Techniques of Immunotherapy

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Consideration is given to the relative merits of two methods of desensitization: the intradermal relief-dose (provocation-neutralization serial dilution titration) method, and the method of subcutaneous "maximum tolerated dose"; the former utilizes intradermally determined optimal strength allergen doses that require no incremental increase and proved rapid relief with no side effects and the latter uses incrementally stronger doses, with significant attendant risks. There is discussion of the several advantages of the relief-dose method over the maximum tolerated dose method, among them that are former may include both offering foods and inhalants whereas the latter includes only inhalants.

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The two papers by Maberly and Anthony represent a welcome addition to our understanding of asthma, its causes, and its better control. They studied 19 consecutive asthmatics intensively in a three-week hospital stay. The hospital environment was carefully controlled to eliminate asthma triggers in the form of airborne particles and volatile chemical gases, and to isolate the effects of individual foods.

The food study was begun by a five-day therapeutic fast on bottled spring water only. By about the sixth day, most patients were symptom free on less medication. This was followed by feeding only one food per meal, three meals per day, in large quantity, to observe their effects.

Foods, which induced decreases of 20 Umin in peak expiratory flow rate, were immediately tested intradermally with serial dilutions. The peak flow (and attendant symptoms such as wheeze, cough, shortness of breath, chest tightness, etc.) was markedly improved within minutes after the intradermal administration of the "endpoint dose" (relief dose). Inhalants were tested by the same method. Chemicals were tested sublingually.

Food challenge caused bronchoconstriction in 18 of the 19 patients. Chemicals caused bronchoconstriction in 10 patients. All patients produced positive wheals on intradermal testing (four of these were prick-test negative).

Patients were discharged with much greater knowledge and understanding of their own individual triggers. They were provided with relief-dose extracts to protect from allergenic foods, inhalants, and chemicals. This allowed a less restricted diet than otherwise would have been required if the only treatment available was attempted avoidance. They were also provided with individually designed rotation diet (allowing most trigger foods), and instruction in how to reduce exposure to relevant inhalants and chemicals. This gave the patients more control over their asthma with less medication.

This study represents a major step forward. It confirms the major role that foods and chemicals often play in asthma. Food and chemicals have been little studied and their roles little appreciated. The correlation of the objective parameter of changes in peak expiratory flow rates with food and inhalant challenges emphasizes the real-life clinical aspect of this valuable study.

Secondly, this study brings to the fore the very powerful but little appreciated beneficial effects of the relief-dose method of testing and treatment. This utilizes the intradermal injection of consecutive concentrations in 1:5 serial dilutions of an allergenic extract. Remarkably, one concentration of an allergenic extract can produce bronchoconstriction within minutes; a different concentration of the same extract can then relive the bronchoconstriction within minutes.

The peak expiratory flow rate changes are objective monitors of these effects. A second objective monitor is the intradermal wheal. In tests, which produce a symptom such as bronchoconstriction, all concentrations stronger than the relieving concentration produce positive wheals as well as bronchoconstriction. The production of a positive wheal requires injecting consecutively weaker concentrations to find the relieving concentration. While injecting consecutively weaker concentrations, one at a time, negative wheals will soon occur. The first (strongest concentration), which produces a *negative* wheal while moving consecutively weaker, is the concentration that provides relief. Wheals are visible, palpable, measurable, and photographable for permanent records. How much more objective can one get?

Ideally, an optimal dose should provide relief quickly and produce no side effects. Conventional immunotherapy seeks to find an optimal dose by building up, over months or years, to “the maximum tolerated dose”. This dose does not *relieve* symptoms. It is often accompanied by marked local, and at times severe, systemic reactions. So it is not really an optimal dose, and is not often totally tolerated.

The intradermally determined relief dose is the true maximum tolerated dose. It provides relief within minutes during the intradermal testing, and within minutes or hours on subcutaneous immunotherapeutic injections. It does not produce even a positive wheal (analogous to a conventional local reaction), and it relieves, not provokes, symptoms (provoked symptoms may be considered analogous to a conventional systemic reaction). When the doses are correct, there are essentially no local reactions or systemic side effects. Therefore, this system can be properly called the Maximum Tolerated *Intradermal* Dose (MTID) method, or more simply, the Relief Dose Method.

Dose determination by the conventional and relief-dose methods stand in marked contrast. So do their effectiveness and safety.

The conventional skin testing system (which exclusively or predominately utilizes prick testing) provides no information concerning what is the safe, effective, or maximum tolerated dose, neither for any one antigen nor for the combined immunotherapeutic antigen mixture. Furthermore, conventional immunotherapy does not yet include foods. Therefore, the conventional system usually mixes all the inhalant allergens together in equal or "guesstimated" quantities to form the immunotherapeutic solution. Some physicians do divide the solution into two or more separate solutions, but the separation is arbitrary and is usually based on antigen class (e.g. dust mites, molds, epidermals, or pollens), rather than on the precise degree of sensitivity to the *individual* antigens (which is not revealed by conventional testing).

