Management of Environmental Diseases A Current Approach to Inhalant, Food and Chemical Sensitivities

Their Investigation and Management

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Today it is apparent that the long-maintained concept that allergy is only due to the classic allergens (house-dust, mites, pollens, etc.) is far too restrictive to explain the range of sensitivity diseases now being recognized. Thus, the spectrum of environmental antigens is more vast than heretofore realized. Not only is food now accepted as an important causative agent, but the huge range of chemicals present in air, food and water to which man is continuously exposed is, from clinical observations, undoubtedly causing allergy problems.

Clinical ecologists, interested in the total allergenic load to which a person is subjected, consider it important to identify allergens of even low sensitizability when these are amenable to immunotherapy. At least such allergens can be counteracted, whereas many environmental allergens cannot be treated by immunotherapy. In the past, the only approach to environmental allergens, especially foods and chemicals, has been elimination (avoidance), but currently their effect is counteracted by neutralization (symptom relieving) guttae.

MAST CELL MEDIATOR RELEASE

A basic understanding of the mechanisms controlling the release of mediators from mast cells is essential for understanding the current views on allergy, especially in the environmental field. Until recently allergy was considered to be caused by IgE antibodies acting on mast cells, causing immediate hypersensitivity.

The presence of such IgE disease is usually shown by raised IgE levels in the serum, by specific responses in RAST, by skin tests and by a definite history, both personal and familial. However, in addition to the effects of IgE, mast cells release their mediators by mechnisms due to IgG4, to immune complexes in Type III Gell and Coombs reactions leading to split products of complement (C3a and C5a), and to lymphokines in Type IV Gell and Coombs reactions.

It must be realized that these mediators (histamine, SRS-A, PAF, EFC-A and serotonin) will cause identical clinical pictures (rhinitis, asthma and dermatitis) by whatever method they are released.

Vasculitis is a common result of Type III disease; it is suggested by oedema, especially of the eylids; acne; bruisings of unexplained origin; arthritic and myalgic pains; mood swings; cerebration problems; headache; and general, low-grade ill health. The spectrum of primary vasculitis[1] includes the PAN group, Wegener's granulomatosis, temporal arteritis (giant cell arteritis), hypersensitivity vasculitis, and Buerger's disease. As both the nose and ears can be initial sites of vasculitis, the otolaryngologist is often the first person from whom advice is sought in the early stages.

Investigations giving supporting evidence include histological changes in a nasal biopsy, the presence of immune complexes (C1q and RAJI cell), a raised ESR and a differential white-cell count with lymphopenia, especially if less than 1,000/mm.[3] Ideally, the T cells and their subsets (helper and suppressor cells) should be counted, the normal ratio being seven helper cells to three suppressor cells. At this stage, differential counts of T cells cannot be readily made, nor can the Frick test for Type-IV-mediated reactions[2] be used; the latter depend on the stimulation of lymphocytes resulting in blastogenesis.

Mast cells are now known to reside on, and not only in, respiratory mucosal surfaces. Certain nonimmunological agents can cause the release of their mediators in a "twitchy" or hyper-reactive lining. Such factors include viral infection, temperature changes, physical exertion and emotional stress.

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Recognition of Inhalant Allergens by Serial Dilution Endpoint Titration

In the past, there had been no trouble in defining the IgE-mediated reactions of the so-called inhalant allergens using the traditional epicutaneous tests (scratch and prick). However, there has been criticism concerning the fact that such epicutaneous tests are not standardized. This problem has been overcome by Rinkel's Serial Dilution Endpoint Titration (SDET),[3] in which a series of 1:5 dilutions are injected intracutaneously in 0.01 ml doses of increasing strength. Inhalants, however, can also be involved in a non-IgE pathway as well as in the IgE mechanism.

As with any test there are certain disadvantages and advantages. Among the disadvantages is the fact that the SDET is relatively more time consuming and more expensive as regards materials than the epicutaneous tests. In addition, with the stronger dilutions used to test less sensitive people, there is a loss of specificity in relation to sensitivity, i.e., some pseudopositive results occur with stronger dilutions. However, the significance of such results may be checked by correlation with the patient's history and/or with the modified Nalebuff/Fadel RAST.[4] In the latter investigation, various classes have been designed to correlate with the SDET endpoints.

There has been great resistance from traditional allergists to the use of SDET and against immunotherapy based on SDET findings. However, on close analysis, criticism is found to be biased and unjust. There are really two main questions to be answered in resolving the confrontation.

