

Bronchial Asthma-Current Concepts

Pages with reference to book, From 50 To 54

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Asthma, a common, chronic disease is characterised by widespread narrowing of the tracheobronchial tree, and by acute exacerbations of varying severity, which resolve spontaneously or by the use of drugs. Recent definitions have included various features that have a role in its pathogenesis but though these components are present they are not unique to asthma and are found alone or together in other conditions¹. A universally accepted definition remains an elusive goal. No data in Pakistan is available but the condition is considered very common. In one study conducted in a thoracic unit of a Karachi teaching hospital, 24% of all admissions during 1982 were due to bronchial asthma, 44 of these were status asthmaticus². It is quite possible that prevalence differs from region to region. Although some irreversible changes in lung function have been reported in small numbers especially in smokers³, asthma unlike other airway diseases like chronic bronchitis, cystic fibrosis, bronchitis and atopic rhinitis is not a progressive disease⁴ and if untreated, may not progress from mild to severe, instead the clinical course is marked by acute exacerbations and remissions. There are conflicting reports as to allergic component in asthma. Some studies suggest that almost all asthmatics are atopic⁵⁻⁶, but these were entirely based on IgE levels, even in the absence of positive skin tests and allergic disease symptomology. Other estimates suggest that 30 percent are not atopic⁷. Deaths due to bronchial asthma have been increasing over the years in Western countries where figures are available⁸⁻¹⁰. Although B2 agonists have been implicated by some^{11,12}, confirmation is lacking when data is further analysed. The most probable cause seems to be non-realisation of the severity of disease on the part of physician, patient or both¹³, coupled with inadequate treatment at the hospitals¹⁴.

Pathogenesis

Asthma is an inflammatory disease of airways, suggesting that mediators of hypersensitivity have an important role in pathophysiology and pathogenesis of this condition. In autopsies of patients dying of status asthmaticus, inflammatory changes consisting of oedema and infiltration of airways by inflammatory cells are seen^{15,16}. In addition epithelium is damaged¹⁷ with sloughing and thickening of basement membrane, goblet cell hyperplasia, hypertrophy of smooth muscle cells and capillaries. The airways of asthmatics are remarkably free of fibroblasts¹⁸.

The precise features of airway inflammation in asthma have not been defined. Environmental stimuli such as antigen, air pollutant or thermal events interact with target cells i.e., mast cell or basophils, releasing powerful biologically active mediators, causing intense reaction which can be neurally amplified¹⁹, affecting the airways and vascular functions. Epithelial cells and macrophages may also participate. Some mediators produce immediate reaction¹⁹ (Figure 1)