The next step in conventional immunotherapy is to give increasingly stronger subcutaneously administered injections of this solution or solutions. This buries the solution beneath the surface of the skin where the *first* overdose, that is, the first positive, pro-inflammatory, mediator-releasing or cytokine-releasing reaction, is not visible. Therefore, the conventional system is unable to reveal the effective anti-inflammatory turn-off dose, which is one dilution weaker than the turn-on dose, which can provide rapid safe relief.

This imprecision is further compounded by the fact that patients often have markedly different degrees of sensitivities, that is, non-tolerances, to different allergens. Their maximum tolerated safe dose for one dust mite may be ten times less than for the other dust mite; for alternaria mold, tolerance may be a hundred times less; for grass it may be a thousand times less; for ragweed, it may be ten thousand times less, etc. In such instances, when the injections of the mixed immunotherapeutic solution are gradually increased over months or years to find the maximum tolerated dose, the patient may have a severe reaction to ragweed or grass, and possibly to alternaria as well, long before reaching an effective dose for either of the dust mites. Persistently increasing the dosage to reach some arbitrary physician-designed dosage level (rather than a patient-focused symptom relieving level) or to stimulate an IgG blocking antibody response (which does not predictably occur nor often correlate with relief anyway) can lead to a tragedy.

By contrast, the relief-dose system determines, by intradermal testing, the precise, accurate, safe, effective, reliable, repeatable, objectively verified, anti-inflammatory, mediator/cytokine turn-off relief dose for *each* allergen separately and individually. The final immunotherapeutic solution contains the best possible dose of each *individual* allergen. It cannot get any better. I have called this dose the Goldilocks' dose because, like the baby bear's porridge, "this dose is *just right*."

Thus, the strongest negative wheal concentration is the true maximum tolerated concentration, the gold standard long sought by allergists the world over and finally found. Any intradermally administered concentration stronger than this would produce

either a visible positive wheal or symptoms, or both. The relieving concentration produces *neither* – it is virtually always *completely* tolerated. When given intradermally, it does *not* produce a positive wheal, and it *relieves*, not provokes symptoms.

When administered subcutaneously in immunotherapy, it not only produces essentially no local or systemic reactions, but also relieves the patient from ongoing current symptoms, often within minutes or hours. When given on a regular immunotherapeutic schedule, it usually provides a much greater measure of protection from allergenic inhalants (and foods as well), and with much greater safety and reliability, than does conventional immunotherapy. However, since asthma is more complex than allergic rhinitis or other allergy syndromes, immunotherapy for asthma must often be supplemented by anti-inflammatory, bronchodilator, antibiotic, or other types of medications.

With relief-dose therapy, no build-up of dosage is necessary or desirable. The best dose has already been determined by intradermal testing. The first treatment injection contains the full, safe, effective maintenance dose for each individual antigen.

Rapid real-life effectiveness is confirmed by the fact that 55% of a group of patients are already noting some improvement before they even finish testing all their allergens. If treatment injections are taken daily at first, 93% report marked improvement within two weeks. This rapidity of response contrasts with conventional response, which is usually of lesser degree and lesser incidence, and measured over years rather than weeks.

With relief dose immunotherapy, even more rapid response can be obtained at the outset by administering several injections daily the first two or three days. Thus, the onset of marked relief can be brought forward to a few days rather than weeks and without side effects. How favorably this compares with conventional “rush” immunotherapy, which is usually accompanied by an unacceptable number of uncomfortable and life-threatening events such as acute generalized urticaria, laryngeal edema, asthma, and anaphylaxis? It is of interest to note that in the United Kingdom, allergen injection immunotherapy for the treatment of IgE-mediated disease has been largely discontinued following the recommendations of the Committee on Safety of Medicines[1]. Concerned with the number of deaths from severe bronchospasm and anaphylaxis, the CSM recommended that injections should be given only where facilities for full cardio respiratory resuscitation are immediately available. This is in contrast to the relief-dose system, which entails far less risk.

The Maberly/Anthony study objectively confirms that food sensitivities contribute significantly to the production of asthma attacks in some patients, and suggests that they may be much more common triggers than previously reported. Secondly, most of their patients were sensitive to a larger number of foods than commonly supposed to be the case. Both findings agree with my own observations. The same is true of chemicals, which are entirely ignored in conventional immunotherapy.

This study should alert physicians to the need to increase their index of suspicion concerning foods and chemicals in the overall management program and to consider the relief-dose system of testing and immunotherapy for safer and more effective management.

[1] CSM update. Desensitizing vaccines. Brit Med J 1986; 293: 948