Images in Allergy and Immunology

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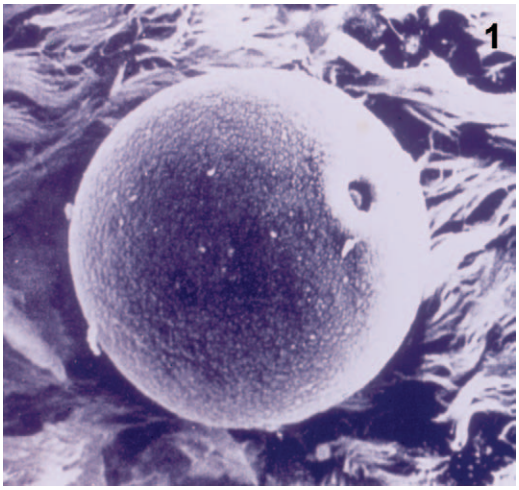
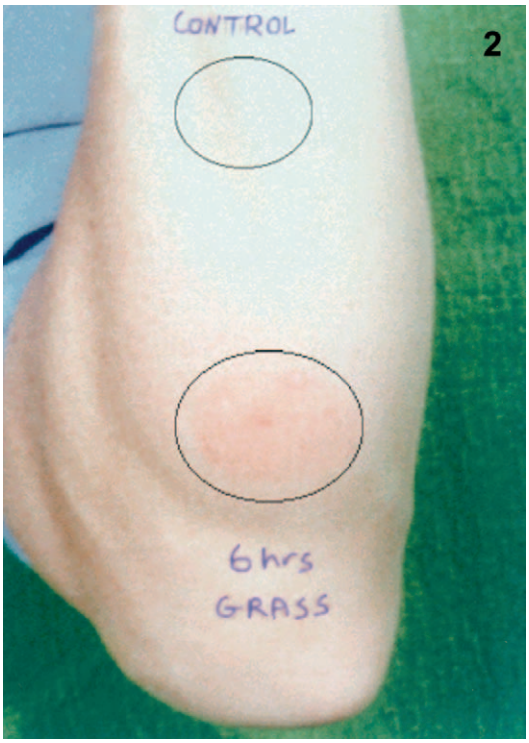
Molecular pathology of immunotherapy

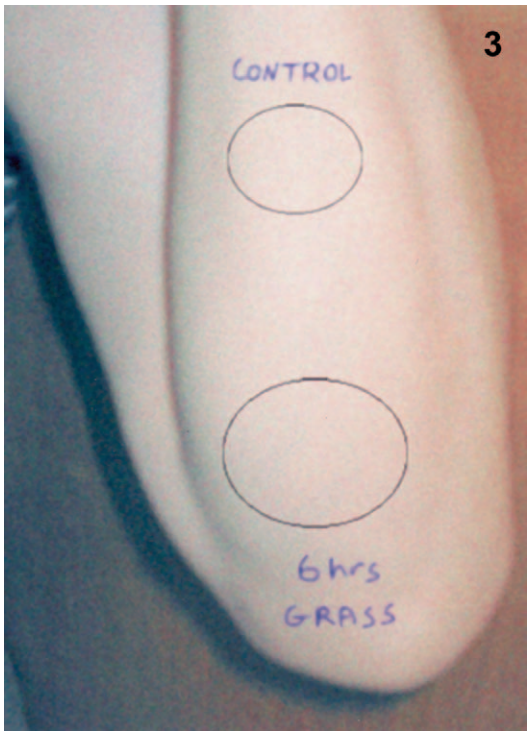
Editor's note: This feature, Images in allergy and immunology, *is designed to highlight current concepts of the immunopathology of allergic diseases and other common immunologically mediated diseases. The presentation will appear as sets of images that involve cross-pathology, histopathology, and molecular pathology and will cover a range of topics of interest to allergists and immunologists.*

Allergen injection immunotherapy is used in selected patients with allergic diseases that are mediated by IgE, including venom anaphylaxis, rhinitis, and, to a lesser extent, asthma. This type of treatment inhibits early- and late-phase responses to



allergen. Experimental late-phase cutaneous response to specific allergen (eg, grass pollen; Fig 1) has been used extensively to examine the effectiveness of immunotherapy and the mechanisms of action of this therapeutic approach. Successful immunotherapy has been shown to be associated with inhibition of late-phase cutaneous response to grass pollen. (Figs 2 and 3 are examples of LPR in the skin after grass pollen