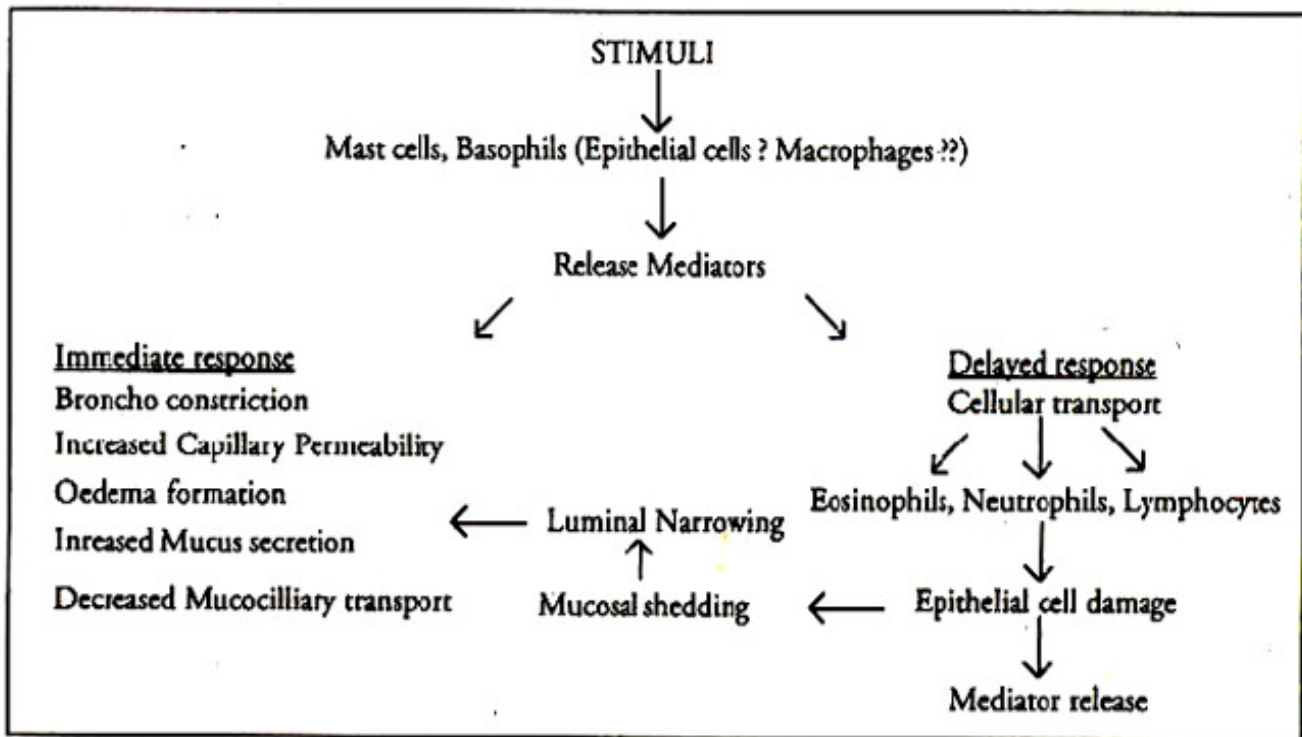


Fig I. Sequence of events believed to lead to airways obstruction after Mc Fadden R.E Jr. (18)

in the form of sub-acute inflammatory reaction characterised by cellular infiltration of mucosa and submucosa with eosinophils, neutrophils and lymphocytes. The role of lymphocytes is not understood as yet. In addition there is epithelial cell damage which leads to mucosal shedding further aggravating the airway narrowing with decrease in mucociliary transport, which may further release mediators. When antigen interacts with immunoglobulin E (IgE) on the surface of the mast cells, two forms of mediators are released; those that are already preformed and stored in the mast cell granules, which when released act rapidly. These include histamine, eosinophil chemotactic factor (ECF), neutrophil chemotactic factor (NCF) while the second group are the newly formed membrane derived mediators that are products¹⁹ of the metabolism of Arachidonic acid (Figure 2).

