Chapter 5. Future Research

A paucity of rigorous data was identified within the existing published literature on allergic rhinitis. The lack of relevant high-quality evidence required that nearly every key question be answered on the basis of suboptimal or incomplete data.

Better Assessment of Allergic Rhinitis is Required

Studies that have focused on nonallergic rhinitis have arrived at this diagnosis by exclusion of allergic diseases (conventional allergy skin testing and/or RAST). There is no specific diagnostic test for nonallergic rhinitis. Until the mechanisms underlying vasomotor rhinitis have been studied further, it is unlikely that a diagnostic test will be developed. The minimum amount of testing required to differentiate between these two conditions remains to be determined. Important questions needing to be addressed include: Does one need a full panel of inhalant aeroallergen skin testing? If so, how big does this panel need to be, and should it vary by geographic region? Might it be feasible to combine groups of similar allergens as a screening panel? For example, a grouping covering the important indoor allergens such as house dust mites, cockroach, cat allergens, and dog allergens; a grouping covering the dominant springtime outdoor aeroallergens (representative local tree and grass pollen species); a grouping covering the dominant outdoor fall aeroallergens (ragweed and other weed pollens); and a grouping covering a mixture of mold spores might prove informative and useful as a screening panel. A similar approach might be applicable to RAST, thus decreasing the number of individual tests (and therefore costs) required. It would be valuable to investigate whether simpler laboratory tests such as measurement of total serum IgE or total eosinophil count might be useful in diagnosing or excluding allergic rhinitis.

One of the major advantages of determining whether allergens are responsible for the patient's condition relates to the benefit that would accrue to the patient from specific allergen avoidance through environmental modification. It would be useful to investigate whether recommendation or implementation of standard measures to minimize exposure to indoor aeroallergens such as house dust mites, pet allergens, and cockroach might be cost effective in the management of chronic rhinitis even in the absence of differentiation between allergic and nonallergic rhinitis and even without determining a patients precise allergic sensitivities.

Additional Studies are Needed to Address Specific Questions

It is not infrequent to encounter patients who claim to derive relief of symptoms of nonallergic rhinitis from use of antihistamines, and azelastine (an H1 antihistamine) is effective for treatment in vasomotor rhinitis. Since there is no evidence that histamine release is involved in the symptoms of nonallergic rhinitis, it is possible that the antihistamines are helping by improvement of rhinorrhea due to their anticholinergic effects, or by some other, as yet unidentified mechanism. This potential benefit is clearly worthy of further study. It is also possible, since many over-the-counter antihistamine preparations in fact are combined preparations that include nasoactive oral agents, that nasal decongestion provided by this agent is the basis of the symptom relief reported by the patients. These possibilities should be teased out by performing specific studies looking at the role of antihistamines in the management of nonallergic rhinitis. If antihistamines are indeed useful

in treatment of nonallergic rhinitis then the need to differentiate between allergic and nonallergic rhinitis would be lessened.

Many of the newer or second-generation antihistamines have insignificant anticholinergic properties. Studies of these agents may help differentiate any benefit from true antihistaminic activity from the benefit associated with the drying provided by anticholinergic mechanisms. Additionally, a new class of antihistamine agents known as H3 receptor antagonists has the potential to offer significant decongestant effects by inhibiting presynaptic mediator release in the nasal tissues, when used in association with an H1 receptor antagonist. Such an agent may offer the benefit of decongestion without the undesirable side-effects such as hypertension and agitation often associated with the vasoactive decongestants (McLeod, Mingo, Herczku, et al., 1999).

Further studies of the role of nasal corticosteroids in nonallergic rhinitis are necessary. Many physicians probably use nasal corticosteroids as a therapeutic trial in the management of nonallergic rhinitis but few studies exist in the published literature documenting that this is a helpful strategy. For reasons similar to those stated for antihistamines, if nasal corticosteroids can be documented to be helpful in nonallergic rhinitis, the need to differentiate allergic from nonallergic rhinitis may be lessened. It might be worth determining how widespread the use of nasal corticosteroids is in patients with nonallergic rhinitis amongst practitioners and to evaluate whether there is any downside to their use.