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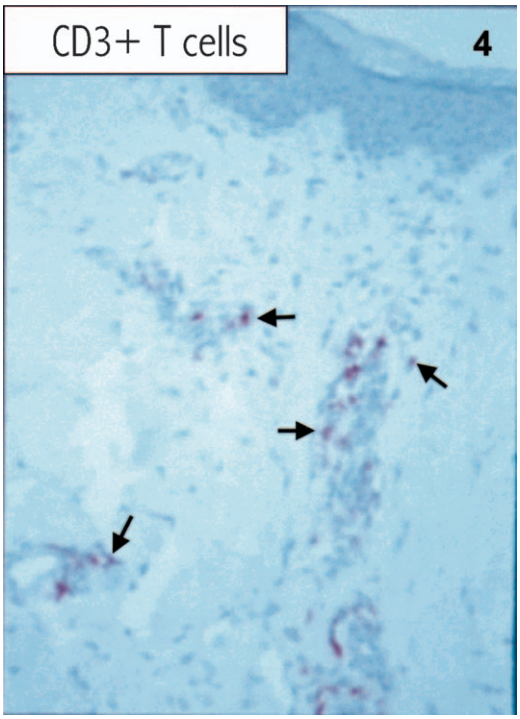
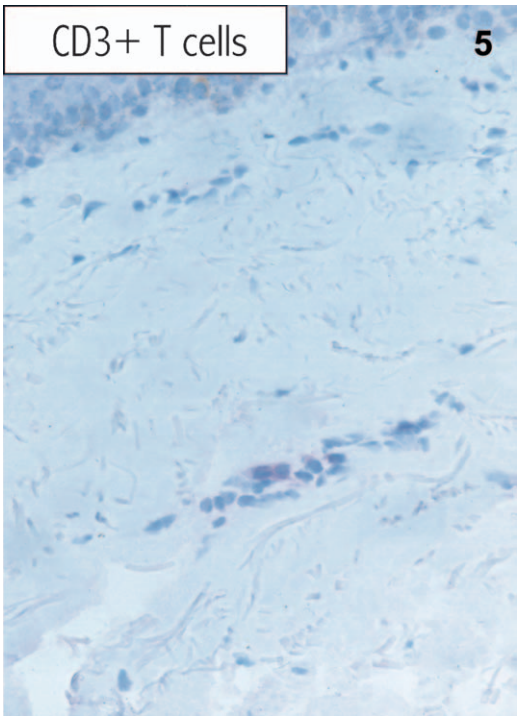
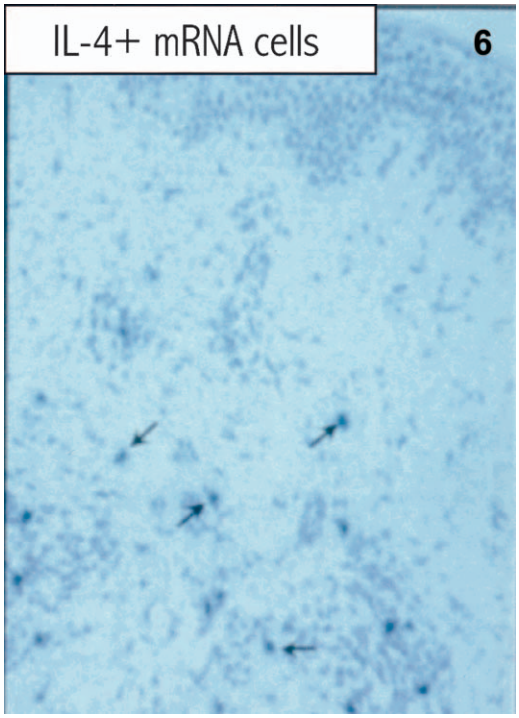
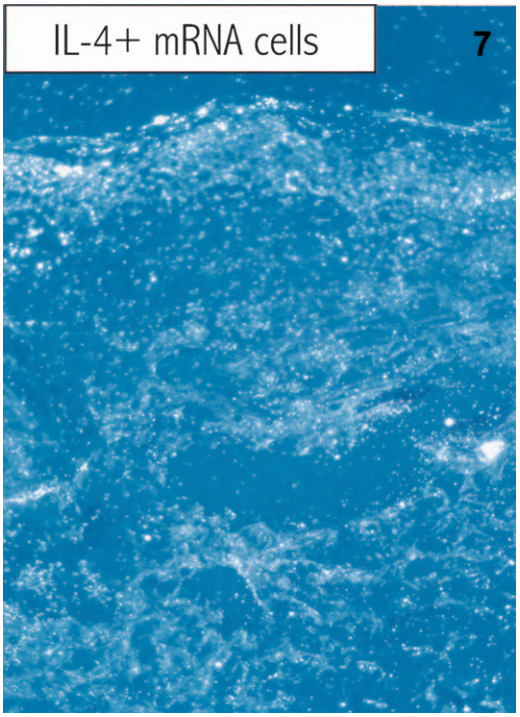
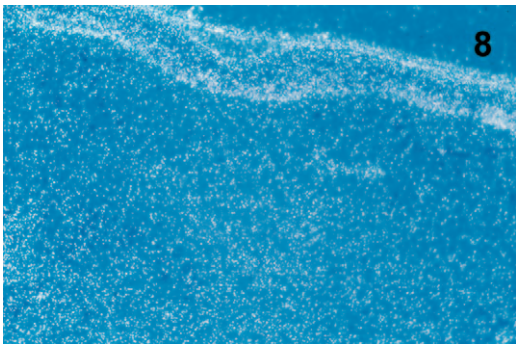


