The possible role of bacterial, viral and fungal infections in the development, exacerbation and treatment of asthma are discussed. Although bacterial allergy has in the past been advocated as an important etiologic factor for asthma, the evidence is inconclusive. Hypersensitization with bacterial antigens is no longer an accepted treatment. Bacterial infection in asthma may be more common than previously thought, but the role of infection in the development, exacerbation and treatment of asthma is still uncertain. Further research is needed to clarify the relationship between infection and asthma.

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Bacterial Allergy and Immunotherapy

In the 1930s and 1940s, bacterial allergy was a popular topic. It was believed that true allergic reactions to bacterial antigens were important in the etiology of asthma. The results of later investigations in this field are controversial. For instance, Koch et al. showed that bacterial antigens released histamine from the leukocytes of patients with intrinsic asthma more readily than from cells from normal controls. However, since these responses fluctuated with time, the evidence is not conclusive.

In the days when bacterial allergy was accepted as one of the mechanisms of asthma, hyposensitization with bacterial antigens was as accepted antiasthmatic treatment. Confirming the findings of many others, Koivikko failed to show any beneficial effect of such treatment in childhood asthma. The findings of a later series of studies are controversial. In one study, injections of mixed bacterial antigens were given over a period of three years and in another, bacterial ribosomal antigens were given as injections in combination with aerosol administration. They reported good results from this treatment among asthmatic patients. However, the studies were not placebo-controlled and the criteria for selection of patients unclear. During the time of treatment, remission may have occurred spontaneously. So far, there seems to be no justification for hyposensitization with bacterial antigens.

Bacterial Infection of Nasal Sinuses and Bronchi

It has been claimed that bacterial sinusitis is frequent in asthma and can act as a trigger mechanism. Friedman et al. did 13 aspirations from nasal sinuses in eight asthmatic patients. All showed bacterial growth and experienced improvement in their asthma during subsequent antibiotic treatment. However, at the same time patients were given intensified antiasthmatic treatment, in some cases including systemic steroids. It is, therefore, difficult to attribute the improvement of the asthmatic symptoms to the antibiotic treatment.

Bachelefsky and co-workers studied chronic maxillary sinusitis in children with respiratory allergy. They found a good response to antibiotic treatment, but asthmatic symptoms were not recorded in relation to the treatment. On the other hand, Slavin et al. have reported a definite improvement of asthma during antibacterial and/or surgical treatment of sinusitis in 28 of 33 patients. Unfortunately, there was no control group. The regular follow-up of patients may contribute to the improvement of the symptoms. Surgical interventions of any kind may bring temporary relief of asthmatic symptoms by nonspecific mechanisms.

The question of co-existent bacterial bronchitis in an acute exacerbation of asthma has not been resolved. Many textbooks advise antibiotic treatment on the assumption that aggravated asthma is always connected with a purulent bronchitis. Graham et al., in a placebo-controlled trial, showed that recovery from an attack of asthma was not enhanced in the group who received amoxycillin compared to the control group. The authors conclude that antibiotics should not be given routinely to patients with acute exacerbations of asthma. The findings from a study of transtracheal aspiration in asthmatic patients do not support the empiric use of antibiotics in the management of unexplained asthmatic relapse. In any case, the effect of antibiotic treatment in acute asthma would not be evident until several hours after initiation of the treatment. Hudgel et al. found that viral but not bacterial respiratory tract infections were significantly increased during wheezing exacerbations in adult asthmatic patients. In some asthmatic patients, the respiratory tract was chronically colonized with "pathogenic" bacteria without increased frequency of asthmatic exacerbations.

It is, however, possible that spasmogenic substances are released during a bacterial infection, thus exacerbating the asthmatic symptoms in some cases. Clinically some patients certainly seem to benefit from antibiotic treatment during the recovery phase after an acute attack of asthma. This treatment should be critical, under specific circumstances, and not routine. One should try to evaluate specific diagnostic criteria, which in the case of sinusitis would be based on radiologic evidence and the findings of a sinus puncture. Sputum production is one of the main symptoms of asthma and should not as such be taken as a sign of bronchial infection. Evaluation of sputum appearance is best done when the eosinophilia, a common cause of purulent looking sputum, has been eradicated with corticosteroids. Bacterial culture of sinus fluid gives reliable results, but the microbiologic findings of a culture of normally expectorated sputum may not be clinically relevant. Our policy when treating acute asthma has been to give an antibiotic if the bacterial infection is obvious, i.e., radiologic evidence of a fluid level in the nasal sinuses, or pneumonia. In doubtful cases we wait. If on the third or fourth day of intensive antiasthmatic treatment (including corticosteroids) the patient has purulent-looking expectorant, we start antibiotic therapy.

Bacterial infections of nasal sinuses and bronchi are probably secondary to mucosal edema, hypersecretion, broncho-spasm and mucociliary dysfunction. There is no evidence that they are the primary cause of an exacerbation of asthma (Fig. 1). It is possible that some bacterial infections will limit themselves, if the pathologic state of the mucosa is reversed and its normal function restored by the antiasthmatic medication.

The question of specific vaccination has been raised recently. Goldstein, in a discussion, objects to manufacturers claiming that asthmatic patients should be included in the risk group who should receive pneumococcal vaccine. As Goldstein points out, asthmatic patients are not at risk of developing pneumococcal pneumonia. The reply from the manufacturer represented by Fiumara is not convincing.

