case report

ENZYME POTENTIATED HYPOSENSITIZATION: V. FIVE CASE REPORTS OF PATIENTS WITH ACUTE FOOD ALLERGY

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Introduction

ENZYME POTENTIATED hyposensitization has been developed from Popper's clinical observation that some, but not all, batches of commercially prepared hyaluronidase could modify hay fever.[5]

The first four papers in this series described the work carried out in this laboratory in order to reproduce the initial chance result in a controlled fashion.[1,2,3,4] Early in this program β glucuronidase was found to be the active agent which potentiated hyposensitization[6] and, while this work has progressed, it has usually been possible to select batches of β glucuronidase which were effective without modification for use in clinical hyposensitization.

The following case reports of patients who have been successfully hyposensitized to foods seem sufficiently objective and interesting to warrant publication at this stage.

Method

The method of treatment and the formulation of β glucuronidase, 1,3, cyclohexane diol, protamine, hyaluronidase, chondroitin sulphate and buffer which is now considered optimal is described in the preceding paper.[4]

The new formulation has only been in use during 1974 and early hyposensitizing formulations employed batches of β glucuronidase which were found to be effective by empirical trial in the clinic. At an intermediate stage N-acetylglucosamine and glucose were both added to the formulation at concentrations of 0.1 mg/ml just before it was applied to the patient.

Food antigens were originally used as simple extracts in Coca's solution[7] but for the improved formulations the extracts have been passed through a gel-diffusion column. Details: Bio Gel P 6. 100 - 200 mesh. Bio Rad Labs. (Exclusion limit 6,000). Column 100 cm x 2.6 cm diameter. Buffer: Per liter distilled water: Na Cl 2.0 gm. K Cl 4.0 gm. Mg SO_4 0.06 gm. Ca Cl_2 0.18 gm. Na Acetate 0.4 gm. pH adjusted to 5.9 with H Cl. Flow approx 60 ml/hr. Void volume 140 - 150 ml. Antigens applied in volumes up to 20 ml.

(100,000 noon units of each antigen required). Collect void to 100 ml. Column stored in azide and protected by 0.45 μ pore size "millipore" filter traps. Prior to use Bovine Serum Albumin (Armour) 200 mg in 10 ml buffer is applied to the column, which is then washed with 1.5 liters of buffer. Extracts from the column (now at 1,000 Noon units/ml) are sterilized by 0.22 μ millipore filtration and stored at +4°C.

In the present clinical formulation food antigens are added to three successive monthly treatments at doses of 0.1, 1.0 and 10 Noon units. For patients with delayed-type food sensitivity the first dose can be omitted. Maintenance doses at four monthly intervals usually contain 10 units of food antigens. A small proportion of patients react adversely to the 10-unit dose. After a few months interval, retreatment with 1 unit of food antigen will produce a further remission and maintenance with the same dose of antigen will be adequate.

Case Reports

Patient 1

A woman of 56 years presented in January, 1971, with a one-year history of swelling of the mouth and throat as soon as traces of egg were eaten. Cakes caused mild irritation of the lips and if she cooked with eggs her hands were irritated. Prick tests were strongly positive for egg yolk and white.

The patient was treated with three doses of enzyme potentiated hyposensitization at monthly intervals using 0.1,1.0 and 10 units of whole egg antigen. After this she was able to eat omelette, scrambled egg and hard boiled eggs with impunity but she has never been able to eat soft-boiled eggs.

Since the spring of 1971, 11 boosting doses have been given, normally at four-month intervals (time of writing is January, 1975). The third desensitizing treatment produced transient local urticaria on the forearm after 24 hours. One of the later boosting doses also caused local swelling. Otherwise treatment has provoked no side effects. Skin tests for egg remain positive.

Patient 2

A 30-year-old train driver presented in April, 1970, with a history of perennial rhinitis and asthma since childhood. In addition he suffered from egg sensitivity, which was sufficiently acute to cause tingling of the tongue and a "rough" sensation in the throat if he took a bite of spongecake. Chicken meat and fresh milk provoked similar symptoms. Milk in tea provoked slight symptoms in mouth and throat but caused asthma in less than 30 minutes. Beer also caused asthma.

