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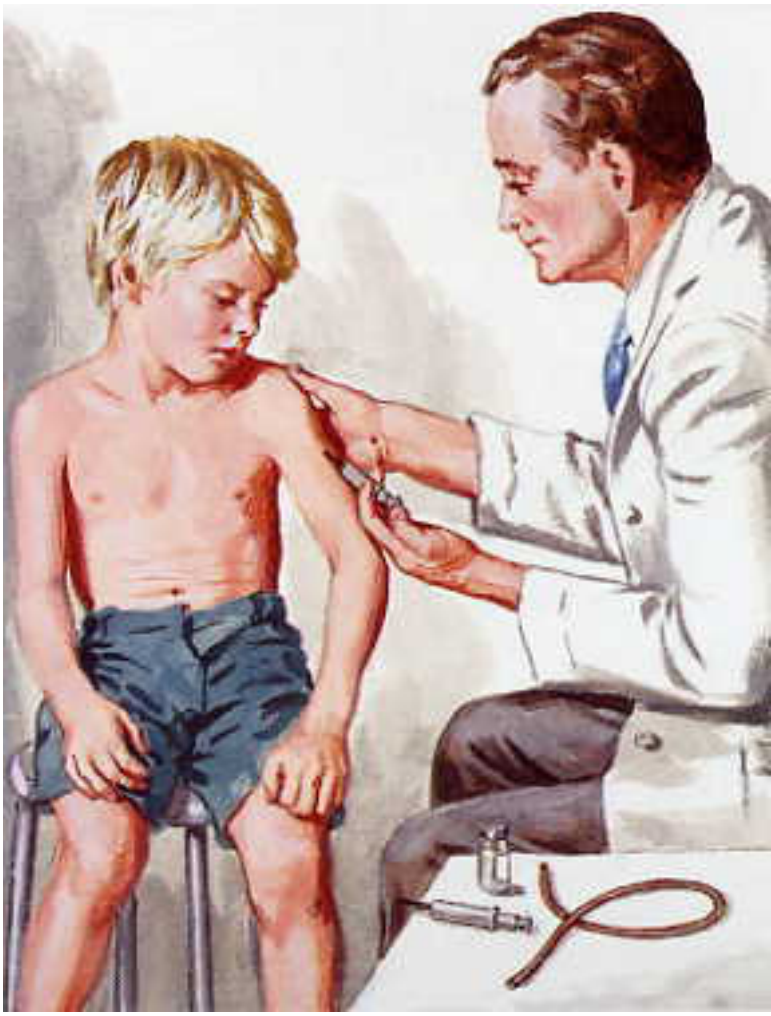
IMMUNOTHERAPY

When symptoms are severe and medications fail, allergy shots offer long-term relief.



About 20% of the population suffers from IgE-mediated allergy to various allergens in the environment. *Subcutaneous immunotherapy* **(SCIT)** is an allergen-specific treatment for allergy to both inhaled and insect-sting allergens.

SCIT, commonly known as "allergy shots," is one of the most effective forms of treatment available for symptoms caused by exposure to specific allergens and can actually change the natural history of the disease process. While airborne allergens can cause severe respiratory symptoms (allergic rhinitis/sinusitis, conjunctivitis, and asthma), insect-sting venom can provoke anaphylaxis in venom-allergic individuals.

When allergen avoidance is ineffective and medications are inadequate, then immunotherapy may present a viable treatment option for allergic individuals. Treatment with **SCIT** can induce specific immunologic tolerance in most allergy sufferers, resulting in diminished symptoms, reduced need for medication and long-lasting benefits. Further, **SCIT** reduces complications directly related to upper-respiratory allergy—such as allergic sinusitis, eustachian tube dysfunction and otitis media—and may prevent the future development of asthma in patients with allergic rhinitis.[1]

The use of **SCIT** in the U.S. began in 1911 by Noonan and Friedman, and now more than 30 million injections are administered annually.

