

Oral immunotherapy: A way forward?

Desensitization therapy was first introduced for hay fever in 1911 to raise immunity to "pollen toxin," and at that time (in keeping with other immunization schedules), it appeared logical that the extract should be injected.¹ As the dangers of injecting allergens became clear, attempts were made during the 1920s to use different routes, e.g., locally to the nose or orally. There are two major arguments for continuing to pursue alternative routes: first, to avoid (or reduce) the risks of anaphylaxis and second, to improve the clinical results. Although there have been several optimistic studies about oral immunotherapy, until recently controlled trials have not produced convincing results.²⁻⁴ In the current issue of the JOURNAL, Taudorf et al. report a successful controlled trial of immunotherapy for seasonal pollenosis with enteric-coated capsules of birch pollen.⁵ In addition, other studies were reported at the Annual Meeting of the European Academy of Allergy and Clinical Immunology in 1986.⁴ The results suggest strongly that oral immunotherapy can produce decreased symptoms during natural pollen exposure and decreased responses to conjunctival challenges, nasal challenges, and skin tests. Perhaps more exciting is an article about a similar study on children that produced an apparent decrease in asthma symptoms.⁶ In evaluating these studies, there are several aspects that need to be considered: (1) how the current oral regimen compares to previous oral regimens and other alternative routes, (2) how do we assess whether this treatment is safe, and (3) the possible mechanisms by which oral immunotherapy might work.

There is obviously a major difference between applying allergen to the symptomatic organ (i.e., nose or lungs) and oral immunotherapy designed to achieve a systemic effect. A large literature exists on local nasal immunotherapy, but despite successful controlled trials, it has not become routine practice. Successful desensitization of the nose does not help the eyes or lungs, and the symptoms caused by nasal allergen may be unacceptable. During nasal desensitization, increasing doses too rapidly appears to cause "sensitization" or "priming" of the nose, which will make symptoms worse.⁷⁻⁹ Repeated bronchial provocation at 3- to 4-day intervals was proposed by

Abbreviation used

BU: Biologic unit

Herxheimer and Prior¹⁰ as a desensitization regimen for patients with asthma. They believed that the procedure could be successful, but their results finally demonstrated that local desensitization of the lung was impractical because of the risk of increasing "sensitization."¹⁰ It is now well established that bronchial challenge with allergen can increase nonspecific bronchial reactivity. The mechanism of increased reactivity in the lungs or the nose is not clear, but it has been related to late reactions that are assumed to include both continued mediator release and a cell influx.¹¹ Oral immunotherapy may have an advantage in that it avoids the risk of local sensitization, perhaps because sensitization does not occur in the intestine, but, in any case, because the intestine is not a normal site of pollen arrival. However, in view of the common theme in other forms of immunotherapy that treatment doses should be spaced, it is surprising that oral treatment can be administered daily. Perhaps this is a hint that the mechanism is different or that oral treatment should be spaced. Interestingly, there has also been a recent study of a trial of sublingual therapy for allergic rhinitis. That trial was less convincing because of its short duration, only 2 weeks.¹² However, that study also used daily doses. More striking were the extraordinarily low doses used. Both the sublingual study and the study by Taudorf et al. reported dosage in biological units (Pharmacia, Uppsala, Sweden); the cumulative dose for oral therapy was 280×10^6 BU and 4 BU/ml for sublingual therapy. (Comparable cumulative doses for conventional immunotherapy would be 5×10^5 BU.) Although it is possible that sublingual absorption is very efficient, it still appears unlikely that a dose as low as 4 BU of mite antigen (≤ 1 ng of *Der p 1*) could achieve a systemic effect. Calculation of the effective dose of allergen in oral immunotherapy is difficult because even allergen in enteric-coated capsules would be extensively digested and because only a fraction of the dose would reach

either the circulation or local immune tissue. Taudorf et al. draw attention to the fact that different allergens vary in their susceptibility to digestion. There are studies demonstrating how rapidly pollen allergens would be denatured in the conditions of the stomach, but little is known about the small or large intestine.¹³ One of the arguments used for trying birch pollen after the previous unsuccessful trial of oral grass pollen was that birch-pollen allergy is often associated with "food allergy." In fact, the food-related symptoms reported by patients with birch-pollen allergy are predominantly itching of the mouth and mild swelling of the tongue and throat. These symptoms develop rapidly after eating several foods that cross-react with birch pollen, especially hazelnuts or apples, but not at a time when absorption from the gut might be expected to be occurring. It would appear unwise to extrapolate from results of oral immunotherapy for rhinitis to the unproven role of oral immunotherapy for food allergy.

Although the dosage used in this study was very large, it was chosen because of the failure of a previous study with smaller doses of grass pollen.¹⁴ The most obvious problem with this course of therapy is that the dosage is impractical. The allergen would cost too much, and indeed for many allergens, it would be difficult to obtain sufficient supplies, which makes it unlikely that the therapy will be made commercially available.

