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Foreword

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Our present view of asthma is based on the underlying pathology of airway inflammation and how this relates to disordered airway function. The recognition that asthma—whatever the severity—is an inflammatory disorder has had profound implications for the diagnosis, treatment, and prognosis of the disease. This view of asthma has been reflected in many national and international guideline documents drawn up by panels of asthma experts around the world. Thus, in a recent Global Strategy for Asthma Management and Prevention that was formulated under the auspices of the World Health Organization and the National Heart, Lung, and Blood Institute, the emphasis for pharmacologic treatment is put on daily antiinflammatory or “controller” medication rather than on drugs that provide only symptom relief. For what is termed mild, persistent asthma by these global guidelines, the three recommended controller medications are nedocromil sodium, sodium cromoglycate, or low-dose inhaled corticosteroids (equivalent to 200 to 500 µg per day of budesonide or beclomethasone). When the asthma is more severe, higher doses of inhaled corticosteroids are recommended. Our focus at this workshop held in Whistler, British Columbia, is on nedocromil sodium, and our aims are

to review its recommended position within the guidelines in light of recent clinical experience with this drug and, particularly, to explore the new scientific data on its mechanism of action.

THE EVOLUTION OF ASTHMA

Also to be discussed is whether we can identify any cellular mechanisms that underlie the chronicity of asthma and, more importantly, whether we can verify the cellular findings by matching them to clinical indices of disease. Mast cells and eosinophils are recognized as key effector cells of the inflammatory response in all forms of asthma through their capacity to secrete a wide range of preformed and newly generated mediators. T-lymphocytes are also pivotal to the inflammatory response through the release of multifunctional cytokines. It is unlikely, however, that the relative contribution of these cells and processes remains static across, for example, allergic and non-allergic asthma or mild and severe disease. New data on mast cells have revealed their capacity for cytokine release and could devolve onto these cells the responsibility for many if not all of the events following allergen provocation in sensitized persons. If mast cells are a driving force in milder forms of asthma, this could explain why nedocromil sodium and cromolyn sodium, with their well-known ability to “stabilize” mast cells, are more effective in cases of milder asthma and in childhood disease. Certainly such a transition of asthma, in which an early dependence on mast cells evolves to dependence on T cells with the eventual enrollment of constitutive elements of the airway wall, could provide a basis for differing needs for drug therapy during the course of the disease and thus validate the current guideline recommendations.

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THE IMPORTANCE OF ASTHMATIC SYMPTOMS

Airway inflammation is manifested in disordered airway function in the form of airway hyperresponsiveness, airflow limitation, and respiratory symptoms. With so much stress having been placed on airway inflammation and our exhortations to maximize symptom relief in the form of regular bronchodilator regimens, there arises a possibility that we are neglecting the importance of respiratory symptoms both as a manifestation of airway inflammation and in terms of their contribution to the quality of life of a patient with asthma. A dangerous area of potential fallibility exists between the policy recommendations of guideline documents and their implementation at the level of primary care around the world. We describe the quite complicated concepts of airway inflammation and the need for controller medication on the basis of the stratification of asthma severity. The primary care physician encounters patients who report wheezing and coughing—not inflamed airways. In addition, a patient's perception of the efficacy of a medication will be based on its effect on symptoms and episodes of exacerbation rather than on the less visible measures of disordered airway function. For a nonbronchodilator medication, nedocromil sodium at a single dose provides impressive protection against a wide range of stimuli that are implicated in both inflammatory and neuronal components of asthma, which provide paradigms for many of the triggers encountered on a day-to-day basis by patients with asthma. We shall examine how these models can elucidate the mechanisms of symptomatology and whether the efficacy of a drug in such

models translates into immediate and long-term clinical effects that will benefit the patient and optimize compliance.

CHLORIDE CHANNEL BLOCKADE: A UNIFYING HYPOTHESIS?

The description of cromolyn sodium and nedocromil sodium as "mast cell stabilizers" has arisen through want of a better understanding of how these drugs work. These agents are by no means the most potent mast cell stabilizers, nor do they work on mast cells alone. The drugs have inhibitory effects on various other inflammatory cells, on mediator release, and on sensory nerve activity, and the extensive literature (nearly 10,000 references to date on these two drugs alone) reflects both the range of their activity and the investigative effort that has been stimulated by the fact that we have never precisely known how these drugs exert their clinical effects. Recent research now shows that nedocromil sodium is capable of inhibiting chloride ion flux in mast cells, epithelial cells, and neurones, and this may provide a unifying hypothesis to explain how it can prevent responses such as mast cell degranulation, the effects of osmolarity changes in the airways, and neuronal activation, which may lead to symptoms such as cough. Because an inhibitory effect on these channels would occur only when the channels open during cell activation, the unifying hypothesis could be extended to explain the specificity of nedocromil sodium for the disease state and, importantly, its lack of toxicity.