SCIT is administered by subcutaneous injection of gradually increasing doses of an allergen. Increasing doses of the allergy serum are given weekly over a period of months until a *target dose* or *maintenance dose* is achieved.

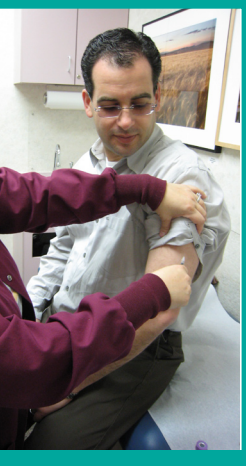
The maintenance dose is the optimum dose which induces immunologic tolerance to the injected allergen(s). A maintenance dose is then administered every 3-4 weeks for a period of 3-5 years, or even longer in unique situations. Many studies of **SCIT** have shown a significant reduction of symptoms within 1-2 years. The treatment is often associated with long-term benefits far beyond the treatment period. In some cases, immunologic tolerance can last a lifetime.

Allergen-specific Immunotherapy

How it works

The mechanism underlying allergen-specific immunotherapy relates to changes in T- and B-cell responses to an allergen, as well as alteration of allergen-specific antibody production. **SCIT** also affects cells involved in the inflammatory process (i.e. eosinophils, basophils and mast cells).

Immunotherapy changes the immunoregulation of responses to allergens by first modulating *T regulator cells* that orchestrate the allergic response. In turn, T regu



latory cells act by stimulating or suppressing *peripheral T-cells* that stimulate or suppress specific anti-allergen antibody production, and cellular secretions (cytokines) that affect the response to allergen exposure. Research reveals that **SCIT** results in a loss of reactivity to the specific allergen when the same allergen is applied to nasal and conjunctival mucosa of the **SCIT**-treated patients. Allergy skin testing reactivity also decreased as a result of this treatment. Finally, many controlled clinical trials support the efficacy of subcutaneous immunotherapy for both allergic rhinitis and asthma.[1 2]

Observed immunologic changes due to SCIT

- Increase in antigen-specific IgG (IgG1 and IgG4), also known as "blocking antibody"
- Decrease in allergen-specific IgE (demonstrated by RAST or skin tests)
- Decrease in seasonal rise of antigen-specific IgE
- Modulation of mast cells and basophils (decreased histamine release)
- Effects on lymphocytes: Increase in T-supressor cells
- Cytokine changes: TNF decreases, IL4 (TH2 associated) decreases

Which diseases benefit from SCIT?

1. Allergic rhinitis and conjunctivitis

Immunotherapy helps control the symptoms of respiratory allergy due to pollen (including ragweed, see Figure 2), dust mites, animal dander and airborne mold spores. Complications of allergic rhinitis, such as eustachian tube dysfunction, recurrent otitis media, and sinusitis may also improve as a result of **SCIT**.

Many studies support the effectiveness of **SCIT** in allergic rhinitis, including a meta-analysis which consisted of 16 prospective, blinded, and placebo-controlled studies of immunotherapy for allergic rhinitis published in English between 1966 and 1996.[1] The studies included grass extract, ragweed, dust mite, cedar pollen, and the mold *Alternaria*. In 15 of the 16 studies, the outcome favored the active treatment.

2. Allergic or extrinsic bronchial asthma

A meta-analysis was performed based on 75 randomized, controlled trials including 3,188 subjects with asthma. Participants who underwent immunotherapy for allergies to house dust mites, pollen, animal dander, mold *(Cladosporium)*, latex, and other allergens experienced a significant improvement in asthma symptoms.[2]

3. Insect venom hypersensitivity

Purified insect venoms have been used in immunotherapy since 1980 and have proven more than 95% effective in preventing insect-sting anaphylaxis (See Figure 1).

