemiological studies [72–76] in random populations generally show BHR to be unimodally distributed, indicating a heterogeneous polygenic, or a polygenic and environmental disease [84]. Although by now a great deal is known about the phenomenon of BHR, we still have no information about its genesis. We are still unable to diagnose the susceptibility to develop BHR. It is tempting to hold genetic factors responsible for this difference in reaction. HOPP *et al.* [85] found a bimodal distribution of methacholine BHR in non-asthmatic parents of asthmatic children, suggesting transmission *via* a genetic component. Healthy, non-atopic parents of asthmatic children had a higher BHR than normal parents of healthy children [86]. Additional information may come from the results of studies of cells or cell systems outside the airways, *e.g.* peripheral blood cells [87, 88] or smooth muscle systems [89].

Several authors [90, 91] have pointed out that in the pathogenesis of asthma in their patients, atopy could not be the only genetic component and that at least one other hereditary factor was needed to explain the observed hereditary pattern; details about this genetic, non-atopic component were not given. We postulate that BHR could very well be this other genetic factor.

In contrast to having a genetic origin, BHR has also been considered to be acquired during life [92].

The effect of age on BHR is as yet not completely clear. BHR has been demonstrated in infants and very young children. It has even been postulated that all children are born with BHR; genetic and environmental factors would then determine which infants would lose their BHR [93].

Based on a study in 124 infants, MARTINEZ *et al.* [94] regard a diminished lung function as an important predisposing factor for the development of the first wheezing episode. Lower respiratory “infections” in early childhood have been considered to function as

pacemakers and supporters of BHR. A problem here is the vagueness of the notion of “infection” in childhood. Precise definitions are lacking, and without these the relationship between acute respiratory illness in childhood and adult chronic pulmonary disease cannot be clarified [95, 96].

BHR has been demonstrated in patients with COPD [97–99]. One of the structural-functional problems here is the influence of bronchial diameter on the degree of BHR, especially in older COPD patients. In younger patients with marked reversibility of airway obstruction and BHR, changes in obstruction may occur without concomitant changes in the BHR, and vice versa. This picture may be less clear in older patients. We feel that there is evidence to consider BHR as a hall-mark of the entire CNSLD-complex. In contrast to the allergic sensitization with its peak prevalence in young adults and its low frequency in the very young and in the aged, BHR is probably present in all age groups (showing a tendency to decrease with age?).

Several mechanisms have been found to be related to the manifestation of BHR: autonomous nervous system dysregulation, epithelial damage [100, 101] including airway permeability, vascular leakiness and exudation [102], changes in the intramural neural control mechanism [103], in the electrophysiology of bronchial smooth muscle [104], and in the releasability of enzymes or chemical mediators of cells within the airways [105, 106]. Inflammatory processes in the airways are thought to play a key-role in the common pathway leading to airway obstruction.

Finally, a few remarks on two aspects which have caused some confusion in the past: the relationship between allergy and BHR, and the relationship between reversibility and BHR:

Allergy and BHR. In the laboratory an allergen challenge leads, *via* inflammatory reactions, to a higher BHR, as measured by a higher susceptibility to histamine and methacholine. In sensitized patients, natural exposure to allergens or occupational asthma-inducers may also lead to an increase in BHR. The severity of the bronchial obstructive reaction following the allergen challenge appears to depend on the degree of the BHR before challenge or exposure. Moreover, the magnitude and duration of the increase in BHR, such as defined by a provocative concentration producing a 20% fall in forced expiratory volume in one second (PC_{20}) measurement when the FEV_1 has already returned to pre-challenge level, is significantly correlated with the magnitude of the late allergic bronchial obstructive reaction.

Chronic allergen exposure causes a longstanding (persisting?) increase in BHR. Conversely, avoidance of environmental allergen exposure, *e.g.* in hay fever patients out-of-season [107], or house dust mite avoidance [108], often results in reduced airway obstruction and a decrease in symptoms, followed by a decrease in BHR.

