causing 20% fall in FEV_1 (PD_{20}) value? Until these issues are resolved it will be difficult to interpret the results of nonspecific bronchial provocation tests with any confidence.

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The relationship between reversibility and hyperreactivity

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Many studies have demonstrated an increased airway reactivity to non-specific stimuli in both patients with asthma (sudden attacks of breathlessness and fully or partly reversible airflow obstruction) and with CAO (chronic dyspnoea of varying intensity and never fully reversible airflow obstruction).

In both patient groups, the initial degree of airflow obstruction is not only related to airway hyperreactivity, but also to the airway response to a bronchodilator. It has, therefore, been suggested that, as a diagnostic test, the response to a constrictor stimulus is the same as, and of no greater value than, the response to a bronchodilator drug.

Airway calibre is determined by autonomic nervous control of smooth muscle cells, inflammation and oedema, mucus production, and loss of elastic recoil. The latter cannot as yet be influenced by therapy. Airway hyperreactivity may be modulated by a decrease in airway calibre (see above), and an increased response of the bronchial smooth muscle (which will not be discussed in this paper). To investigate smooth muscle contraction, investigators generally focus on the parasympathetic bronchoconstricting nervous system and the bronchodilating beta-adrenergic receptor-system. The non-adrenergic non-cholinergic bronchodilating system is still difficult to investigate, as the neurotransmitter remains uncertain. Studies with corticosteroids may elucidate the influence of inflammatory processes on airway calibre. To unravel the relationship between airway hyperreactivity and airway dilatation, an analysis of studies with anticholinergics, beta-mimetics, and inhaled or oral steroids in different patient populations will be useful.

The theory, that airway hyperreactivity and dilatation are interchangeable seems to be supported by the finding that the bronchodilator response to isoprenaline correlates with the constrictive response to histamine in patients with a broad range of airflow obstruction [1]. The numbers of patients with asthma (seven) and CAO (seven) in this study are, however, small. This influences the results considerably as the degree of airflow obstruction does not overlap in the two groups.

There is evidence against the interchangeability of airway hyperreactivity and reversibility, as the response to a bronchoconstrictive and bronchodilating stimulus does not necessarily run parallel. In asthma, sponteneous changes in airway resistance have been observed without changes in airway hyperreactivity, and vice versa. Moreover, the relationship between the baseline airflow obstruction, as measured by forced expiratory volume in one second (FEV_1), and the degree of airway hyperreactivity, as measured by the provocative concentration causing 20% fall in FEV_1 (PC_{20}) of histamine or methacholine, does show a large scatter. Most studies only observe a good correlation with a baseline FEV_1 below 70% of the predicted value, or PC_{20} for histamine below 0.4 $mg \cdot ml^{-1}$ [2]. In the range of 0.4–128 $mg \cdot ml^{-1}$ histamine no significant correlation with FEV_1 % predicted (70–120%) was observed [2].

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In patients with CAO and no reversibility to a bronchodilator, a considerable bronchoconstrictive effect can occur with methacholine challenge. The finding, that pretreatment with fenoterol without any bronchodilator effect, nevertheless, changes airway hyperreactivity to methacholine, supports the idea that initial airway calibre is not the sole factor influencing the degree of airway hyperreactivity.

Several studies, in asthmatic patients have looked at changes in PC_{20} in the first few hours after a single dose of drug, at a time when the drug causes bronchodilation. In these studies beta-memetics and anticholinergics have both caused a reduction in airway hyperreactivity. The reduction in airway hyperreactivity for the inhaled beta-mimetic is usually 2–4 doubling-doses.

With increasing doses of salbutamol, HANLEY *et al.* [3] found that both the increase in FEV_1 and the reduction in airway reactivity were dose-related. Results for the anticholinergic drug show some variation, but in general the change in airway hyperreactivity has been between 0.5 and 1.5 doubling-doses. In comparing salbutamol and ipratropium bromide in asthmatics, a similar dose-related increase in FEV_1 was observed for both drugs [3]. In contrast, however, there was little change in airway hyperreactivity for ipratropium bromide. Thus, for a given degree of bronchodilation, the anticholinergic drug causes less change in airway hyperreactivity than salbutamol. This suggests, that the effect of beta-agonist on airway hyperreactivity is not due to bronchodilation alone.

