

IS IMMUNOTHERAPY FOR ASTHMA WORTHWHILE?

ALTHOUGH allergen immunotherapy has been used to treat allergic asthma for over 70 years, its role remains controversial. The consensus report on diagnosis and management of asthma of the National Institutes of Health recommends that allergen immunotherapy should be considered only when asthma is poorly controlled with drug therapy or when it is impossible to avoid allergens,¹ whereas the British Thoracic Society Guidelines do not recommend immunotherapy under any circumstances.² There have been many trials of immunotherapy, but the results are often difficult to interpret because of the use of allergen extracts that are not standardized, poor study design, and the participation of too few patients. A recent meta-analysis of 20 double-blind, controlled studies showed a small but significant improvement in the control of asthma with immunotherapy.³

The study by Creticos et al. in this issue of the *Journal* provides further evidence of the efficacy of immunotherapy in asthma.⁴ In this double-blind, placebo-controlled, multicenter trial, a purified extract of ragweed pollen was given to patients with asthma who were symptomatic during the ragweed-pollination season. The immunotherapy, administered for longer than two years in the majority of patients, was successful in that skin-test sensitivity and the bronchoconstrictor response to ragweed were reduced in the immunotherapy group. The results also showed a small but statistically significant increase in peak expiratory flow and a reduction in the use of asthma medications in the immunotherapy group during the first year, but there was no difference in symptom scores or in airway responsiveness to methacholine challenge. Many of the small benefits seen in the first year of immunotherapy were not apparent in the second year of treatment, however.

Any benefits of immunotherapy need to be weighed against its adverse effects. Allergen immunotherapy can induce local and systemic side effects that are estimated to occur in 5 to 35 percent of patients with asthma.⁵ Local wheal-and-flare reactions at the site of injection are common and in themselves not usually a problem, although they may herald the onset of a systemic response. Systemic responses usually start within minutes of the treatment — within 30 minutes if they are severe^{6,7} — and may be organ-specific (rhinitis or asthma) or generalized (urticaria, angioedema, or anaphylactic shock). Bronchospasm and anaphylactic shock may be fatal. In the United States, a questionnaire survey identified 19 deaths associated with immunotherapy between 1987 and 1991, at least 16 of which were in patients with asthma. Accidental overdose or unstable asthma was believed to be the main contributing factor.⁸ In the study by Creticos et al., about 10 percent of the participants had systemic reactions, although none were severe; only two patients dropped out because of side effects. Adverse effects are likely to be minimized

in a carefully controlled trial conducted in specialized centers, as compared with the use of immunotherapy in general practice.

Immunotherapy with purified extract of ragweed pollen may be the best possible test of immunotherapy in asthma, since seasonal asthma is often mild and there is a limited period of allergen exposure. Few patients with asthma have symptoms confined to the pollen season, however, and this is reflected in the small number of subjects found eligible for the current trial after screening — 77 of 1000.⁴ Most patients with asthma are allergic to multiple aeroallergens. In temperate climates, perennial asthma is usually due to exposure to house-dust mites, but other allergens, such as cat dander, molds, and cockroaches, may also be important. Immunotherapy with a single allergen is unlikely to affect the patient's responsiveness to other allergens. Immunotherapy with perennial allergens, such as house-dust mites, appears to be less effective than immunotherapy with seasonal allergens,⁹ suggesting that the role of allergen immunotherapy in the treatment of most patients with asthma is likely to be very limited.