BHR and reversibility. Some authors consider these as two different expressions of one basic phenomenon. The ATS statement also notes that “bronchial hyperreactivity

may be present in patients with COPD as measured by an improvement in airflow following the inhalation of beta-adrenergic agents or worsening after inhalation of methacholine or histamine". We do not agree with this concept and consider BHR and reversibility as separate, but closely linked phenomena: for instance, allergen avoidance first causes a decrease in airway obstruction; the decrease in BHR may lag many weeks behind. The same holds true for the effect of treatment with inhaled corticosteroids in allergic patients with BHR and partly reversible airways obstruction [109]. Treatment with beta-adrenergic drugs, on the other hand, causes bronchodilatation and an increase in BHR after cessation of administration [110, 111].

The modulating influence of age and gender on the manifestation of allergy and BHR. In the process of ageing, important changes take place in many systems of the body. In CNSLD, ageing often runs parallel with an increasing load of exogenous factors (e.g. smoking, air pollution); these factors may be so dominant that it becomes difficult to determine the role of other, age-dependent, specific factors that may modulate the expression of CNSLD or its components, including allergy and BHR.

This confounding influence of exogenous factors is also present with the modulating factor of gender. Exogenous factors (smoking) undoubtedly play a role in the well-known preponderance of males in older CNSLD patients. As the prevalence of smoking is increasing in women, it will be interesting to see whether the CNSLD gender-ratio will change in the future. However, there are also differences in prevalence of CNSLD in younger boys and girls, and we do not yet know exactly how to handle this information. We are familiar with a change in CNSLD complaints in puberty and menopause. Primary endocrine abnormalities have not been demonstrated in CNSLD patients [112], but adrenal and sex hormones may modulate the immunological processes that are known to play a role in some CNSLD patients [113].

Complications. Complications in the course of the disease may be partly responsible for the phenotype of the CNSLD patients. Apart from the well-known, major, acute or end-stage complications like pneumonia or pulmonary heart failure, bacterial infections are the main complications. Patients with CNSLD are especially prone to bacterial bronchial infections; the incidence of respiratory viral infections is not different from that in the normal population [114].

Apart from the effect on acute health, respiratory virus infections may have other important consequences: facilitating the allergen-antibody contact, and promoting or temporarily increasing BHR.

Many (viral or bacterial) respiratory infections leave no residual lesions, although some may do so. However, it will be difficult to prove, e.g. in a patient with a more severe course of the obstructive disease in adulthood, who had respiratory syncytial (RS)-viral complications in early childhood, that the former is the

consequence of the latter; both may be related to the severity of the underlying obstructive airways disease [115].

Other pulmonary diseases. It is hardly surprising that a disease-complex like CNSLD with its high prevalence will coincide with other pulmonary diseases, e.g. sarcoidosis [116], tuberculosis [117], or pneumoconiosis [118]. In the past, symptoms or signs of diffuse airway obstruction, which are occasionally present in these diseases, were considered to represent special forms of the latter. Careful history-taking will, however, often reveal the presence of CNSLD in a period that far antedates the origin of the other pulmonary disease. This coexistence may not only modulate the expression of both diseases, but the presence of CNSLD may even have an unfavourable effect on the course of these diseases.

Smoking, although not in the strict sense a disease, may be considered in this context as a special form of coexisting, complicating disease. As such it is the most important environmental hazard. Its chronic-irritating and possibly cumulative destructive-toxic effect, especially in genetically predisposed individuals, may be of far greater importance than the combined effect of the other complications and coexisting diseases.

Conclusions and recommendations

The Dutch Hypothesis was formulated in 1961. An essential component was the assumption of a common, genetic root of the disease-complex of asthma-chronic bronchitis-emphysema. According to the DH, the phenotype of the patient is the result of a combination of genetic and environmental factors, modulated by age and gender. It was also pointed out that the diagnostic labels of asthma, bronchitis, and emphysema were impracticable and the use of a neutral umbrella-term (CNSLD or CARA) was strongly advocated, in combination with well-defined defining criteria. Up to now, the hypothesis has not been proven or refuted. Final proof must come from genetic research that is currently being carried out. Figure 1 illustrates the concept of the DH.

In 1990, many investigators and clinicians are inclined to accept a role for genetic factors in the origin and course of many chronic diseases. It was recently stated that "most major chronic diseases probably result from the accumulation of environmental factors over time in genetically susceptible persons" [119]. The recent ATS statement distinguishes asthma from COPD but the authors acknowledge that overlap patients exist.