The first concerns the validity of the SDET technique itself. Although Golbert[5] and Gieco[6] both maintain that the technique gives rise to many pseudo results (both positive and negative), the system nonetheless is frequently used by experimental immunologists in assessing their results. It is also recommended as the easiest and most reliable way to compare the potency of allergens from batch to batch or from manufacturer to manufacturer. The report by Norman, Lichenstein and Ishizaka,[7] in which there is a comparison of the results of RAST, SDET and the quantification of histamine released from basophils, shows that there is a very good correlation among all three. Kniker[8] has stressed that the endpoints 1 and 2 may be unreliable, thus requiring verification based on a clear-cut history or supporting RAST results. In the author's experience, this is undoubtedly true and applies especially to pollens but less to moulds.

The second and perhaps most important argument concerns the use of SDET in determining immunotherapy dosage. Traditionalists point to numerous papers based on double-blind studies involving ragweed hyposensitization (such papers include those by Van Metre, et al[9] and Hirsch, et al.[10]). However, these papers all incorporate a gross misrepresentation of Rinkel's teachings, claiming that he considered maintenance therapy always to be based on the so-called 50x dose (x being 0.01 ml of the endpoint dilution as determined by SDET). However, Rinkel[3] stated that the main purpose of SDET is to determine a safe, effective starting dose once treatment is started; the maintenance dose is not an empirical amount as it must be determined by clinical response. In certain cases, one may need to give a 1,000x or larger dose. This is especially necessary when the endpoint is at 6 to 8 uncommon findings. Usually, endpoints range from 2 to 4; then a 50x dose is often adequate. The final proof that immunotherapy is effective when based on SDET and given in adequate dosage is to be found in Kniker's recent article[11] on a double-blind study involving the use of Mountain Cedar pollen.

SDET has many advantages, which may be enumerated as follows:

1. It gives a safe, effective starting dose.
2. Between multiple allergens of varying endpoint strength, the appropriate dosage for, and the balance between, each allergen is maintained at all times.
3. It is the only standardized skin testing technique.
4. Coseasonal treatment may be given without problems.
5. Flash reactions[3] are detectable only with SDET. Such reactions include excessive response to an antigen whether it be given by scratch, prick or intracutaneously, but not exhibited on a repeat test after some time (usually 24 hours).
6. It is essential in the calculation of sublingual guttae, either for treatment or testing.
7. As with any intracutaneous test, it will reveal IgG4 reactions, which are not detected by epicutaneous tests.[12] Again, delayed reactions may suggest possible Type III and Type IV reactions.

Recognition of Food Intolerance and Its Management – the Provocation/Neutralization Test

Rinkel's Cyclic Theory

When food reactions are IgE-mediated (embracing approximately 20 per cent of the cases), they may be identified by history, food diary, intracutaneous food screen and RAST. When food reactions are not IgE-mediated, they may be identified by using Lee's Provocation/Neutralization tests.[13] These are performed initially by administering intracutaneously 0.05 ml of a strong dilution (1:100) to provoke symptoms after which successively weaker 1:5 dilutions are administered until the symptoms are eliminated by one particular dilution (the neutralizing dose). Such tests may also be carried out using sublingual methods[14] or subcutaneous methods.[15]

According to Rinkel,[16] food sensitivity mechanisms may be divided

into two groups. There is the so-called "fixed" food reaction, which is an IgE-mediated type. Applied to food, it invariably produces the same reaction no matter how long the interval since food was last eaten. Fixed food sensitivities represent about 5 per cent of the total number of food reactions. The remaining 95 per cent of food reactions are dynamic types which depend on continued exposure to certain types of food. This is called the "cyclic" reaction since the degree of intolerance to a food will depend on the frequency of its consumption. If the food is avoided for some weeks or months, tolerance returns. But, after only four to 10 days of abstinence, sensitivity reaches the maximum level. For this reason, oral challenge testing (which is aimed at enabling a physician to make a diagnosis but not to assess a treatment dosage), is performed after avoidance of the particular food for four days. On the other hand, in carrying out a provocative test for a certain type of food with the object of determining a neutralizing dose whether by sublingual, intracutaneous or subcutaneous means, it is imperative that the food be kept in the diet immediately before testing. The reason for this is that, when a treatment dosage is being assessed, one needs to know the reactivity at the usual everyday level and not at the hypersensitivity level.