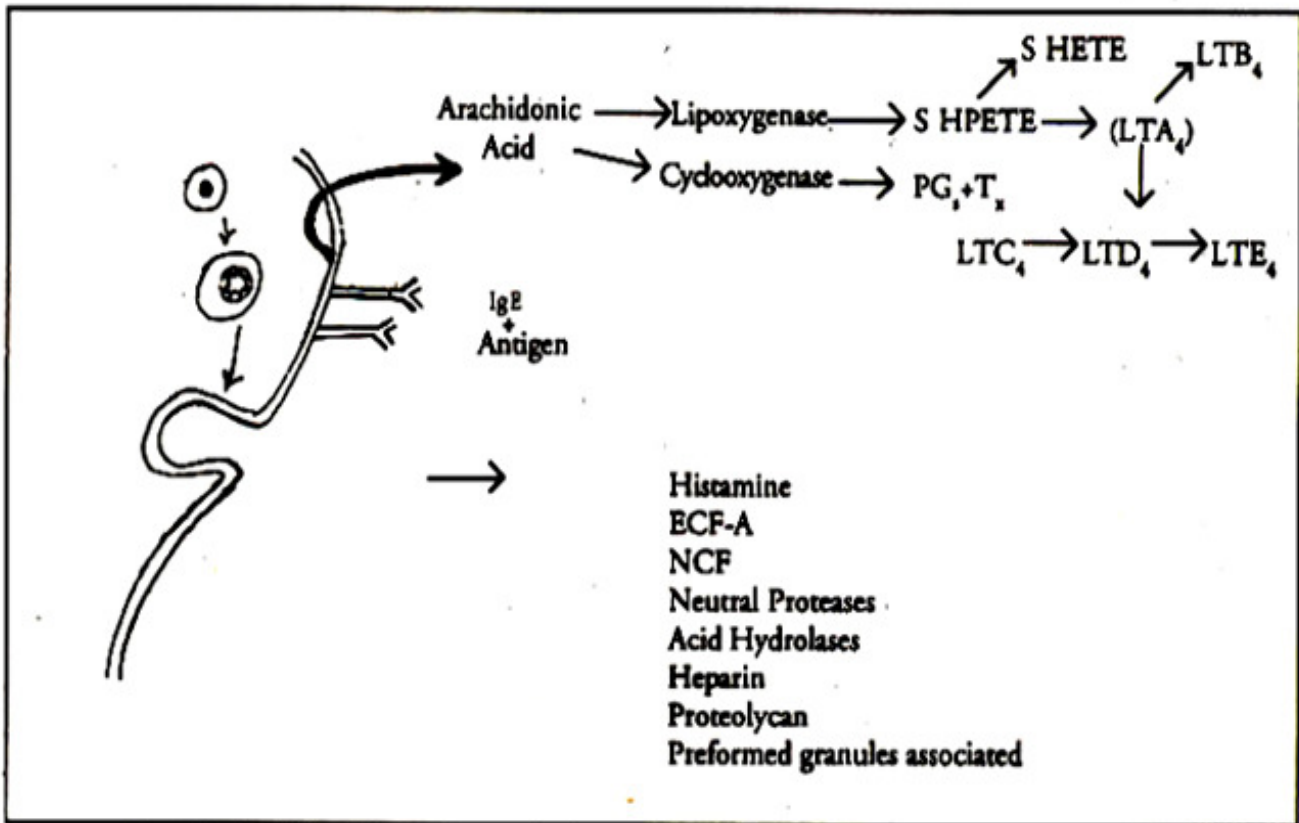


Fig. II. Arachidonic Acid Metabolism after Barnes and Castello (19)

This compound is present or can be generated by all of the 40 or so odd cell types that are resident in normal lungs, as well as inflammatory leukocytes that can infiltrate paranchyma and airways. Arachidonic acid once formed is rapidly metabolised by lipoxygenase and cyclooxygenase pathways. The important products of Lipoxygenase being mono hydroxyeicosatetraenoic acids (5-HETE) and leukotrienes B₄, C₄, D₄ and E₄. Leukotriene C₄ and D₄ are the most potent bronchoconstricting agents yet studied. Major sources of leukotrienes in the lung are epithelial cells, mast cells, basophils, neutrophils and macrophages. The products of cyclooxygenase pathway are prostaglandins (PGs), those with major activities are (PGD₂), PGE₂, alpha and thromboxane (TXA₂) and prostacyclin (PGI₂). PGD₂, and PGF₂ alpha are potent broncho constrictor while PGE₂ is a broncho and vasodilator, and its endogenous release may be important in control of airway and vascular tone. PGD₂ also has chemotactic effect and increases secretions from sub-mucus glands. The mediators most likely to produce immediate response are histamine, prostaglandin D₂ (PGD₂), leukotriene C₄ (LTC₄) and leukotriene D₄ (LTD₄) while leukotriene B₄ (LTB₄) neutrophil chemotactic factor (NCF), eosinophil chemotactic factor of anapylaxis (ECF-A) and platelet activating factor (PAF) participate in delayed response. This phase takes many hours to develop, but once it occurs the cells can, produce more arachidonic acid and hence increases both Immediate and delayed reactions by initiating feed-back loop. Inflammatory cells hypothesis though very attractive has not been confirmed, as mediators have also been recovered from patients without asthma. Fiberoptic bronchoscopy biopsies²⁰ and bronchial lavage studies before and after antigen challenge²¹⁻²³ have shown increased bronchovascular permeability with oedema and increased mast cells^{23,24} epithelial cells²⁵, neutrophils^{22,27,28} lymphocytes^{24,26} and especially eosinophils^{22-26,28} and macrophages²⁹ Eosinophils increased significantly in delayed response. Importance of eosinophils in delayed response in asthmatics is based on, a) their presence in sputum and blood during exacerbations and b) toxicity of proteins in their granules. One of the proteins "Major basic protein (MBP) readily kills ciliated respiratory epithelium"²⁹⁻