We recently measured bronchoconstriction using histamine, acetylcholine, and propranolol in 28 patients with CAO. Bronchodilation was measured following inhalation of terbutaline (500 µg) and ipratropium bromide (40 µg). All patients showed evidence of emphysema according to history, physical examination, lung function data, and chest X-rays. There was a broad range in FEV_1 % predicted (34–90%), PC_{20} histamine (1–32 $mg \cdot ml^{-1}$, normal values: >32 $mg \cdot ml^{-1}$), PC_{20} acetylcholine (3.2–256 $mg \cdot ml^{-1}$, normal values: >256 $mg \cdot ml^{-1}$) and PC_{20} propanolol (6.5–15 $mg \cdot ml^{-1}$, normal values:>15 $mg \cdot ml^{-1}$). In this patient population, we observed a significant correlation between PC_{20} values of histamine and acetylcholine, although the reactivity to histamine on a molar base appeared to be greater than to acetylcholine (fig. 1). This contrasts with studies in asthmatics, where these responses are shown to be comparable. Moreover, although all patients reacted to acetylcholine, only 50% reacted to propranolol (in asthmatic patients ±70% react). Patients were shown to be more reversible on ipratropium bromide than on terbutaline (though both were correlated). PC_{20} histamine, acetylcholine, and reversiblity on terbutaline and ipratropium bromide were all significantly correlated with the degree of airflow obstruction, represented by FEV_1 % predicted.

Nevertheless, no significant correlation was observed between PC_{20} histamine, or propanolol, and reversiblity on terbutaline and ipratropium bromide, suggesting that

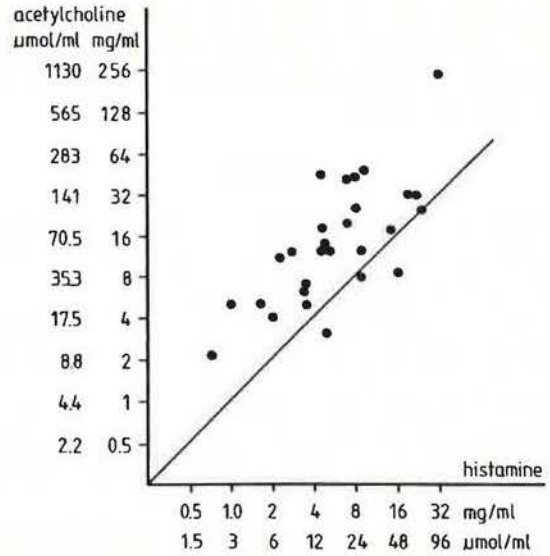

Fig. 1 – Relationship between PC_{20} acetylcholine and PC_{20} histamine in 28 patients with chronic airflow obsruction

different mechanisms play a role in bronchoconstriction and bronchodilation. These findings also show that airway hyperreactivity in patients with CAO, as measured by bronchoconstriction to histamine, acetylcholine and propranolol, differs from that in patients with asthma.

Effects of corticosteroid treatment have mainly been investigated in asthmatics. MATTOLI *et al.* [4] were unable to show an effect of eight days oral methylprednisolone on FEV_1 or PC_{20} methacholine in twelve well-controlled asthmatics (FEV_1 % predicted ranging from 73–100%). It is known that a seasonal increase of airway hyperreactivity induced by natural exposure to environmental allergens, is eliminated by one week of corticosteroid treatment. This suggests that only the allergen-induced component of airway hyperreactivity is corticosteroid responsive, *e.g.* by influencing inflammatory processes, whereas the "baseline" hyperreactivity remains unchanged. KRAAN *et al* [5]. observed, in fourteen asthmatics that inhaled steroids (800 µg budesonide) taken for up to eight weeks, did not increase FEV_1 % predicted after two weeks of treatment, but did improve airway hyperreactivity slowly over the following six weeks (table 1). Thus, steroid effects on airway hyperreactivity appeared to be time-dependant. Moreover, their study showed a decrease in peripheral eosinophils after eight weeks treatment, possibly reflecting a dampening of the well-known inflammatory reactions after allergen exposure. Studies on the influence of long-term treatment with inhaled steroids on airway hyperreactivity in CAO are eagerly awaited, as their results may provide new information on airway hyperreactivity.

