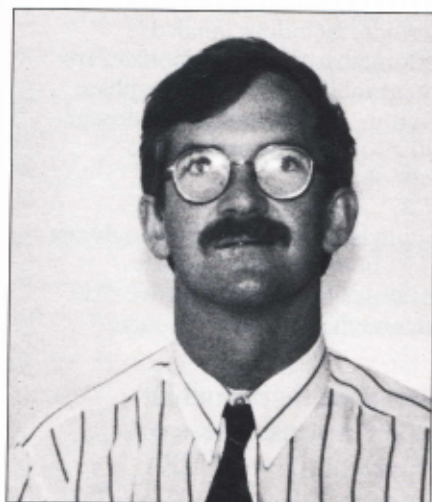


## New Concepts in Bronchial Asthma

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### Curriculum vitae

Adrian Morris graduated from UCT Medical School in 1983. After his housemanship at Groote Schuur Hospital, his SHO posts included paediatrics at Red Cross Children's Hospital and emergency medicine at Groote Schuur Hospital. He then completed GP Vocational training in Surrey, (England) before returning to Cape Town in 1988, to join a group family practice in Newlands. He obtained the DCH(SA) in 1989 and the MFGP(SA) in 1990. Allergy and clinical immunology are his special interests. He is a member of the British Society for Allergy and Clinical Immunology, and was a delegate at their annual conference in London in 1991.

### Summary

*Bronchoscopic studies which have confirmed the inflammatory nature of bronchial asthma, indicate that reversing the bronchospastic element by means of bronchodilators alone may mask the underlying late-phase inflammatory process. This ongoing process together with the resultant bronchial hyperresponsiveness (BHR) may be causative factors in asthma death and in the development of chronic obstructive lung disease.*

*Therapeutic approaches should therefore aim to reduce both the inflammatory process and the bronchospastic element in even the mildest asthmatic.*

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### KEYWORDS:

Asthma; Inflammation; Death; Bronchial Spasm; Lung Disease, Obstructive; Bronchodilator Agents.

*"Death during an attack is unknown. The asthmatic pants into old age."*

William Osler 1892

This has been a common misconception of bronchial asthma for almost one hundred years.

During the past few years, a revolution in the understanding of the pathophysiology of bronchial asthma has taken place. No longer is it accepted that asthma is simple smooth-muscle broncho-constriction in isolation which is reversed by bronchodilator therapy. For with the

advent of fiberoptic bronchoscopy, bronchial biopsy and bronchoalveolar lavage, it has been demonstrated that asthma is a chronic, ongoing, eosinophilic inflammatory bronchitis with intermittent acute exacerbations.<sup>1,2</sup> It has been speculated that the long-term sequel to poorly controlled asthma may be irreversible airflow obstruction, a condition which has in the past been usually attributed to smoking or to chronic lung infections.<sup>1</sup>

A more descriptive terminology for asthma would be "chronic eosinophilic desquamative bronchitis".<sup>2</sup> This pathological process includes the shedding of bronchial epithelial cells; hypertrophy of bronchial glands and smooth muscle; thickening of the basement membrane; mucosal oedema and infiltration of eosinophils; lymphocytes; neutrophils and mast cells. Such changes are observed in most asthmatics, ranging from those with mild symptoms to asthma death necropsy specimens.<sup>2</sup> (See Fig 1)

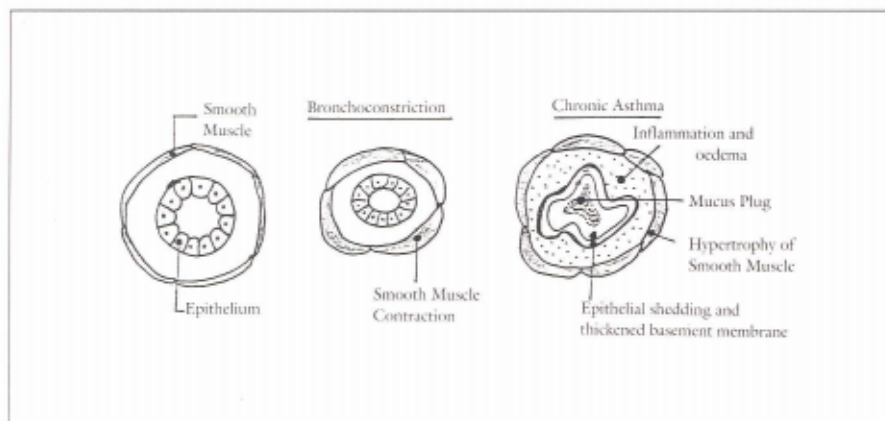
The concept of early and late-phase bronchoconstriction reactions, bronchial hyperresponsiveness and the increased incidence and mortality in asthma have recently attracted considerable academic and clinical interest.