³¹ and has been found in the sputum during severe episodes in concentrations that are toxic to respiratory epithelium, potentially exposing sensory nerve endings and activating neurogenic inflammatory pathways. Effect of human MBP on human bronchial epithelium has also been studied²². 100 ug/ml of human MBP for 19 hours causes the surface epithelium to detach from lamina propria and to be sloughed. These findings may not be specific as they have also been reported in a variety of other pulmonary diseases³². There is limited data comparing the BAL findings and biopsies obtained at the same time, which show poor correlation. In chest biochemical and cellular mechanism involved in asthma are incompletely understood, the mechanism of hyperresponsiveness remains undiscovered. Although there is ample evidence as to the acute inflammatory in the airways mechanism however remains obscure.

Diagnosis

Cough, dyspnoea and wheeze either alone or in combination are the main features of asthma. In active disease patients awaken at night or early morning with one or more of these symptoms. Nocturnal symptoms are so common³³, that some believe that its absence should raise doubts about the diagnosis. Frequent exacerbations are seen on exposure to non-specific stimuli⁴, i.e., exercise, cold air, or respiratory irritants like perfumes etc. Clinical impressions in view of non-specific symptoms must always be confirmed by lung function demonstrating reversible obstruction of airways. Spirometric values will show reduction of expiratory volumes and flow rates and elevation of functional residual capacity (FRC) and residual volume (RV) or both³⁴. The airway obstruction is considered reversible if forced expiratory volume in one second (FEV1) is improved by 15 percent after B2 antagonist inhalation. In asymptomatic patients increased airways response can be confirmed by histamine or methacholine challenge³⁵. Once the diagnosis is confirmed, improvement or otherwise of the treatment can be monitored by Peak Expiratory flow rate (PEF).

Therapy

The objective in treatment of asthma is to achieve a stable asymptomatic state with the best possible lung functions, with the drugs that are least toxic, are required in small doses, with minimum of untoward reactions. In view of the fact that asthma is an inflammatory disease, some physicians have suggested that anti-inflammatory drugs like Cromolyn sodium and inhaled glucocorticoids should form the first line of treatment, and B2 agonists should be reserved for symptomatic relief¹. Though this seems a reasonable approach, there is very little evidence as to anti-inflammatory properties of inhaled steroids and Cromolyn sodium. Two recent studies^{20,29} have examined the effects of inhaled steroids on airway inflammation, using serial biopsies. Reduction of mast cells and eosinophils was seen in both on light microscopy; in one of the studies²⁰ this reduction was accompanied by decrease in airway reactivity, but no change in mast cell degranulation on electron microscopy. In the other²⁹, there was a decrease in free eosinophilic granules on electron microscopy, but neither this change nor the other cellular changes had any effect on airway responsiveness²⁰. Steroids have no effect on degree of basement membrane thickening²⁰. No such data is available for Cromolyn or methylxanthines. Although Cromolyn and inhaled steroids have been in use for the past 2 decades, morbidity and mortality have been rising. In general these agents work best in mild disease and their effectiveness decreases with the severity of the disease. B2 agonist on the other hand is not only a more potent stabilizer of mast cell than Cromolyn, but also prevents and reverses asthmatic symptoms. Even though B2 agonists have been used for the past many decades both in acute and chronic asthma, it has been suggested that the use of these agents not only produces poor control of symptoms¹¹ but can be harmful due to adverse reactions which include paradoxical bronchoconstriction³⁶, tachyphylaxis^{37,38} adverse effect on airway^{38,39} reactivity and development of life threatening episodes due to over dose¹². These responses are extremely rare when millions of doses used every year are taken into consideration, and

