

# United airways disease: therapeutic aspects

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During the past few years the global pathogenic view of respiratory allergy has changed. The link between rhinitis and asthma—that is, upper and lower airways—has been underlined by epidemiological and clinical studies. Taken together, these have led to the operative definition of “allergic rhinobronchitis”<sup>1</sup> or, as we have proposed, “united airways disease (UAD)”<sup>2</sup>. In recent years more evidence has been provided of the frequent co-existence of rhinitis and asthma, the possible role of upper respiratory infections, and the importance of paranasal sinus infections. These relationships are particularly notable in children. Detailed knowledge of the mechanisms sustaining allergic inflammation in the respiratory tract allows a greater understanding of the functional relationships between the upper and lower sections of the tract. In this respect it is logical to assume that allergy is not a disease confined to a specific target organ, but rather a disorder of the whole respiratory tract which has a broad spectrum of clinical manifestations. The concept of “united airways disease” also has therapeutic implications.

## Epidemiological evidence

Early epidemiological studies described the association between allergic rhinitis and asthma. One of the earliest observations on a large sample assessed the effects of specific immunotherapy.<sup>2</sup> This association has been further investigated and substantiated in more recent studies.<sup>3</sup> It has become clear that the association between rhinitis and asthma is very strong,<sup>4–7</sup> that bronchial hyperresponsiveness is frequent in patients with rhinitis,<sup>8</sup> and that rhinitis itself is a primary risk factor for subsequent asthma.<sup>9–11</sup> Moreover, it has recently been shown that, when a rigorous diagnosis is made, the prevalence of rhinitis in asthmatic patients approaches 100%.<sup>12</sup> All observations suggest that progression of the disease occurs from the upper to the lower respiratory tract.

## Immunological and pathogenic aspects

The respiratory tract can be considered as a unique morphofunctional entity covered by ciliated epithelium and mucinous glands and served by an extensive vasculature and neural innervation. The neural innervation is a common feature of the two compartments. Moreover, the respiratory mucosa is rich in mast cells and the lymphoid tissue which constitutes the bronchial (mucosal) associated lymphoid tissue (BALT or MALT). The upper respiratory tract functions as a physical filter, heat exchanger, and humidifier for inhaled air. A failure of any of these functions usually results in an alteration in the homeostasis of the

lower respiratory airways. The only relevant functional difference between the two compartments is the presence of bronchial smooth muscle.

When an allergic reaction occurs, an early phase mediated by histamine takes place within minutes. This reaction is followed by a complex network of inflammatory phenomena involving T lymphocytes, cytokines, and adhesion molecules. The adhesion machinery, in particular, seems to be crucial for the recruitment of inflammatory cells at the target organ. During the early phase specific adhesion molecules are expressed on the surface of the endothelium and epithelium, thus favouring extravasation and epithelial infiltration of inflammatory cells. Interestingly, a weak inflammatory infiltration is present at the mucosal level even in the absence of symptoms when a subliminal exposure to the allergen persists. This is called “minimal persistent inflammation (MPI)” and has been demonstrated in both mite<sup>13</sup> and pollen<sup>14</sup> induced rhinitis, as well as in asthma. The MPI also involves a weak and persistent expression of the CD54 (ICAM-1) molecule which is the major receptor for human rhinoviruses.<sup>15</sup> This is important in view of the fact that asthma exacerbations are closely related to upper respiratory viral infections in children.<sup>16 17</sup>

The following mechanisms have been proposed to explain the effect of rhinitis on asthma: (a) the rhinobronchial adrenergic reflex; (b) the failure of the heater/humidifier system; and (c) the humoral activation of bone marrow precursors.<sup>18</sup>

## Therapeutic implications

Two main observations are of relevance from a therapeutic perspective: (1) the unity of the respiratory airways and the influence exerted by the nose on the bronchi and (2) the fact that both symptoms and allergic inflammation should be targets for treatment. Indeed, there is some evidence to suggest that optimal control of rhinitis has a beneficial effect on asthma in terms of reduction of bronchial responsiveness during natural exposure to the offending allergens.<sup>19 20</sup> Moreover, in a double blind, double dummy study it was observed that intranasal beclomethasone was more effective than inhaled beclomethasone in reducing carbachol induced bronchoconstriction in patients with asthma.<sup>21</sup>

On the other hand, the existence of a persistent inflammation suggests the need for continuous rather than on demand treatment with antiallergic drugs.<sup>22</sup> This concept has been shown experimentally with several second generation antihistamines. Continuous use was found to be better for controlling symptoms,

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allergic inflammation,<sup>23 24</sup> and the occurrence of upper respiratory infections in children.<sup>25</sup> These findings, usually seen in small groups of subjects, were observed in the large ETAC study population in which continuous antihistamine treatment was shown to prevent the onset of asthma.<sup>26</sup> One of the new clues to the treatment of united airways disease is the evidence of a synergistic effect of drugs used in both rhinitis and asthma—for example, anti-leukotrienes added to antihistamines<sup>27</sup> or inhaled corticosteroids, or  $\beta_2$  agonists added to antihistamines. This aspect is relevant since it would allow treatment to be harmonised, possibly reducing the dosage of each drug. Ultimately, this may result in better control of the disease(s) and fewer side effects.

### Conclusions

A Galilean procedure applied to united airways disease implies clinical observation, the formulation of a hypothesis, and the validation of the hypothesis by controlled and reproducible experiments. At present epidemiological observations suggest that the hypothesis of united airways disease is tenable, and there is an increasing amount of direct and indirect experimental evidence to support this hypothesis. United airways disease is beginning to be considered as an evidence based entity and a new therapeutic approach to the management of respiratory allergy is therefore possible.

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