### Early and late-phase reactions

Antigen binding specific IgE in sensitised individuals, as well as non-specific irritants (cold air, gases, smoke and pollutants), can induce mast cell degranulation and release of preformed mediators including histamine. This results in immediate but transient bronchoconstriction and increased airway secretions, a process now referred to as the early-

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Figure 1: Pathology of Asthma:



phase asthmatic reaction and lasts for one to two hours.

Commensurate with the onset of the early-phase reaction, inflammatory leucocytes, mainly eosinophils and lymphocytes, are recruited from the microcirculation and retained in the airway wall. These cells release

Our basic understanding of asthma has changed radically

further inflammatory mediators, including Leukotrienes (LT), Platelet activating factor (PAF) and eosinophil Major basic protein (MBP), which cause further bronchoconstriction, mucosal oedema, epithelial desquamation and mucus secretion. In turn further mast cell degranulation takes place.

This process which takes three to twelve hours to occur and lasts up to twenty four hours, is known as the late-phase asthmatic reaction. (Fig 2)

Environmental control and potential

allergen avoidance will reduce this inflammatory process.

Beta adrenoceptor agonists, cholinergic antagonists and theophyllines will inhibit the early-phase reaction, but have little effect on the late-phase reaction.<sup>3</sup>

Steroids, including inhaled beclomethasone dipropionate, are potent inhibitors in the late-phase reaction. A continuous low dosage will also limit the early-phase reaction.

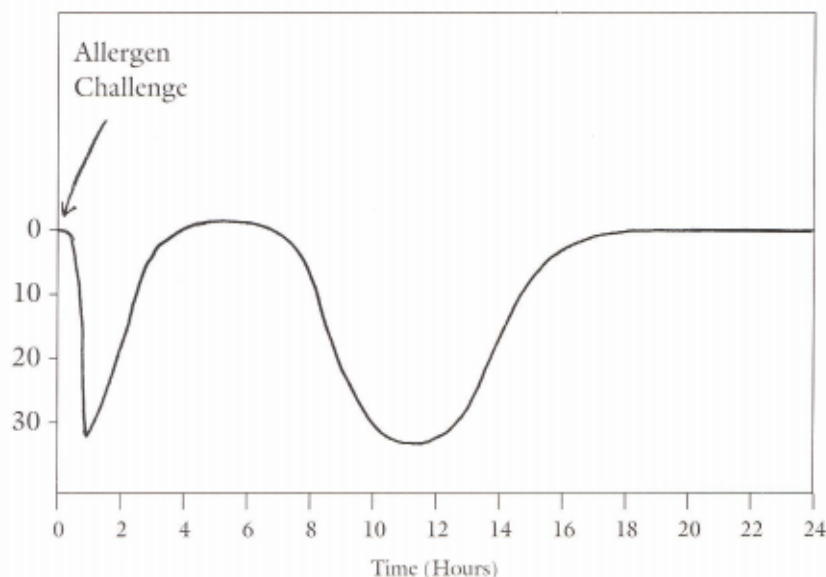
Prophylactic sodium chromoglycate limits both the early and late responses but is less effective than beclomethasone dipropionate.<sup>4</sup>

Non specific bronchial hyperresponsiveness or hyperreactivity (BHR)

Non-specific BHR can be defined as an increase above normal in both the ease and the magnitude of airway narrowing on exposure to a number of non-specific bronchoconstrictor stimuli<sup>5</sup> (including exercise, cold air, cigarette smoke, viruses, irritant gases and environmental chemicals.)

The late-phase reaction with its resultant bronchial epithelial

Figure 2: Early and Late-phase Reactions:





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desquamation and inflammatory mediator release sets up a "vicious cycle" whereby further casual exposure to allergen or to a minor irritant triggers a marked airway hyperresponsiveness which may last weeks or even months after the initial allergen provocation. BHR may manifest as episodic bronchoconstriction, circadian variation in pulmonary function or increased response of the airway to cold air, exercise and environmental irritants. (Fig 3)

Once environmental irritants have been removed or avoided, asthma therapy should combine bronchodilators, primarily B<sub>2</sub> adrenoceptor agonists, with non bronchodilator antiasthma preparations, such as sodium chromoglycates and glucocorticoids.<sup>6</sup>

Glucocorticoids are potent anti-inflammatory agents which block the late-phase reaction and reduce bronchial hyperresponsiveness.<sup>3</sup> Oral use of steroids should be restricted on account of their side effect profile. Inhaled steroids are now being re-evaluated following recently expressed concern regarding suppression of hypophyseal - pituitary - adrenal axis which has accompanied higher dosages.