do not justify limiting their use. If patients are doing well on sympathomimetic agents, there does not seem any reason for change. If on the other hand they are doing poorly in spite of maximal therapy including oral steroids there is a need for careful evaluation to exclude adverse reactions of B₂ agonists. To provide rapid symptomatic relief the first line of treatment should be inhaled B₂ agonist. As aerosols produce prompt bronchodilatation with minimum side effects, patients who have difficulty in coordination⁴⁰ a spacer device should be used. This acts as a form of reservoir for the drug, which can be inhaled at will⁴¹. If nocturnal symptoms predominate a long acting theophylline or slow release B₂ agonist should be included in the regimen. In patients with active disease and unstable pulmonary function, (indicated by persistent and increased symptoms), Cromolyn or inhaled steroids or both should be used. The choice between Cromolyn and steroids is open to debate. In some studies^{42,43} steroids proved better in controlling asthma than Cromolyn, while in others the effect of both were equal⁴⁴, since both these drugs take weeks to produce desired effects, along with acting theophylline or a short intense course of oral steroids in the dosage of 40-60mg prednisolone, reducing every 4th day for a period of 16-20 days till asymptomatic should be given. During this state it is mandatory to monitor the peak flow rate and adjust the dose of medication according to lung function and symptoms^{1,33}. Once an asymptomatic state has been achieved, B agonists should be systematically withdrawn, starting with the most toxic, determining the lowest possible dose required to maintain symptoms free state. Reduction of dose and hence total quantity of drug will minimise untoward effects. There should be close communication between the physician and patient, along with objective measure of disease activity. Oral drugs should be withdrawn first followed by aerosols. Various approaches are employed once an asymptomatic state is reached. Some reduce B₂ agonists from regular use to whenever they are required while maintaining inhaled steroids and Cromolyn, while others first reduce anti-inflammatory drug dosage, maintaining B₂ agonists and finally reduce the dosage of sympathomimetic agents. There is no data available to suggest superiority of one regimen over the other. If the patient is going to have problems, lung functions will diminish before symptoms appear and peak expiratory flow rate will show circadian variation³³. If these changes appear and the patient is asymptomatic no therapeutic adjustment should be made till PEF return to normal which may take weeks; if however the patient becomes symptomatic, he should receive effective doses of medicines. Patients whose medication cannot be adjusted and require long term glucocorticoid treatment other anti-inflammatory immunosuppressant agents such as methotrexate^{45,46} and gold^{47,48} has been suggested, but these have very little effect on the disease activity and are potentially very toxic hence their use should be considered experimental⁴⁷⁻⁴⁹. If the patient is unresponsive to intense treatment with bronchodilators and anti-inflammatory drugs, or dose of the drugs cannot be reduced, other reasons for pulmonary abnormalities i.e., upper airway obstruction, embolic phenomena, vasculitis, congestive cardiac disease and chronic sub-acute bacterial or fungal infection⁵⁰ should be explored. In short it is obvious that there is an inflammatory process in asthmatics even when they are asymptomatic. Sources of the cells involved have all the potential to produce many of these changes seen, but the mechanism remains unknown. Reducing the inflammation therefore remains the main stay of therapy, to keep patients in symptomatic stable state.

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