4. Other possible disease entities that SCIT may benefit:

- Chronic rhino sinusitis
- Allergic fungal sinusitis

The allergens

Allergens used to treat respiratory allergy include pollen (tree, grass, weed), pet dander (e.g. cat pelt), dust mites, airborne molds, and occupational aeroallergens. Allergens used to treat insect hypersensitivity include honey bee, yellow jacket, hornets, wasps, and fire ant. Honey bee, yellow jacket, hornet and wasp venoms are biologically standardized and collected by electroshock or dissecting out the venom sac. **SCIT** with these insect allergens has yielded extraordinary protection from insect-sting anaphylaxis, offering recipients up to 95% protection.

Allergy testing

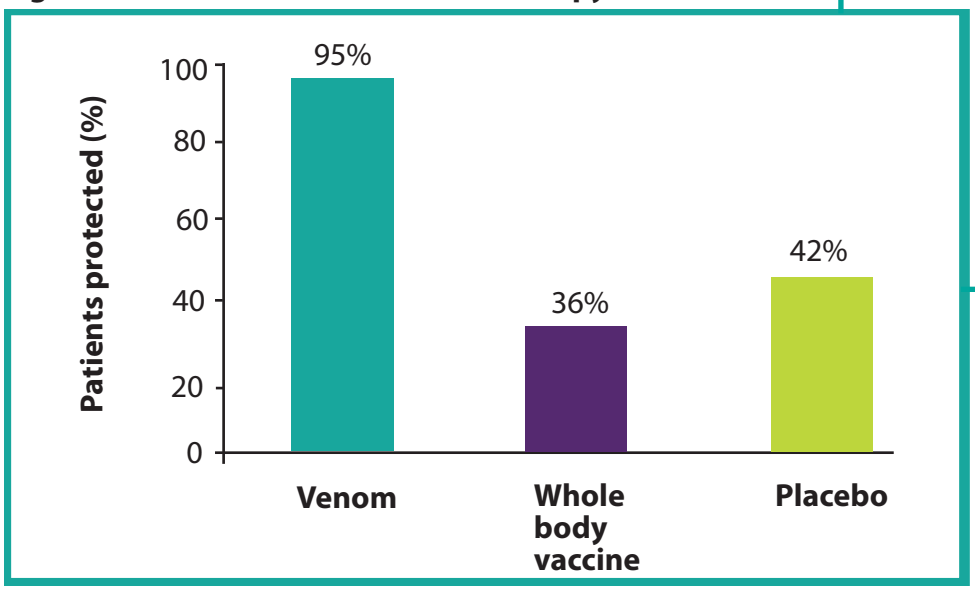
Allergy skin testing

Careful selection of appropriate allergens used in testing, combined with excellent skin testing technique and a thorough clinical history leads to the formulation of an optimum allergy serum. Allergy skin testing offers the most sensitive method for identification of IgE-mediated allergy.

A distinct advantage of allergy skin testing over lab studies (e.g. RAST or Immunocap™) in detecting allergy is that the same allergen(s) used to skin test are also used to prepare the allergy serum used in treatment. The same is not true for treatment based on lab studies, in which the allergy serum often comes from a different source than the one used in testing. Using the same allergen source for testing and preparation of the allergy serum insures that all relevant allergens are present. This level of attention to detail may lead to a better clinical outcome.

RAST assay or Immunocap™ are accurate laboratory tests that can identify circulating allergen-specific IgE (allergy antibody). These lab tests have the advantage of convenience, do not require physician's time and expertise, are not affected by antihistamines, and pose no risk of systemic reaction. However, they appear to be less sensitive than skin testing in diagnosing allergy.