The worldwide increase in asthma morbidity and mortality

Despite more active treatment and improved medical services, the number of asthma deaths worldwide have increased in recent years. This may be due to increased bronchial sensitisation and hyperresponsiveness from environmental pollution, or may reflect the increasing diagnosis of chronic cough as asthma.

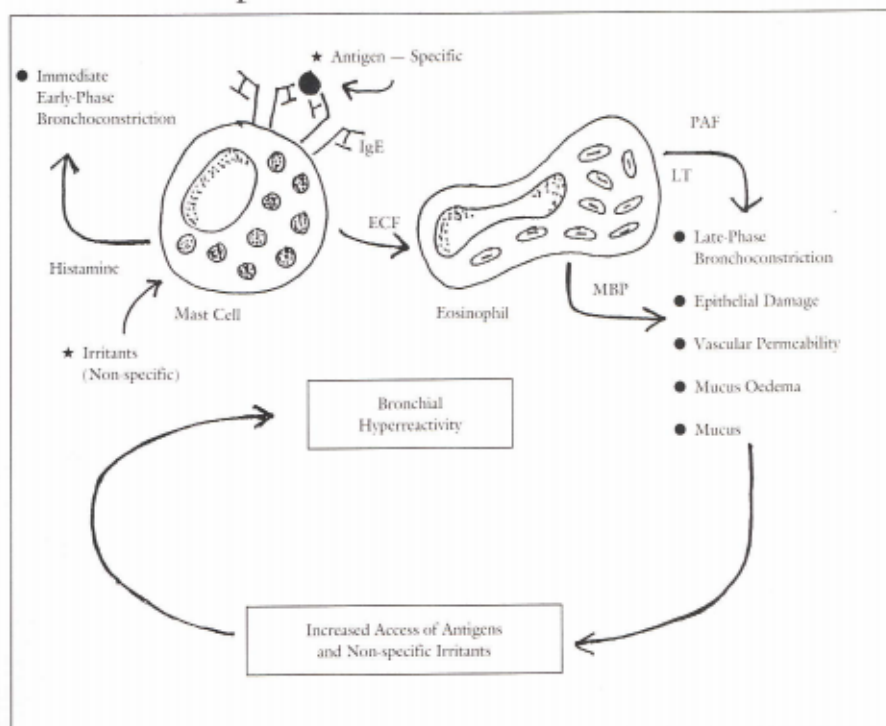


Figure 3: Airways Inflammation and Bronchial Hyperreactivity

In 1990 Sears et al<sup>7</sup> in New Zealand tried to implicate the widely used beta adrenoceptor agonists, at present the mainstay of asthma prophylaxis and treatment. Excessively frequent use and high dosage of bronchodilators<sup>8</sup> and under-use or inappropriate use of

treatment. A consequence of this dilatation of inflamed airways may mean further allergen exposure, further inflammation and hyperresponsiveness. It has been proposed that perhaps bronchoconstriction is a physiologic protective mechanism to limit allergen exposure to the lung mucosa.<sup>9</sup>

Asthma is seen as a chronic eosinophilic desquamative inflammatory process of the airways

In the past, despite their efficacy, too much reliance<sup>4</sup> has been placed on routine bronchodilator therapy in asthma, and it is now recommended that they be used as required to avoid possible tolerance developing.

corticosteroids may mask the severity of the chronic inflammatory underlying process and delay the patient seeking further medical

The inflammatory process has been largely ignored in the past and there is a need to encourage the prophylactic use of sodium

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chromoglycate, ketotifen or low dose inhaled steroids in all but the most mild intermittent asthmatic. Patients often appear asymptomatic despite having severe ongoing airflow limitation, therefore regular peak flow monitoring is essential to identify the "at-risk" patient.

### Conclusion

Our basic understanding of asthma has changed in that it is no longer seen as isolated bronchoconstriction, but as a chronic eosinophilic desquamative inflammatory process of the airways.

After environmental manipulation and allergen-avoidance measures have been implemented, the treatment of asthma should be reviewed. Any asthmatic requiring a beta adrenoceptor agonist more than three

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**Review the treatment of any asthmatic needing a beta adrenoceptor agonist more than 3 times per week**

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times per week should be treated with prophylactic regimes such as sodium chromoglycate or ketotifen (especially in children) or inhaled steroids.<sup>10</sup> Although theophyllines are among the cheaper drugs available, their unacceptably high side-effect profile and narrow therapeutic range<sup>11</sup> will probably reserve them as second line therapy for more resistant asthmatics. It is important in a third-world situation, where costs of medication are a significant limiting factor, to weigh up the advantages and disadvantages of the various therapies.

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