Randolph's Adaptation Theory

Randolph[17] has modified Rinkel's ideas; he considers cyclic reactivity to be akin to a drug addiction. The effect of the food is biphasic, i.e., immediately following the ingestion of an addictive food, there is a stimulatory phase (this is the same as the "high" which a drug addict feels after the ingestion of his addicting drug). However, this phase is followed by a second or "withdrawal" phase during which the subject reaches a point when he must ingest the food again (i.e., take another "fix"). The periodicity of the phases varies usually from a few hours to perhaps a few days (it takes at least four days for the body to eliminate a food by fasting). Such people often experience insomnia, which can only be relieved by "refrigerator raiding" during the middle of the night. A great paradox to the food addict is the realization that although the food makes him "feel good", it actually is his enemy.

Probably most of us have some degree of food allergy, especially to common foods such as cereals, tea, sugar and yeast. However, we do not manifest problems because we remain "adapted". People exhibiting a problem, however, have passed into the "maladapted" stage. This concept is supported by the well-known physical experiments of Selye[18] who exposed a series of rats to intense cold for an indefinite period. Initially, each rat was shocked. Soon, however, each became adapted to the cold, settling down to an apparently normal existence. Suddenly and unexpectedly, one of the rats died; soon afterwards all the others died as well. Their metabolic responses had reached a stage of exhaustion and they could no longer cope with the stress, thereby becoming maladapted.

Randolph considers that man adapts similarly to all his life stresses; finally, with an increasing load, his adaptive abilities fail. This is heralded by the onset of an illness which rightly can be regarded as ecological. Another important concept is that the susceptibility to breakdown is a highly individual matter – only certain persons succumb to overexposure to certain antigens. This point separates ecological from toxicological illness, the latter having uniform effects on all exposed people. Another feature that distinguishes between sensitivity and toxicity is the fact that ecological illness gives manifestations at ambient concentrations which are within accepted standard levels of safety. The history of "growing out of an allergy" to milk, for example, is an excellent show of adaptation. Thus, an infant who initially cannot tolerate cow's milk (stage of shock) within a few years apparently is able to ingest it without ill effect (stage of adaptation). However, many of these individuals when undergoing provocation tests still manifest their latent sensitivity. Later in life, they may again reach a stage of maladaptation if exposed excessively.

Interestingly, a common observation is that a food that is disliked and refused by a child is frequently an allergen. Many children are castigated for refusing to eat certain foods when nature is telling them to avoid these items. An example is the marked tendency of infants sensitive to cow's milk to limit or even refuse such milk products in later life.

Management of Food Intolerance

Food intolerance can usually be managed by elimination of the offending product from the diet; however, if this is impossible, then a diet rotation is instigated in which the food is eaten not more frequently than once every five days. After elimination of cyclic food allergens for a sufficient period of time, tolerance is acquired. Foods can then be re-introduced on a trial basis, using the rotation five-day interval.

The definite validation of intracutaneous neutralization with food extracts (yet to be published, but available on tape) has recently been described by two speakers,* in a study undertaken by William Rea's group at Dallas. While there are

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* *(1) Podell R. Double-blind evaluation of effectiveness of neutralization treatment with a food extract. Paper presented at the Society of Clinical Allergy 16th Advanced Seminar, Banff, October 1982.*

(2) Sprague DE. Double-blind evaluation of effectiveness of neutralization in response to a food challenge. Paper presented at the Pan-American Allergy Society Annual Meeting, San Antonio, March 1983.

many anecdotal accounts indicating the validity of neutralization techniques, there are increasing numbers of double-blind studies which cannot be ignored (Rapp,[19] Millar,[20] King,[21] O'Shea, et al.[22]). In very difficult cases involving large numbers of reactive foods, neutralization therapy, in the form of injections or sublingual guttae, is administered before food is taken in order to enable the patient to maintain an adequate level of nutrition. This also provides a method for overcoming social embarrassment when faced with eating nontolerated foods outside the home. Nutrition is extremely important and may be a source of great concern to the patient. There are dieticians who now understand the requirements of rotation or elimination and who can satisfactorily arrange adequate diets with the aid of computerization.

The Chemical Environment and Its Management

Undoubtedly, the atmosphere today is extremely polluted with chemicals. Confirmation of this may be made by noting the tremendous damage to famous marble statues of the Old World; such damage has required their removal to a safer environment. These inanimate objects have no adaptive powers compared with living creatures which survive by adaptation of varying degrees, depending on individual susceptibility.

Chemicals are also identified by provocative-neutralization tests, which are usually applied sublingually. The same 1:5 dilutions (in series), as is used in SDET, are employed.