Figure 1: Effects of venom immunotherapy



Systemic anaphylaxis was prevented in 95% of the subjects treated with venom immunotherapy, compared with 36% and 42% of the subjects treated with whole-body vaccines and placebo, respectively. [3]

Clinical History

Without a supportive clinical history, allergy testing on its own cannot provide the information necessary to prepare an effective allergy serum for treatment. A careful and complete patient history includes relevant information regarding allergen exposure at home, work, indoors and outdoors, as well as the locations and timing of symptoms. Positive allergy testing identifies the presence of circulating allergen-specific IgE. However, this alone is insufficient in identifying the cause of the patient's symptoms. **The patient's symptom history must correlate with allergy test results to determine which allergens are relevant.** Only these allergens should be included in the allergy serum.

Receiving SCIT

Subcutaneous injection(s) of an allergy serum customized for each patient are given on the lateral aspect of the arm(s). Injections usually begin with a very low dose of diluted allergy serum. Each week, the dose is increased until the full, or maintenance dose is achieved. It often takes 6-9 months to reach a maintenance dose, which is then administered every 3-4 weeks for a period of 3-5 years or more.

On rare occasions, a course of immunotherapy can be accelerated by a technique called ***rush immunotherapy***. Rush immunotherapy is a method in which injections of allergens during the "build-up" phase are administered every 20-60 minutes, allowing the patient to achieve maintenance levels within days. This approach may take two or more full days of patient time and engenders a much higher risk of local and systemic reaction. Because for the increased risk of anaphylaxis, rush immunotherapy is rarely used as a treatment protocol.

Following allergy injection(s), patients should wait in the medical office for 30 minutes, since most significant reactions occur within this time. Though severe reactions are rare, we recommend that patients carry an Epi-pen™ or TwinJect™ with them after leaving the office. Patients are cautioned not to exercise 1-2 hours prior to and following **SCIT** and to avoid the use of beta blockers.

Allergy serum and dose adjustments

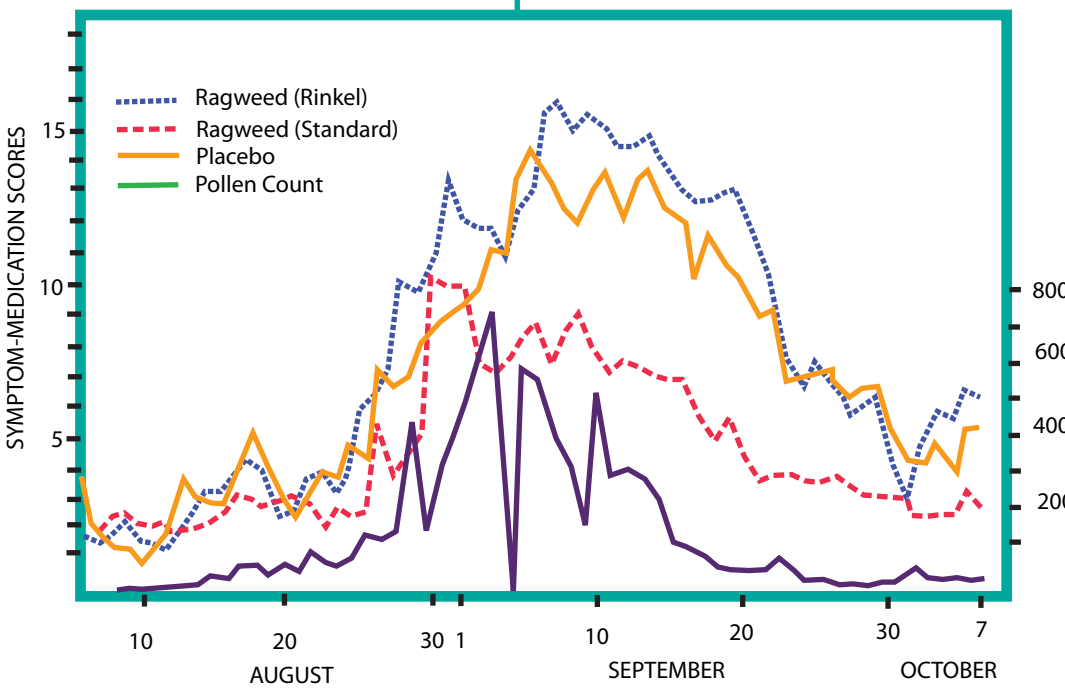
■ *Allergy Serum*

Allergy serum formulations are based on the type and severity of the patient's particular sensitivity, as identified by the patient history and allergy tests. Antigens are grouped and placed in separate treatment vials to prevent one allergen's protease inactivating another group of allergens and thus lessening the potency of the serum. They are also placed in separate vials to maximize the dose of each allergen.

