SPECIAL FEATURE

Enzyme potentiated desensitization (EPD): a potential revolution in allergy care

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Enzyme potentiated desensitization (EPD) is a low-dose method of immunotherapy developed by Len McEwen. EPD significantly expands the range of sensitivities and allergic syndromes that may be treated by immunotherapy. As opposed to the production of blocking antibody, a Th2 to Th1 lymphocyte switch, or lymphocyte anergy, EPD is thought to work by changing the balance of T-cells in the patient, yielding highly effective, safe, and long-lasting results. The effectiveness of EPD has been reported in seven double-blind, placebo-controlled studies, all of which found statistically significant improvement of the EPD treatment group over the placebo group.

Attention has now switched to the role of interleukin 10 (IL10). There is speculation that IL10 release may also downregulate allergy to antigens that are not included in immunotherapy. Although no changes in circulating IL10 have been detectable after the classic forms of immunotherapy, a blind laboratory study showed significant IL10 effects after EPD. Curr Opin Otolaryngol Head Neck Surg 2000, 8:273–276

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Abbreviation

EPD enzyme potentiated desensitization

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As an otolaryngologist, I was introduced during my residency to the need for allergy treatment in the practice of our profession. At that time, we were using the old scratch-and-prick technique and were quite limited in the options we could offer to patients for symptom relief. During my first year of practice, I was introduced to end-point titration and, subsequently, spent a week with Carlton Lee learning provocative food testing. Over the years I have developed a rather large allergy practice, but there were always cases that frustrated my best efforts to afford the patient relief. After years of searching for another tool to add to my arsenal, I came upon enzyme potentiated desensitization.

Enzyme potentiated desensitization (EPD) is a low-dose method of immunotherapy developed by Len McEwen [1], a noted English immunologist. Since its first clinical use in the 1960s, no serious complications have been reported in more than 300,000 doses administered worldwide. Chief among its advantages is that EPD significantly expands the range of sensitivities and allergic syndromes that may be treated by immunotherapy. It has been used successfully in many patients who failed to gain relief of symptoms through other treatments.

Traditionally, allergies have been treated through either antibody mediation or low-dose tolerance, neither of which tends to have long-lasting effects. Either continuation of medication or avoidance of the allergen is required without repetition of treatment. EPD, on the other hand, affects the balance of T-cells in the patient, yielding highly effective, safe, and long-lasting results. Allergy appears to result from a failure to modulate immune responses. EPD appears to restore a proper balance, probably by generating allergen-sensitive T-lymphocytes which release downregulating cytokines. Interleukin 10 (IL10) is likely to be important.

In the process of developing EPD, McEwen became convinced that the effective ingredient was a "contaminant." By separating the contaminants and adding each in turn to purified hyaluronidase, he isolated the effective ingredient as beta-glucuronidase. Because beta-glucuronidase is a naturally occurring enzyme in humans, the danger of anaphalactoid responses of patients to treatment was eliminated. Adding beta-glucuronidase, stabilized with protamine, to a small dose of allergen greatly

enhanced the desensitizing effect. The dose of allergen is also important, of course, in that too large a dose can switch the effect from hyposensitization to hypersensitization. After much testing, an optimal dose level of 10,000 molecules of antigen, stabilized with chondroitin sulphate, was established as providing a reliable method of immunotherapy. The effectiveness of EPD has been reported in seven published double-blind, placebo-controlled studies [2–8] (Table 1). In evaluating reduction of symptoms, symptom-free days, and/or the use of drugs, all seven studies found statistically significant improvement of the EPD treatment group over the placebo group. All the trials of EPD for pollen allergy evaluated the effect of a single preseasonal dose. Businco investigated the effect of EPD for asthma caused by D. pteronyssinus by giving 2 doses 8 weeks apart [8].

Once desensitization has become effective, other treatments may become unnecessary, but at the start, EPD should be used in parallel with optimal conventional therapy, including drugs. Some drugs used to treat allergy may interfere with the development of immune tolerance. There are usually ways in which this can be avoided.