The available evidence suggests that bacterial infections in asthma and allergic rhinitis may not always need treatment, and if they are treated, this may not be sufficient to reverse the symptoms of asthma (Fig. 1). Prophylactic treatment of...
infection means prophylactic treatment of the underlying disease.

The role of bacterial infection in exacerbations of asthma probably has been grossly exaggerated. Repeated bacterial infections may play a role in the deterioration of lung function seen in some patients with severe asthma and not responding to normal antiasthmatic treatment. These aspects are dealt with elsewhere in the present symposium.

There is some anecdotal evidence of bacterial infection having a temporarily beneficial effect in asthma, at least if in connection with fever. Artificially induced fever was once used in the treatment of asthma. King William of Orange, who is said to have had asthma, was wounded in his shoulder in one of his battles against the Catholics. The wound, slow in healing, was purulent for months. During the time when the infection was obvious, the king was free from asthmatic symptoms.

VIRAL INFECTIONS

Mechanisms of bronchial obstruction caused by viral infections have been studied. Normal subjects demonstrate exaggerated reactions—obstruction and cough—to histamine, methacholine, carbamylcholine and citric acid up to six weeks after a viral upper respiratory tract infection. This reaction can be prevented and reversed by administration of isoprenaline and atropine. Empey and colleagues concluded that viral infections cause damage in the epithelium which exposes and therefore sensitizes the vagal receptors. Viral infections may also reduce beta-adrenergic responsiveness, thus enhancing bronchial hyperactivity. In some individuals, the beginning of asthma as a clinical disease seems to be attributable to a respiratory viral infection. It is possible that these patients, if tested, would have been hyperreactive prior to the infection.

Jenkins and Breslin failed to show any increase in bronchial obstruction or hyperreactivity in asthmatics after respiratory tract infection. Their patients probably had mild asthma, only three patients of 13 required daily medication.

Opinions vary as to the importance of respiratory viral infection in asthma. According to Roldaan and Masural and Minor, acute respiratory viral infections are frequently the cause of exacerbations of asthma. On the other hand, Clarke found that the great majority (almost 90 percent) of 111 exacerbations of asthma during 18 months in 51 patients were not due to respiratory tract infection. Kava found that a respiratory infection was the trigger mechanism in 25 percent of 233 exacerbations in 67 patients, followed for six months. It may be very difficult to differentiate the symptoms of an upper respiratory viral infection from those of worsening asthma. The difference in defining infection and the clinical features of the patients may account for the different results mentioned above.

Carlsen and Ørstavik showed that in children, especially rhinovirus and respiratory syncytial virus provoke attacks of asthma.

Infections are believed to play an important role especially in intrinsic asthma, but according to Roldaan and Masural the development of viral exacerbations in asthmatic patients is not determined by whether the patient is allergic or not. It seems probable that one of the facts which determines whether an asthmatic will have an exacerbation of the disease during a viral infection is not atopy, but the severity of the disease. The clinician will see relatively more exacerbations of asthma during viral infections in the patient with intrinsic asthma, because clinically, intrinsic asthma is often more severe than atopic asthma.

Although the evidence of benefit is not conclusive, it has been recommended that all patients with severe asthma, except for those with egg hypersensitivity, should be immunized annually against influenza. On the other hand, several reports have suggested that asthmatic patients may experience an exacerbation of bronchial symptoms following immunization with killed or live influenza vaccine.

To investigate the possible adverse and beneficial effects of such vaccination, we conducted a multicenter placebo controlled study. Patients with moderately severe chronic asthma who were known to have exacerbations of their disease in connection with upper respiratory viral infections were followed closely during the week after vaccination and thereafter at regular intervals over the following six months. There was no significant decrease in the mean peak flow rates during the first post-vaccination week in the 321 immunized patients as compared to the placebo-group. Atopic status, ASA intolerance, history of exacerbations of asthma in connection to respiratory infections, the use of oral corticosteroids or duration of the asthma did not influence the asthmatic symptoms after vaccination. The antibody response to vaccination was normal. Unfortunately, the protective effect of the vaccination could not be estimated since there was no epidemic of influenza during the following year. However, this has been shown in other patient groups.

There is no reason to believe that asthmatic patients could not be protected from viral infection in this manner. We concluded that there are no risks connected to immunization with inactivated vaccines in asthmatic patients. The fact that all our patients were placed on optimal anti-asthmatic treatment before the trial may have contributed to the favorable result.

The effect of recurrent viral infection on the prognosis of asthma is hard to evaluate. There are no investigations on long-term effects of recurrent infections or on the beneficial value of preventing them.

FUNGAL INFECTIONS

The intrabronchial growth of Aspergillus fumigatus may
cause exacerbations of asthma. The mechanism of this exacerbation is not direct infection, but its immunologic consequences. This is seen in bronchopulmonary aspergillosis (APBA), in which the antibody response to the fungus adhering to the bronchi causes worsening of the asthma. The management of this condition consists of vigorous treatment of the asthma including corticosteroids. Antifungal treatment is not beneficial in APBA. Probably corticosteroids lessen the antigen-antibody reaction and restore the normal defense mechanisms of bronchial mucosa. As a result the mycelium is expectorated. In APBA, prevention of acute exacerbations is essential to avoid permanent damage of the bronchial tree.

Colonization of the pharynx with Candida albicans in patients taking steroid aerosols occurs frequently, but has not been shown to have aggravating effects on the asthma.

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