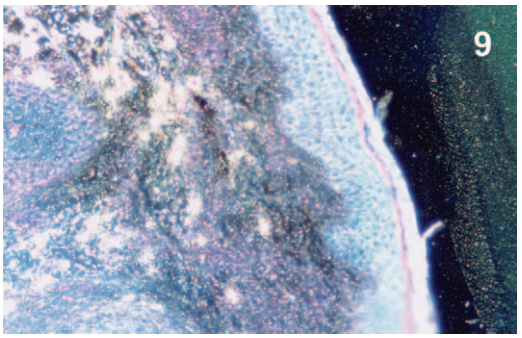






injection before [Fig 2] and after [Fig 3] successful immunotherapy; note the absence of induration and redness after immunotherapy.) This inhibitory effect can be maintained for a long period of time after cessation of immunotherapy. Clinical response in the skin is associated with a decrease in the number of T cells (Figs 4 and 5 are examples of CD3 immunostaining of a skin biopsy specimen after antigen challenge before and after immunotherapy) and eosinophils. There are decreases in T_H2-type cytokines, particularly IL-4. (Fig 6 is an example of bright-field radioactive IL-4 in situ hybridization after antigen challenge before immunotherapy, and Fig 7 is an example of dark-field illumination in situ hybrid-





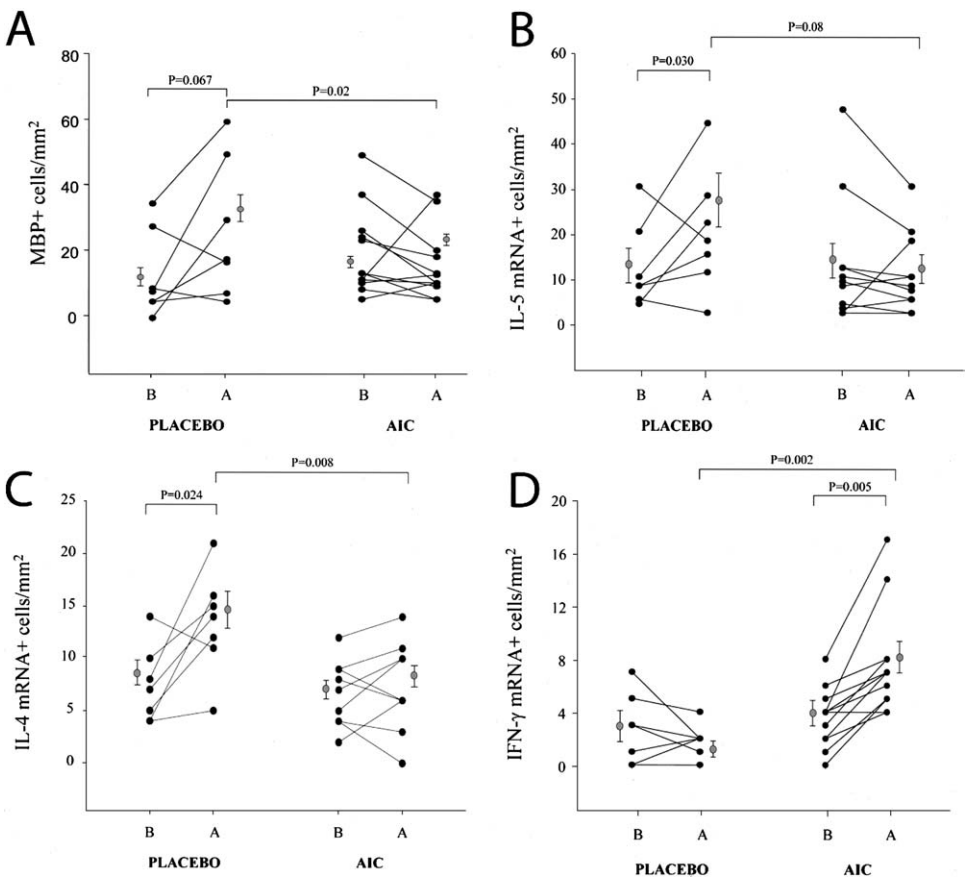
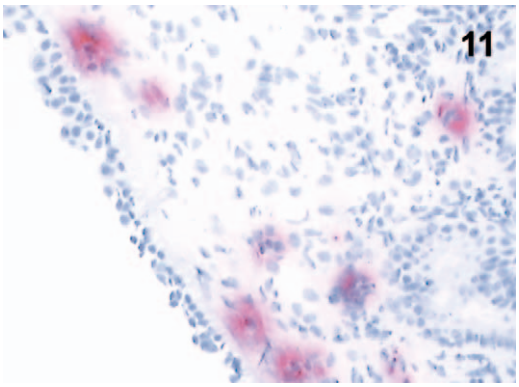
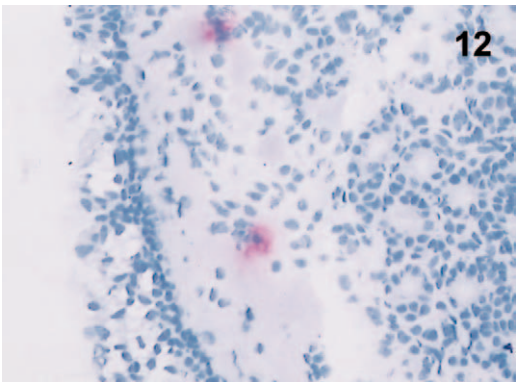