■ *Dosage*

High-dose therapy is now recom

Figure 2: Aeroallergens



Rise and fall of symptom-medication scores were significantly correlated wtih rise and fall of ragweed pollen counts for a standard ragweed group. [4]

mended since it appears to elicit the best results. Initially, diluted allergy serum beginning with a subcutaneous injection of 0.05 cc is gradually increased by .05 cc weekly until a dose of .35 to 0.5 cc is reached. This process is repeated with more concentrated allergy serum until a maintenance dose is achieved.

■ *Dosage adjustments*

Since individual patients vary in their tolerance to allergens, dosage schedules are modified in order to prevent reactions. The standard **SCIT** dose may be adjusted according to the patient's history of response to previous injections, seasonal allergies (for Delaware Valley pollen counts, visit **asthmacenter.com**, updated daily) or diagnosis of pregnancy.

The goal is to raise the dose as quickly as possible without inducing reactions. Local reactions causing a quarter-sized wheal that resolves quickly will usually not require a change in dose. Large local reactions (wheals larger than a golf ball) lasting more than one day are considered precursors to a systemic reaction and in this case, the next dose is lowered by 30-50%. Patients developing hives, respiratory allergy symptoms, or evidence of anaphylaxis require a 90% reduction in their next dose.

Alternative routes of immunotherapy

Although **SCIT** is the most common form of immunotherapy in the U.S., some other methods of allergen-specific therapy have been investigated and proven effective in controlled studies.

■ *Nasal immunotherapy:* Allergens are sprayed onto the nasal mucosa. This technique is not currently available or FDA-approved, though it appears to be effective. Clinical trials have revealed frequent local side effects.

■ *Oral immunotherapy:* Allergens are orally ingested. This technique has proven effective in some studies, though it is not currently available or FDA-approved. Oral immunotherapy offers some promise as a future treatment for food allergy.

■ *Sublingual immunotherapy (SLIT)* has proven effective in European studies, using much higher concentrations of allergens than that used in injection therapy (**SCIT**) here in the U.S. Although there appears to be no consensus on the most effective dose, allergen concentrations may be as high as 50-300 times the amount of allergen currently used in **SCIT** allergy serums.

Understanding SUB-LINGUAL IMMUNOTHERAPY

In a 6-year study comparing **SCIT** to *sub-lingual immunotherapy* ***(SLIT)***, Tahamiler, et al (2008) enrolled 193 patients with allergic rhinitis due to dust mite allergy. Half the participants received **SCIT**, while the other half received **SLIT** for 3 years, followed by 3 more years of follow-up. Prick tests showed a greater reduction in sensitivity with **SCIT**. No systemic reactions occurred in either group. However, side effects with **SLIT** included oral pruritus (48%), rhinitis (31%), and gastro-intestinal symptoms (12%). **SLIT** studies generally revealed a 30% reduction in symptoms. It would appear that **SLIT** is most effective for patients suffering from mild to moderate symptoms. In addition, investigators felt that **SCIT** was more effective than **SLIT** for treatment in perennial allergic rhinitis due to dust mites. It should also be noted that anaphylaxis with **SLIT** has been reported as well.[6]

SLIT appears to work best as a mono-therapy, when a single allergen, such as grass pollen, is the cause of symptoms. **SLIT** does not appear to work well when used to treat patients with multiple allergies.