A major argument for trying oral immunotherapy would be its safety. The present article concludes that the regimen as described "is safe"; however, this is clearly only a relative statement, since the incidence of severe reactions to allergen injections is about 0.2%, whereas the incidence of death is <1:2,000,000.^{15, 16} That systemic reactions can occur during oral immunotherapy is not doubted. One of the patients in the present study developed urticaria, one patient in another study developed rectal bleeding, and there is an as yet unpublished occurrence of a patient who developed an anaphylactic reaction 24 hours after taking an allergen capsule.⁴ Additional patients have been reported who developed anaphylactic shock after eating "bee pollen" that contained pollen from the Compositae family.¹⁷ It is worth remembering that Sampson and Albergo¹⁸ have demonstrated relapse of atopic dermatitis after challenge with capsules of allergen. As with all enteric-coated capsules, there must be marked variations in the rate of release, and rapid release might occur at some time after ingestion. Although it is likely that oral ingestion is *less* dangerous than injections, the available results are not sufficient to define how low the risk is. The regimen of daily

capsules would only be practical if it could be administered at home; however, there is insufficient data at present to assume it is safe for home use.

The most interesting question about oral immunotherapy is how does it work? The assumption is that the mechanism is the same as for other forms of immunotherapy; however, that assumption does not help very much. Although there is good evidence that increased serum IgG antibodies are related to successful immunotherapy for venom sensitivity, the situation with respect to immunotherapy for hay fever or asthma is not so clear. Serum and nasal "blocking" antibodies can increase during conventional immunotherapy, but the increases do not correlate with decreased symptoms. The change in nasal antibody is generally much smaller than changes in serum antibody and almost certainly too small to explain the effects of the treatment.^{19, 20} An animal model has been reported in which oral antigen produces systemic tolerance and mucosal immunity.²¹ It is possible that oral immunotherapy could produce a generalized increase in mucosal antibody with less effect on serum antibody. Similarly, it is possible that oral immunization might activate the suppression of IgE antibody production that normally occurs late in a course of immunotherapy without boosting IgE production early in the course of treatment.²² However, the available data on the present study does not support either of those theories. Dr. Bjorksten (one of the authors in this article⁵) stated in a recent editorial that the serum IgG response to oral immunotherapy was modest.⁴ It would be surprising if large increases in local antibody were achieved because attempts to achieve a marked increase in nasal antibody by nasal application of allergen have not been successful.⁹ Given the large doses of allergen used, it is possible that oral immunotherapy had produced desensitization of basophils and mast cells. By contrast, it appears unlikely that the treatment established high-dose tolerance, since this is difficult to achieve in immune animals, particularly in the presence of immediate hypersensitivity.²³ It would be a mistake to confuse basophil desensitization (which is a possibility) with high-dose tolerance (which is most unlikely). At present we have no evidence that high levels of allergen are absorbed even after these very large oral doses. If large quantities were absorbed, the likely outcome would be severe reactions.

If the oral route is effective, it raises interesting parallels both with experimental models and with the treatment of another human disease. Oral "immunotherapy" has for many years been regarded as effective treatment for poison ivy, not only (perhaps mythically) by the North American Indians but also by many der-

matologists who prescribe a commercially available oral extract. Poison ivy is regarded as a pure form of contact hypersensitivity mediated by T cells, with little or no involvement of antibodies. Similarly, it is well established that feeding mice on a contact sensitizing agent, e.g., dinitro chlorobenzene, can prevent subsequent attempts to establish contact sensitivity to the same agent.²⁴ In this situation both the contact sensitivity and the active suppression are known to be mediated by T cells. Thus, oral administration of low-molecular-weight antigens can produce antigen-specific systemic changes in T cells. It is well established that allergic patients have circulating T cells capable of responding specifically to allergens and producing interleukins *in vitro*.^{25, 26} Furthermore, it is known that the *in vitro* allergen-specific responses of T cells can be altered by injections of allergen extract.²⁶ However, it is not clear what role T cells play in the symptoms of allergic disease or whether changes in T cell function are involved in the response to immunotherapy. It is possible that T cell-mediated local recruitment of basophils and mast cells contributes to many aspects of allergic disease.²⁷⁻³⁰ If this is correct, then altering T cell responses by immunotherapy may be exactly what we are trying to accomplish, and the oral approach may be an interesting way of changing different parts of the immune response to allergens. The next move forward would be to examine more carefully how T cells function in allergic disease, i.e., which interleukins are relevant and need to be measured.³¹ If we take this line of reasoning to its logical conclusion, the mouse model suggests that oral "desensitization" would be far more effective before the patient became sensitized. Perhaps Dr. Doolittle³² would have solved this problem by incorporating pollen antigen into the glue on children's Easter Seal stamps.

One conclusion about the present trial of immunotherapy is that allergists still do not understand the mechanism of one of our main lines of treatment. Consequently, we are unable either to specifically design improvements in the treatment or to monitor the relevant immunologic changes during treatment. However, we now have the ability to measure all the relevant classes and subclasses of antibody, we are close to being able to sequence, clone, and produce fragments of allergen molecules, and we are already able to measure the production of several different interleukins by T cells. Obtaining an easily measured marker of successful desensitization should still be considered as a priority. Although oral immunotherapy is not at present a practical option, the success of the present trial should spur further efforts both to

improve results with this approach and to understand the process.

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