The DH still defends the assumption of a common genetic root for the whole CNSLD group. Essential for any research and communication on research is the use of standardized procedures and a common terminology. Diagnostic labels are a kind of clinical shorthand; they are based on agreement and on generally accepted defining criteria; they have no intrinsic value. A sensible solution in the case of CNSLD would be to refrain, for the time being, from further attempts to categorize or

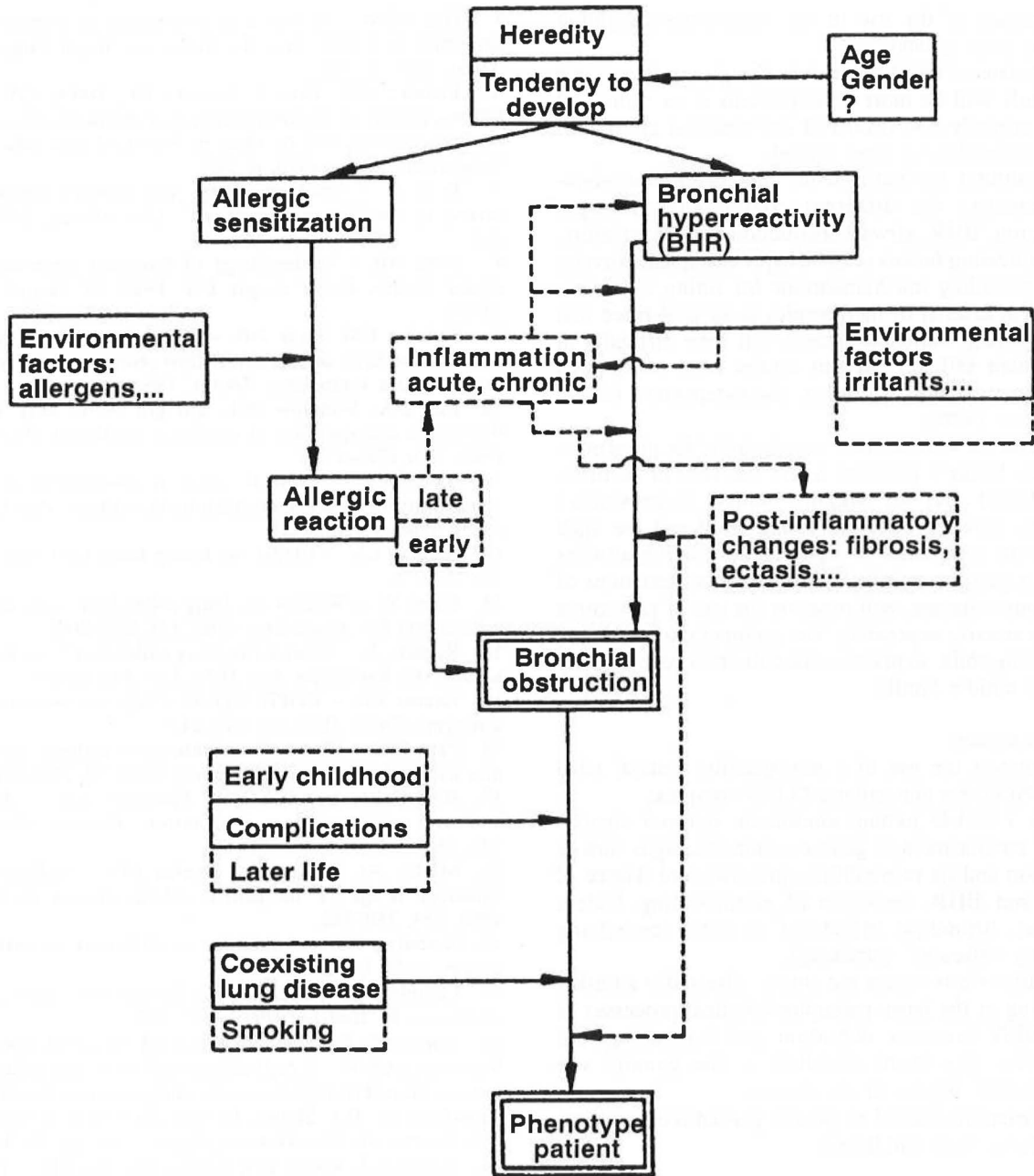


Fig. 1. – Schematic presentation of the Dutch Hypothesis 1990. The dotted lines indicate the increase in knowledge and insight in the period between 1961 and 1990.

classify, and to rely for scientific and practical therapeutical purposes on exactly defined criteria. Some of these defining criteria are evident and clear; about other defining criteria (history, physical examination, reversibility, allergy, BHR) we still need international consensus, as to the ways of assessing or expressing the parameters in a standardized way.