Beta-glucuronidase is an active enzyme only at acid pH. At neutral pH, it is an adhesion molecule concerned with interactions between resting T-lymphocytes, keratinocytes in the skin, and polysaccharides such as hyaluronic acid in the intercellular space [10,11]. In cultures of human lymphocytes, the enzyme is a mitogen [12]. Under normal circumstances, beta-glucuronidase is likely to be a significant physiological up-regulator of the lymphocyte immune response.

Immunologists believe that an unregulated Th2-type CD4+ T-lymphocyte response to allergen is the basis of atopic allergy, and the same may be true for nonatopic intrinsic asthma. There is evidence that conventional immunotherapy injections switch the T-cell response to allergen from Th2 to Th1 (tuberculin-type). In contrast, EPD does not produce the Th2 to Th1 switch. Simon McEwen [12] has shown in mice that EPD will significantly reduce contact hypersensitivity to 2,4 dinitrofluorobenzene, which is a TH1-type response.

Th1 and Th2-lymphocytes differ in the cytokines which they produce (Th1: IL2 and gamma interferon, Th2: IL4 and IL5). The mechanisms of conventional injection immunotherapy have been investigated chiefly by identifying T-lymphocytes with these cytokine profiles. Attention has now switched to the role of IL10, which downregulates T-lymphocyte responses and is released in response to allergen by T-lymphocyte cultures from patients who have received immunotherapy [13]. There is speculation that in a nonspecific way, IL10 release may also downregulate allergy to allergens that are not included in immunotherapy. As yet, no changes in circulating IL10 have been detectable after the classic forms of immunotherapy. This puts EPD in a new light. A blind laboratory study of blood IL6 and IL10 before and after EPD (Table 2) showed that both cytokines increased significantly 24 hours after treatment [14]. Subsequently, the IL6 fell to normal levels, but the IL10 was still raised after 15 days. It seems that EPD is unique in producing a measurable rise in circulating IL10 [14].

In my office, we offer individuals multiple options in their approaches to allergy. Although EPD is an exciting new option for treating allergic patients, it should be considered neither a replacement for all other treatment protocols nor appropriate for all allergic patients. The trials of EPD for simple pollen allergy have shown that even a single preseasonal injection can be effective without specific patient preparation, but for more complex allergies, the patient preparation regimen is more complicated. Specific protocols address vitamin therapy, short-term diet restrictions, and allergen and chemical avoidance around the time of each injection, requiring a highly motivated and cooperative patient for success. These restrictions are necessary to aid in the development of the allergen-sensitive T-lymphocytes that play such an integral part in this program. All is not

Table 1. Published double-blind, placebo-controlled studies of enzyme potentiated desensitization

Authors	Allergens	DBPC	Active	Placebo	Symptoms, *P*	Symptom-free days, *P*	Use of drugs, *P*
Fell & Brostoff* [2]	Grass	Yes	22	22	NA	NA	< 0.02
DiStanislao *et al.* [6]	Grass	Yes	20	20	NS	< 0.005	< 0.05
Longo *et al.* [4]	Grass	Yes	9	7	< 0.001	< 0.001	NS
Astarita *et al.* [3]	Parietaria, grass	Yes	10	10†	< 0.001	NA	NA
Angelini *et al.* [5]	Parietaria, olive	Yes	11	10	0.001	< 0.005	< 0.001
Businco *et al.* [8]	Dust mite	Yes	10	10	< 0.05	< 0.001	< 0.01
Caramia *et al.* [7]	Grass, dust mite	Yes	8	8	< 0.001	NA	< 0.001
			27	27	< 0.001		< 0.001
Totals: 4 sensitivities			**117**	**114**	**7 trials, all significant**		

*In the Fell & Brostoff study, subjects had unlimited intranasal steroid aerosol. All subjects titrated themselves to comfort during a 14-day observation period at peak of pollen season. †Excludes second control group treated with allergen alone who were not "blind." DBPC, double-blind, placebo-controlled. From [9], with permission.