Chemicals are multitudinous, reaching man through the air he breathes and the food and water he consumes; it is not possible to test all substances to which a person is exposed. Fortunately, there are several basic chemicals commonly present in most commercial products that have been identified as potential excitants; these can be tested for and treated against, if necessary. Such basic chemicals include (1) phenol (the basis of plastics, perfumes and disinfectants); (2) formaldehyde (present as a "dressing" or "permi-press" agent in fabrics; it is also present in tobacco smoke, in roof insulation materials; in glues and resins of particleboard and chipboard, in disinfectants, deodorants, perfumes, news print and pesticides as well as wood preservatives such as pentachloraphenol; (3) chlorine (in halogenated pesticides and swimming pool purifiers); (4) ethanol (a petrochemical product found in many substances, e.g., automobile exhaust fumes, diesel fumes and perfumes).

The average home is the greatest source of chemical exposure for most individuals. If one has a problem with chemicals, he must create an "oasis", especially in the bedroom, that is free from such excitants. This will entail, amongst other things, the following measures:

1. Replace all gas units in the house with electrical heaters and cookers.
2. Remove all new carpets, especially if these contain nylon fabric and are rubberbacked.
3. Avoid the use of or contact with all pesticides and wood preservatives.
4. Cotton clothing and blankets should be used as well as iron-framed beds with innerspring mattresses.
5. No cosmetics, especially perfumes, hair sprays and after-shave lotions should be used.
6. Use air filters and ionizers.
7. Use aluminium foil or ceramic tiles to cover walls; stone for ceilings or walls, parquetry, glass and steel may also be utilized.
8. No insulating materials should be used in the roof.

Since commercially grown food has almost invariably been sprayed with various pesticides, a patient should try to eat less chemically contaminated food. Also with regard to food, it should be remembered that additives, preservatives (SO_2, benzoates, sorbates, metabisulphite, nitrites, BHA, BHT), colouring materials (F & C dyes) and flavourings (MSG) are all chemicals.

Water is also a potent, occult cause of problems in highly sensitive patients. The use of water filters frequently removes chlorine and other chemicals, but fluoride can only be removed by a special process.

An excellent method of investigating such a difficult "ecological patient" is the ECU (Environmental Control Unit), in which the patient is cleared of both inhaled and ingested pollutants. This is achieved by filtering the air, while other possible chemical contaminants are eliminated as described in the home oasis; the consumption of tap water is prohibited, with either a variety of mineral waters being offered instead to the patient, or a 'safe' water being identified. It is necessary that such a patient fast for five days in order to clear the alimentary canal. Basic observations such as pulse rate, urinary output, weight, sleep patterns, demeanour, subsidence of food demands and clearance of presenting symptoms are closely monitored features for assessing the symptom clearing response. Important objective evidence of reaction to tests and response to treatment are obtained by measurement of reaction time, blood sugar levels, hand writing and joint swelling.

Feeding with commercially grown food, one type at a time, four times daily, is undertaken. The patient is observed in order to identify safe, non-reactive foods. After several days, the patient is also subjected to chemical tests in a steel and glass "telephone booth"-type unit and again observed for reactions. By employing such procedures, food and chemical intolerances are revealed. At all times during testing, whether it is an ECU or an office unit, placeboes are included in the tests. One of objec-

tives of ecological management is to limit the administration of drugs to the absolute minimum, as they themselves contain all manner of chemicals. However, it is not always possible to avoid limited pharmacological support.

SUBLINGUAL THERAPY

The use of sublingual guttae therapy is controversial. However, all acknowledge that many drugs administered sublingually are effective. Evidence supporting antigenic absorption has been established by Pepys and Mackarness (personal communication) in a P-K type experiment. Several subjects were injected intracutaneously with serum from a peanut-sensitive patient; none of the recipients was sensitive. Following the administration of a peanut extract under the tongue of each recipient some hours later, definite erythema occurred at the site of the injection. The author has also found significant improvement in the clinical status of 46 patients after a two-year period of sublingual therapy with a marked lowering of total IgE levels (greater than 25 per cent in 82 per cent of the patients). The administration of an antigen using the sublingual route is very acceptable to most people, especially children, who can be treated according to the Nalebuff/ Fadel RAST scores.

In conclusion, the function of the clinical ecologist is to attempt to identify the inhalants, foods and chemicals causing disease due to maladaptation by the methods previously detailed. Troublesome inhalants, if IgE-mediated, are treated by immunotherapy if avoidance is not possible. The purpose is to reduce the total allergenic load and thereby indirectly counter the chemical load which is often difficult to nullify in everyday living. Troublesome foods, chemicals and even inhalants when non-IgE-mediated can be managed by provocation and neutralization methods when avoidance is not possible.

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