While there is a distinct possibility that **SLIT** will be approved in the future for high-dose mono-therapy in the U.S., its availability may be limited to just a few allergens. Further, **SLIT** may be significantly less effective than **SCIT,** especially when multiple allergens need to be administered as part of the treatment program.

Physicians currently offering **SLIT** therapy in the U.S. are prescribing an allergy serum not approved by the FDA for **SLIT**. Therefore, **SLIT** is not recommended for treatment at this time by the American Academy of Allergy and Immunology or other major academic organizations. Furthermore, the cost of this therapy may be quite high (estimated $1000-$1500 per year) and is usually not covered by medical insurance.

Although **SLIT** holds promise as a new and effective future treatment for allergy, the use of an unapproved therapy is an unwise choice when a highly effective therapy for allergy is readily available.

Special considerations

Pregnancy: Pregnancy is not a contraindication to immunotherapy. However, it is wise to reduce the immunotherapy dose and not raise it again until delivey.

Use of beta-blockers: In the event of an adverse reaction to an allergy injection, a beta-blocker would interfere with effective emergency treatment by suppressing the response to treatment (epinephrine) and possibly worsening any underlying asthma.

Patient's history of previous severe reactions to SCIT: Patients who have repeated or serious previous reactions may not be good candidates for **SCIT** for non-life-threatening allergic disease.

Severe or unstable asthma: When asthma is unstable, it is prudent to withold immunotherapy.

Duration of treatment

The length of therapy can vary according to the patient's response. Most patients who show improvement by the second year of treatment will be likely to maintain improvement in the future. Once maintenance is reached, therapy is usually continued over a period of 3-5 years. Patients that show no improvement during the first year of maintenance are unlikely to benefit from treatment.

Cost vs. Benefit

Once a patient has reached the maintenance dose, the cost of a

year's treatment, including the allergy serum and monthly injections is often less than $1000 per year. However, the cost rises for patients requiring multiple vials of allergens. In contrast, the cost of medications (including prescription antihistamines, physician visits nasal sprays and eye drops and other medication) can often exceed $2500 each year and may be less effective than **SCIT** in controlling severe allergy symptoms.

Causes of immunotherapy failure

- Lack of good correlation between allergy testing results and clinical history
- Inadequate dosing. Use of low dose treatment, mixing too many antigens in the same vial causing dilution of dose, mixing incompatible antigens in the same vial (i.e. dust and pollen or mold and pollen)
- Missing clinically relevant allergens in allergy serum
- Poor compliance with scheduled dosing
- As with any other medication failure, immunotherapy just may not work for certain patients.

The future of IMMUNOTHERAPY

SCIT is currently the most effective form of immunotherapy available and has been the subject of many studies which support its efficacy. However, the cost of production of these allergens is high and there is a risk of systemic reactions.

As a result of these limitations, scientists have tried to modify the allergens used in **SCIT** to lower their allergenicity and increase their immunogenicity. In this way, lower doses of less-reactive allergens could induce tolerance with a much lower incidence of side effects and perhaps greater convenience.

Experimental chemical treatments of allergens have produced new preparations—including polymerized allergens, formaldehyde-treated allergens and allergen conjugates. These have proven successful in some clinical trials. However, they are not yet approved for treatment in the U.S.

Another approach has been to absorb allergens by using an aluminum-precipitated extract or product in order to slow the release of injected allergy serum and reduce allergic reactions. However, the variety of allergens is limited with this form of allergen extract.

Finally, a new immunologic treatment with anti-IgE (Xolair) which is a non-specific allergy treatment, can benefit allergy sufferers by globally removing much of the circulating IgE. Unfortunately, its approved use is currently limited to moderate to severe extrinsic asthma patients and its associated cost can top $30,000 per year per patient.

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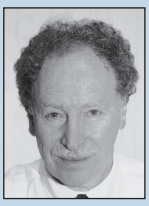
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