Table 2. Plasma IL-6 and IL-10 (ng/ml) in grass pollen-sensitive asthmatic and healthy children before treatment, and at 24 hours and 15 days after enzyme potentiated desensitization

	Patients $n = 17$	Controls $n = 17$	P
IL 6 baseline	17.08 ± 8.09	5.84 ± 2.15	< 0.002
24 hours	20.54 ±12.37	6.89 ± 4.20	< 0.005
15 days	10.64 ± 6.29	9.10 ± 4.27	NS
IL 10 baseline	112.46 ± 18.51	64.39 ± 10.15	< 0.005
24 hours	146.54 ± 26.31	53.65 ± 12.73	< 0.005
15 days	143.04 ± 12.57	66.87 ± 18.54	< 0.005

IL, interleukin. From [14], with permission.

dismal, however, because the frequency of treatment initially consists only of one to four injections on the forearm every two months. After approximately three treatments, the interval between injections is increased gradually until most patients can go many months between injections before symptoms begin to reappear. At that point, the patient must return for a booster vaccine to update desensitization. The average number of treatments is 16 to 18 in a lifetime, but this varies per individual and immune system.

The ideal candidate for EPD is a patient for whom conventional allergy care has not provided relief or for whom food allergies or chemical sensitivities are major problems. Most EPD patients reach my office having failed the medical approach, and they are left with injections as the only course of therapy. Once patients decide they would like to consider EPD, they are asked to do a stool analysis so that we can make certain that there are no pathologic bacteria or yeast that would adversely affect the therapy. Neither the restricted diet nor the study of the gastrointestinal flora is necessary in the hay fever patient unless the patient has another symptom, such as migraine, which might be caused by food allergy. It is imperative, we believe, to have the gastrointestinal tract functioning as normally as possible for total success with this therapy. Once this has been accomplished, the candidate is asked to read the American EPD Society's Patient Instruction Booklet and to attend a three-hour EPD class conducted by a specially trained nurse in our office. After completion of these steps, the patient meets with the physician or the physician assistant to decide the type of treatment that will be best for the individual. For some patients, the restrictions and the cost of EPD are prohibitive. Others are delighted after years of failure with other treatment protocols to have an alternative.

As mentioned earlier, it takes a special person to cooperate with the rules and regulations as to vitamin therapy, diet restrictions, and allergen and chemical avoidance to make EPD succeed. These restrictions are necessary to encourage the allergen-sensitive T-cell development, to avoid blocking the effectiveness of EPD, and to prevent hypersensitization. During what we refer to as the three critical days (the day before, the day of, and the day after each injection), the patient is highly susceptible to developing new sensitivities and must avoid exposure to inhalant allergens and to chemicals. We advise patients to board the family pet and to thoroughly clean house before beginning the three critical days. They are told to avoid completely exposure to tobacco smoke, make-up, hair products, inks, and other scented chemicals and to use hypoallergenic Simple Soap and Simple Shampoo (Smith & Nephew, Birmingham, England), mineral rock or baking soda instead of deodorant, and baking soda or sea salt instead of toothpaste on the three critical days. Depending on the type of work the patient does, staying home may be an option to consider.

Table 3. Foods approved for use during the three-day "critical" diet

Lamb, rabbit, venison, fresh fish
Cooked carrots, celery, cabbage, white potatoes, sweet potatoes, parsnips, rutabagas, rhubarb
Lettuce
Tapioca granules, flour, and powder, plain
Pure baking soda (no additives)
Sea salt, not iodized
Granose margarine

EPD, enzyme potentiated desensitization.

An important element to guard against developing new sensitivities is a three-day diet limited to the foods in the accompanying chart (Table 3), fewer if the patient is allergic to any of them, plus bottled or distilled water. We offer our patients recipes and lists of vendors who supply useful but unusual foods, such as white sweet potato flour and some prepared baked goods. We also offer frozen Granose (Haldane Foods Group, Newport Pagnell, England) margarine at the office as a convenience because it is available from only one U.S. supplier.

Experience has shown that patients should follow a regimented approach to taking certain vitamins starting as early as 11 days prior to and continuing for at least 4 weeks after each injection. These vitamins, which enhance the effectiveness of EPD, are listed in the accompanying chart (Table 4).