FIG 10. Effect of AIC on allergen challenge after the ragweed season. The numbers of MBP-positive cells (**A**), IL-5 mRNA-positive cells (**B**), IL-4 mRNA-positive cells (**C**), and IFN-γ mRNA-positive cells (**D**) at baseline (*B*) and after nasal allergen challenge with ragweed extract (*A*) in ragweed-sensitive patients 4 to 5 months after treatment with placebo (n = 7) or AIC (n = 12) are shown. *Circles* alongside the data represent mean values ± SEMs.

ization of IL-4 mRNA after successful immunotherapy.) There is also upregulation of T_H1 and T_H1-like cytokines, namely IFN-γ and IL-12. (Figs 8 and 9 are dark-field preparations of an in situ hybridization preparation for IFN-γ; note the very low level of IFN-γ before immunotherapy in Fig 8. Fig 9 is a simultaneous in situ hybridization for IFN-γ and immunocytochemistry for CD3 after immunotherapy; note the strong signal for IFN-γ which is mostly localized to CD3. Both preparations are from skin biopsy specimens obtained after antigen challenge.) Recent studies have demonstrated the involvement of IL-10, which has been shown to be upregulated in biopsy specimens after antigen challenge of the skin after successful





immunotherapy. In target organs, as with the nasal mucosa of patients with allergic rhinitis, similar changes in cytokine profile can also be observed after immunotherapy. However, a number of studies have failed to demonstrate a decrease in T cells in patients who received immunotherapy after antigen challenge or natural exposure. There has been very little information published on immunopathologic changes in bronchial mucosa after immunotherapy.

There have been a number of recent developments in immunotherapy, including the introduction of adjuvants and immunostimulatory sequences of DNA-containing CpG motifs. It has been recently shown that immunostimulatory sequences conjugated to ragweed (Amb a 1) when given by means of injection require a relatively long period of time before being able to reduce nasal mucosal eosinophilia and IL-4 expression and induce IFN-γ expression in patients with allergic rhinitis after intranasal challenge. (Fig 10 is an illustration of the effect of Amb a 1 on nasal mucosal inflammation [see legends]. Fig 11 is MBP immunoreactivity in nasal mucosa after antigen challenge in a patient who received placebo, and Fig 12 is an example of MBP immunoreactivity in nasal mucosa after antigen in patients who received active treatment with Amb a 1.) The effect of this type of treatment on asthma is currently under investigation.