The DH is more than a scientific challenge. By accepting the principle of the DH: the interaction of the same genetic and varying environmental factors in all patients of the CNSLD-complex, one must pay attention to all potential contributing factors. This holds true even

in patients in whom this would not seem immediately relevant, e.g. reversible airway obstruction in an elderly patient with mainly dyspnoea on exertion. Another important consequence of the DH is that disease episodes occurring in different periods of life are recognized as parts of one disease. Neglecting disease manifestations in childhood by assuming that the child will outgrow its disease, may negatively influence the results of medical intervention during episodes in later life. The DH emphasizes the importance of starting preventive and therapeutic measures as early as possible.

The impact of the use of the standardized defining criteria is even greater:

- 1) it stimulates scientific research. The groups of patients under study will be more homogeneous if we define all patients properly; the results of one research group will then be accessible to other groups;
- 2) it constitutes the basis of the therapeutic considerations, because the different components (allergic sensitization, BHR, airway obstruction and reversibility, and complicating factors) can be expressed quantitatively, thereby providing the foundations for fitting treatment. Our present arsenal of therapeutics is so well-filled that new drugs (e.g. antileukotrienes) will have difficulty in proving their efficacy. Recent studies have shown that BHR and airway obstruction are also independent factors in prognosis [120];
- 3) it provides a well-defined starting-point for preventive measures. Today's problem is not the lack of facilities for treatment, but the lagging behind of preventive measures. Viewing both the young child and the aged person with symptoms or signs of obstructive airways disease as persons exhibiting different manifestations of one common disease, will promote the use of preventive measures as early as possible. The centre of interest should be the young child; in practice this will often automatically mean the child's family.

In conclusion:

- 1) we support the use of a non-specific, general label (e.g. CNSLD) for the asthma-COPD-complex;
- 2) every CNSLD patient should be defined clearly. Defining criteria are: age, gender, symptoms, signs, airway obstruction and its reversibility, presence and degree of allergy and BHR, presence of complicating factors (bacterial, bronchial infection) or other coexisting pulmonary "diseases" (smoking);
- 3) scientific efforts should not only be directed at a further unravelling of the basic pathophysiological processes of the CNSLD, however important and fascinating, but should also pay more attention to the genetic and environmental aspects of the disease;
- 4) more attention should be paid to preventive measures, especially in early childhood.

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Hypothèse Hollandaise sur les maladies pulmonaires chroniques non spécifiques: remise en question. H.J. Sluiter, G.H. Koëter, J.G.R. de Monchy, D.S. Postma, K. de Vries, N.G.M. Orie.
 RÉSUMÉ: En 1961, l'hypothèse dénommée ultérieurement l'Hypothèse Hollandaise (DH) était avancée selon laquelle l'asthme, la bronchite chronique et l'emphysème devraient être considérés comme diverses expressions d'une seule entité pathologique dans la pathogénie de laquelle agissaient à la fois des facteurs endogènes (hôte) et exogènes (environnement). Une prédisposition héréditaire à développer l'allergie et l'hyperréactivité bronchique a été considérée comme étant un déterminant important de la susceptibilité à l'égard de la maladie. Le phénotype ultime développé par le patient était aussi déterminé par les complications et les maladies génératrices de complications. Dans ce document, nous discutons dans quelle mesure cette hypothèse est encore valable en 1990. Jusqu'à ce jour elle n'a par été réfutée et des preuves indirectes en sa faveur se sont accumulées, quoiqu'une preuve formelle fasse toujours défaut. Les recherches à venir devraient porter plus d'attention aux aspects génétiques de la maladie. Des arguments sont développés contre l'utilisation des termes asthme, bronchite chronique et emphysème comme indicateurs d'entités pathologiques, et en faveur de l'utilisation d'une terme général "terme parapluie", par exemple, maladies pulmonaires chroniques non spécifiques, pour autant qu'en outre chaque patient soit caractérisé par l'emploi de critères de définition. *Eur Respir J.*, 1991, 4, 479–489.