1. STANDARD IMMUNOTHERAPY

Immunotherapy by repeated subcutaneous injections of increasing doses of crude extracts of allergens redirects allergic immunologic responses. At first IgE antibodies increase but then they decline slowly. Serum IgG antibodies rise markedly, and secretory antibodies increase modestly. Serum IgG and secretory IgA and IgG antibodies can block in vitro antigen stimulated mediator release by IgE antibody sensitized mast cells and basophils. After immunotherapy, allergic subjects show reduced immediate responses to allergen challenges to the nasal or bronchial mucosa.

1.1. T Cell Role

Patients receiving immunotherapy also have a reduction of several antigen driven in vitro activities attributable to T cells. Furthermore, after immunotherapy, late phase responses to allergen challenges, by both clinical observations and measurements of local mediator release, are reduced. The potential role of downregulation of T cell activity in the immunologic management of allergic conditions is therefore being studied in man. The information obtained could lead to improvements in immunotherapy that would lessen the risk of allergic reactions to parenterally administered allergens and improve efficacy.

2. CONTROLLING T CELL REACTIVITY

The recognition that the level of IgE antibody depends on T cell regulation leads to consideration of how to alter or downregulate T cell stimulation of the B cells that synthe-
size antibody. This is reinforced by the realization that the T cells that appear to play a direct role in allergic inflammation are probably the same CD4+ cells. Downregulation of these cells could at the same time reduce IgE synthesis and limit inflammatory responses to allergens.

2.1. T Cell Epitopes

T cells and antibodies interact with different ligands on allergens. IgE antibodies attach to complex B cell epitopes that require intact tertiary structures. T cell receptors, on the other hand, respond to short peptides from the allergen imbedded in surface mixed histocompatibility molecules on antigen presenting cells (APC). T cell activation occurs when presentation is accompanied by pro-inflammatory second signals. These events usually engender immunity against foreign antigens, but can cause pathologic immune reactions such as allergies or autoimmune diseases.

The identification of T cell epitopes on allergens is now progressing rapidly. A number of major allergens have been cloned, sequenced and expressed. These include proteins from honey bee venom, cat, ragweed, rye grass and the house dust mites, *D. pteronyssinus* and *D. farinae*. Knowing the full peptide sequence of an allergen allows the synthesis of a series of overlapping peptides or generation of a series of deletion mutants that can be used as test materials for T cell stimulation.

2.2. T Cell Tolerance

Induction of tolerance (anergy) of T cells has been studied extensively in vitro and in vivo. This type of tolerance is to be distinguished from clonal deletion in the thymus. The T cells survive but their reactivity is down regulated. Of greatest interest therapeutically is tolerization of T cells with peptides derived from disease producing antigens. Such tolerization may be achieved in vitro by exposure of T cells to peptide fragments bound to class II MHC molecules without costimulatory activity from APC. Tolerization of two clones of T cells from a *D. pteronyssinus* sensitive patient was also achieved in vitro by exposing them to high concentrations of the clone specific peptide in the absence of APC. During such exposure, however, there was considerable production of IL-2, IL-4 and IFN-γ. Subsequent cultures of tolerized cells with APC and peptide showed inhibition of IL-4 production while still producing IFN-γ. To quote the authors: “This information may be relevant in the design of immunomodulatory agents for potential use in the treatment of allergic or autoimmune diseases.”

Preliminary study of T cell lines from patients with ragweed allergy shows that a degree of T cell tolerance can be induced in vivo by standard immunotherapy. The T cell lines were grown in the presence of ragweed allergen Amb a 1, along with IL-2 and IL-4, rested and then restimulated by allergen in the presence of irradiated mononuclear cells as APC. Cell lines from untreated patients regularly showed proliferation, whereas lines from patients receiving ragweed extract immunotherapy showed much less proliferation. In some cell lines there was no proliferation post treatment. Furthermore production of IL-2, IL-3 and IL-4 during restimulation was reduced in the treated individuals. These results confirm that T cell anergy can be induced in man.

2.2.1. Costimulatory Signals. In vivo tolerization with peptides or proteins depends on administration in such a way as to preclude a costimulatory signal. This has been done in mouse strains susceptible to autoimmune encephalomyelitis (EAE) induced by immuni-