In conclusion, growing evidence suggests that airway hyperreactivity is not the same as airway reversibility. Airway hyperreactivity seems to be different in mechanism and appearance in patients with asthma and CAO. They are, therefore, not interchangeable and both provide useful information.

Table 1. – Influence of 8 weeks of treatment with 800 μg budesonide on airway calibre and airway hyperreactivity in 14 asthmatics

Budesonide 800 μg	Week				
	0	2	4	6	8
FEV_1 %predicted	84	93	93	92	92
PC_{20} methachline	0.91	1.84	1.89	1.99	2.74

From reference [3]

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Bronchial hyperreactivity in smokers

N.B. Pride

Non-specific bronchial hyperresponsiveness (BHR) is regarded as central to the development of airway narrowing and symptoms in subjects with asthma. Because the intensity of BHR is related to the clinical severity of asthma, some experts believe that the major aim of treatment in asthma should be to remove (or at least attenuate) BHR, rather than to treat symptoms as they arise. BHR is also found in many smokers with developing airflow obstruction. This raises two questions: 1) is BHR in smokers important in the pathogenesis of progressive airflow obstruction? (as proposed by the 'Dutch hypothesis' of Orie and Van der Lende in the 1960s) and, if so, then 2) will attenuation of BHR slow down the progression of airflow obstruction in continuing smokers? This report considers these two hypotheses.

There is widespread agreement that bronchial hyperresponsiveness (BHR), - usually assessed as the response to inhaled histamine or methacholine, is found consistently in middle-aged male smokers with mild or moderate chronic airflow obstruction [1]. Male smokers who have shown preceding, accelerated annual decline in forced expiratory volume in one second (FEV_1) also show abnormal BHR to inhaled bronchoconstrictor or bronchodilator drugs. The presence of an association between low baseline FEV_1 and an accelerated annual decline in FEV_1 ('horse-racing effect') has recently been discussed and criticized [2], however, it appears to be a feature of middle-aged male smokers.

The association of these three changes is compatible with the accuracy of the Dutch hypothesis but does not indicate whether the BHR observed is important in pathogenesis or merely one of many unimportant consequences of smoking.

Is the BHR of smokers 'endogenous' or acquired?

The original Dutch hypothesis implied that BHR in smokers was likely to be similar to that associated with asthma and atopy and so to be 'endogenous' or 'constitutional' and presumably present at the onset of smoking. Such 'endogneous' allergic BHR is sufficiently common in the population of pre-smoking age that it must account for a proportion of BHR found in smokers, unless smoking is so disturbing to those individuals with pre-existing BHR that they all give up. (Some studies, including our own, have found that positive skin tests to common inhalant allergens are more common in ex-smokers than continuing smokers). So the questions are really a) is BHR often acquired after the onset of smoking? If the answer is 'yes', b) in the population of smokers with BHR, what is the relative prevalence of endogenous and acquired BHR?

Cross-sectional evidence suggests that BHR is often acquired. In contrast to findings in asthmatics, there is a relatively strong inverse association between the intensity of BHR and reduction in lung function. Review of various studies of BHR in smokers with normal lung function, suggests that BHR is not increased in young smokers but is in middle-aged smokers [3]. This is confirmed by a recent community-based study in England, which found that prevalence of BHR among smokers increased with increasing age [4]. Although the answer to question (a) would therefore seem to be positive, there is little information yet on question (b) although this should come from various community studies in progress, in particular the follow-up of the original Netherlands studies of Van der Lende.

Concerning our major questions, whether BHR is