Table 4. Vitamins considered essential for enzyme potentiated densensitization

EPD multivitamin
EPD trace mineral
Magnesium citrate
Calcium complex
Folic acid, 5 mg
Vitamin A, 25,000 IU
Vitamin D-rocaltrol, 5 mcg
Zinc, 20–30 mg
Vitamin C is forbidden for 4 days before and 4 weeks after the EPD shot. After that time, it is limited to 3000 mg/day

EPD, enzyme potentiated desensitization.

The American EPD Society, under the direction of W.A. Shrader, has an ongoing computerized audit under an Institutional Review Board. As yet, the results of this study, which includes more than 9,783 patients having progressed beyond three doses of EPD, have not been completed. Though legally and ethically I cannot provide details, the preliminary data indicate that the results are very good.

Acknowledgment

I would be happy to entertain questions regarding the qualifications needed to participate in the EPD program, or you can contact W.A. Shrader, MD, at Santa Fe Center for Allergy & Environmental Medicine, 141 Paseo de Peralta, Suite A, Sante Fe, New Mexico 87501, USA.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • Of special interest
- •• Of outstanding interest

1 McEwen LM, Nicholson M, Kitchen I, White S: Enzyme potentiated hyposensitisation III: control by sugars and diols of the immunological effect of beta-glucuronidase in mice and patients with hay fever. Ann Allergy 1973, 31:543–550.

2 Brostoff J, Fell P: A single dose of desensitisation for summer hay fever. Eur J Clin Pharmacol 1990, 38:77–79.

3 Astarita C, Scala G, Spoviero S, Franseze A: Effect of enzyme potentiated desensitisation in the treatment of pollenosis: a double-blind placebo-controlled trial. J Invest Allergol Clin Immunol 1996, 6(4):248–255.

4 Longo G, Poli F, Bertoli G: Clinical efficacy of a new hyposensitising treatment, EPD (Enzyme Potentiated Desensitisation) in the therapy of pollenosis. Riforma Med 1992, 107:171–176.

5 Angelini G, Curatoli G, D'Argento V, Vena GA: Pollinosi: una nuova metodica di immunoterapia. Med J Surg Med 1993, 253–256.

6 Di Stanislao C, Di Berardino L, Bianchi I, Bologna G: A double-blind, placebo-controlled study of preventive immunotherapy with EPD in the treatment of seasonal allergic disease. Allergie et Immunologie 1997, 30(2):39–42.

7 Caramia G, Franceschini F, Cimarelli ZA, Ciucchi MS, Gagliardini R, Ruffini E: The efficacy of EPD, a new immunotherapy, in the treatment of allergic diseases in children. Allergie et Immunologie 1996, 28(9):308–310.

8 Businco L, Cantani A, Ragno V, Monteleone A, Lucenti P: Enzyme potentiated desensitisation in children with asthma and mite allergy: a double-blind study. J Invest Allergol Clin Immunol 1996, 6(4):270–276.

9 McEwen LM: Enzyme Potentiated Desensitization in Food Allergy and Intolerance, 2nd Ed. Edited by Brostoff J and Challacombe SI. London: Bailliere Tindall; in press.

10 Gilat D, Hershkovitz R, Goldkorn I, Calahon L, Korner G, Vlodavsky I, Lider O: Molecular behaviour adapts to context: heparanase functions as an extracellular matrix-degrading enzyme or as a T-cell adhesion molecule depending on the local pH. J Exp Med 1995, 181:1929–1934.

11 Hershkovitz R, Marikovsky M, Gilat D, Lider O: Keratinocyte-associated chemokines and enzymatically quiescent heparanase induce the binding of resting CD4+ T cells. J Invest Dermatol 1996, 106(2):243–248.

12 McEwen SM: Master of Science Thesis 1997. Hammersmith Hospital, London University.

13 Akdis CA, Blaser K: IL10-induced anergy in peripheral T cells and reactivation by microenvironmental cytokines: two key steps in specific immunotherapy. FASEB Journal 1999, 13:603–609.

14 Ippoliti F, Ragno V, Del Nero A, McEwen LM, McEwen HC, Businco L: Effect of preseasonal enzyme potentiated desensitisation (EPD) on plasma IL-6 and IL-10 of grass pollen-sensitive asthmatic children. Allergie et Immunologie 1997, 29(5)120:123–125.