The potential benefit of cromoglycate in nonallergic rhinitis warrants further study. It is now an over-the-counter preparation with minimal side-effects and two studies have shown benefit for cromoglycate in nonallergic rhinitis. The mechanism of action of this medication is poorly understood as are the mechanisms underlying a majority of cases of nonallergic rhinitis. Accordingly, this may prove a fruitful line of investigation both with respect to disease mechanisms and development of new therapeutics.

Allergen avoidance, after specific diagnostic testing to identify the specific allergic sensitivities is a well-founded treatment recommendation, routinely employed as the first step in the management of allergic rhinitis. Comparative prospective studies would be useful to determine whether, at least in the first instance, empiric prescription with antihistamines or nasal corticosteroids is of value in allergic rhinitis and whether only the more "severe" cases need more specific evaluation as to which allergic sensitivities are present so that allergen avoidance strategies can be recommended. Alternatively, since recommended allergen avoidance measures frequently revolve around modification of the indoor living environment to decrease exposure to house dust mites, cat and dog allergens, and possibly molds, should these recommendations be automatic in patients with allergic rhinitis? Might that approach obviate the need for diagnostic testing in a substantial proportion of patients?

The increasing recognition of the close relationship between the pathophysiology of allergic rhinitis and epidemiological data is very important. Studies to accurately determine whether interventions for allergic rhinitis can have preventive effects for asthma are urgently needed. Such studies will, of necessity, have to be prospective, large in number, and long-term. Since mortality and morbidity from asthma are increasing (especially in urban populations) despite newer pharmacologic treatment agents - such an approach assumes strong imperative.

Our evidence review indicates that many drug interventions are effective in decreasing symptoms, yet data on individual variation in preferences for, responses to, and costs of different therapies are limited. Drug interactions require clarification. A host of complementary therapies are now employed in the treatment of nonallergic rhinitis, but with little rigorous testing of their efficacy.

The low numbers (or absence) of studies that address a variety of clinically meaningful questions may reflect that to date, many drug trials are efficacy trials conducted for purposes of FDA approval of a new pharmaceutical product or post marketing comparisons with competitive products. Postmarketing trials may enroll the minimum number of subjects to establish efficacy, for example, by showing equivalence between a new preparation and an established, approved one. If a product has no commercial potential (e.g., because it is no longer patented) funding to support its investigation will likely suffer.

The challenge for the healthcare research community transcends the biomedical dimension of allergic rhinitis management to encompass its societal and human aspects. Research studies must address prospectively and in increasing depth issues of importance to patients and clinicians (patient preferences, satisfaction with care, the proportion who improve with care, treatment side-effects), providers and payers (costs), and researchers (optimal trial design and reporting). Patients and their families must be invited to help formulate research priorities and to advise in the design of trials themselves, such as suggesting outcomes of interest and novel ways to assess them, e.g., via the Internet (Silberg, Lundberg, and Musacchio, 1997).

The Need for Higher Quality Studies and for Multiple but Standardized Research Variables

Standards for allergic and nonallergic rhinitis treatment trials must adhere to those for clinical trials in general. After the FDA approval of a drug, additional high-quality trials of rhinitis relief are still needed to understand the optimal use of the drug in specific populations and settings. The trials should enroll greater numbers of patients for longer intervals than has generally been true in the past; apply blinding and "active" placebos when appropriate or uniform control treatments otherwise; and employ adequate between-arm washout intervals, and assess side-effects.

A major limitation of the data identified in this analysis is the heterogeneity of inclusion and exclusion criteria, tests, outcome measures, and circumstances of testing found in the RCTs. This situation makes synthesizing the research results difficult. Reducing this heterogeneity by implementing a set of standardized research variables would greatly assist in comparing studies.

The characteristics of patients enrolled in studies need to be clearly defined. This is critical to ensure internal validity and to allow for study comparisons, data analyses, and in applying the results to clinical practice. Standardization of research variables would also aid in identifying the best strategies for detection of patients with allergic or nonallergic rhinitis.