The medication for asthma currently in use is highly effective, and inhaled glucocorticoids are of particular value.¹⁰ There have been no controlled studies comparing allergen immunotherapy with drug therapy in asthma. In a study that compared allergen immunotherapy with topical steroids in the treatment of seasonal rhinitis, the steroids were very clearly more beneficial, in terms of both greater efficacy and fewer adverse responses.¹¹

Creticos et al. also considered the costs of allergen immunotherapy. Although the cost of the injections is similar to that of inhaled glucocorticoids, the cost of administering the injections is much greater. This cost may be difficult to justify for the relatively small clinical gain obtained.⁴

The mechanisms of the beneficial effects of allergen immunotherapy are far from clear. There is an initial increase in specific-IgE concentrations, followed by a slowly progressive decrease, although specific IgE rarely disappears completely. Allergen-specific IgG antibodies ("blocking" antibodies) increase during the course of allergen immunotherapy. One hypothesis is that these antibodies may intercept allergen before it can bind to IgE and trigger an allergic response. This seems unlikely, since clinical improvement usually precedes the increase in allergen-specific IgG. It is also improbable that such antibodies could block the binding of allergen to IgE at mucosal surfaces in the respiratory tract. A more likely mechanism is that allergen immunotherapy alters the balance of cytokines released from helper T lymphocytes in the respiratory tract, with a shift from the type 2 helper T cells that release interleukin-4 and interleukin-5 in association with allergic inflammation toward type 1 helper T cells that release interferon- γ , which inhibits type 2 helper T cells.¹²

Because allergen immunotherapy may be a relatively specific approach to the treatment of allergic asthma,

there has been hope that it could alter the natural history of the disease. Uncontrolled studies in children have suggested that allergen immunotherapy may result in total remission. This cannot be accepted as evidence that immunotherapy alters the natural history of asthma, since spontaneous improvement in asthma is commonly seen during childhood. At present there is no such evidence; indeed, when the treatment is discontinued, symptoms of asthma rapidly recur.⁵ Although there is some evidence that with prolonged administration allergen immunotherapy becomes more efficacious in controlling seasonal rhinitis, the study by Creticos et al. indicates that the reverse may be true in asthma. Any clinical benefit of the treatment was lost in the second year of treatment.⁴

There can be few indications for the use of allergen immunotherapy in the routine management of asthma in adults or children, in view of its low efficacy, the risk of adverse effects, the relatively high cost of treatment, and the availability of safer and more effective drug therapies, particularly inhaled glucocorticoids. The use of allergen immunotherapy in conjunction with inhaled glucocorticoids should be studied carefully in patients whose symptoms are not controlled by inhaled glucocorticoids alone. Future developments may include the production of pure allergens by molecular cloning and the development of peptide fragments of allergen that induce unresponsiveness in type 2 helper T cells.¹³ Other novel approaches, which may necessitate intravenous administration, include monoclonal antibodies against IgE that may prevent allergen-induced activation of mast cells¹⁴ and the use of allergen-antibody complexes whose mode of action is unknown.¹⁵ While such approaches are being evaluated, drug therapy, combined when possible with the avoidance of aller-

gens, is the recommended approach to the management of asthma.

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SOCIAL, INSTITUTIONAL, AND ECONOMIC BARRIERS TO THE EXERCISE OF PATIENTS' RIGHTS

DURING the past 30 years, the autonomy of patients has displaced beneficence on the part of physicians as the chief tenet of medical ethics.¹ Respect for patients' autonomy is now considered fundamental to the practice of medicine. It is best exemplified by the universally recognized doctrine of informed consent. Patients have the right to information about their own medical care, as well as the right to accept or reject any recommended treatment. The physician formulates alternatives for dealing with a medical problem and advises the patient about the risks and benefits of these alternatives. The choice among them is the patient's. The doctrine of informed consent resolves the tension

of authority between patient and doctor in favor of the patient.

The historical focus on doctor and patient, however, has neglected the influence of other parties on patients' rights. Society, hospitals, other medical institutions, and increasingly, health care insurers and organizations have interposed substantial barriers to the right of patients to be informed and to consent to the way they receive medical care. The rapid growth of managed care has magnified the potential for forces outside the doctor-patient relationship to undermine this right. Patients' autonomy can be eroded in many different ways by many elements of the system.

SOCIAL AND INSTITUTIONAL BARRIERS

The right of patients to information about their doctors is by no means established. There is continuing strain between the right of doctors to fairness and confidentiality and the right of the public to information