Skin tests were strongly positive to egg yolk and white and milk, weakly positive to cheese and yeast. There was also a strongly positive skin test to budgerigar, the patient had one in his house which he knew provoked symptoms and his rhinitis and asthma improved slightly after the pet was removed

Enzyme potentiated hyposensitization was started in May, 1971, using 1 Noon unit of egg, milk and yeast. Inhalant antigens were included in the doses. After the third dose, when 100 units of foods and inhalants had been given, the patient's asthma stopped and has never recurred. Chicken and beer no longer caused reactions but milk and egg hyposensitization had only caused a slight increase in the quantities of these foods which could be eaten without provoking symptoms. Nevertheless hyposensitizing treatment was continued and the milk sensitivity improved steadily. Egg sensitivity suddenly decreased after the 11th treatment in September, 1973, since when the patient has been able to eat everything except raw eggs and

a large quantity of fresh milk.

Maintenance desensitization continues to be given three times per year. Skin tests, repeated in 1974, are unchanged in spite of the altered clinical state. The treatment produced no side effects at any stage.

Patient 3

A boy presented in 1969 at the age of 15 with a history of six attacks of facial edema in the previous year caused by eating fruit. Apples, pears, peaches and raisins had all precipitated attacks. His gums would ache while the food was being eaten, then edema would appear extending from lips to eyelids. In one attack the boy's throat had become "tight."

Enzyme potentiated hyposensitization was started with mixed nut antigen (containing almond, brazil, walnut, peanut and coconut extracts) in doses of 0.1, 1.0, 10, 100 and 1000 Noon units at monthly intervals. There were no reactions. After the 100-unit dose the lad was able to eat apples freely, but he relapsed two months after the 1000-unit dose, and seven boosting doses in the course of the next 14 months were necessary before it became possible to reduce the frequency of maintenance treatment to the usual four-month intervals.

After a further year the patient left home to start work and was unable to return to the clinic for regular treatment. Six months later the food sensitivity returned. The patient is now a married man. He has recently contacted the clinic again. His food sensitivity persists and he would like to re-start enzyme potentiated hyposensitization.

Patient 4

This patient, a girl aged 18 years, was first seen in August, 1969, complaining of immediate irritation and swelling of the lips and mouth caused by contact with eggs, milk and many varieties of fruit and nuts, especially apples, plums and peanuts. These symptoms had started 10 years previously. Peanut sensitivity was so acute that the girl would sneeze if there was a bowl of them in the same room. If her boyfriend ate peanuts at lunch time and kissed her in the evening, her lips would swell.

Skin tests were strongly positive to milk and peanut, negative to egg.

Enzyme potentiated hyposensitization was started with 0.01 units of mixed nut extract plus 1.0 units of egg and milk. Twenty hours later the patient suffered a typical migraine attack which lasted for two hours after a short visual prodrome. She had not previously suffered from migraine. In view of this the same dosage was given for the second hyposensitization one month later.

At this stage a minor surgical problem prevented the patient's return and she did not come to the allergy clinic again until March, 1970. She then reported that since September she had been able to eat everything without symptoms except peanuts.

During the next few months bilateral nasal polyps appeared and the patient lost her sense of smell. She continued a normal diet, excluding only peanuts. By April, 1971, five further doses of enzyme potentiated hyposensitization had been given using 1.0 unit of all food antigens. The polyps had disappeared and the sense of smell had returned.

Two further treatments at four-month intervals were given in 1971 but then the patient did not return for six months. When she did, she reported that she had become wheezy after an attack of bronchitis a month previously. She was now married, taking an oral contraceptive and she had become depressed. There was no recurrence of her polyps and she was still eating a full diet.

Two boosting hyposensitizations to foods had no effect on the patient's wheezing and when last seen in October, 1972, she had developed a new immediate-type sensitivity to cheese. At this time she was still using an oral contraceptive and was severely depressed. She declined further investigation and treatment.

Patient 5

This man, a senior civil servant now aged 57, has been treated by injections for his hay fever with moderate success since 1950. In 1965 he volunteered the information that drinking small quantities of milk gave him diarrhea. As a demonstration he drank a glass of milk. The specimen of stool he passed 24 hours later was rejected by the laboratory staff because it resembled urine. When reassured, they reported, "Turbid watery fluid containing a little mucus. Microscopy: Moderate number of neutraphils with scanty eosinophils. A few R.B.C.s." Skin tests to milk were negative.

In 1967 the patient's sensitivity to milk was unchanged, so he received three monthly doses of enzyme potentiated hyposensitization with 10, 100, and 1000 units of milk extract. Thereafter he could drink milk in unlimited quantities and has continued to do so. On two occasions maintenance treatment has been suspended until the first sign of relapse. The first interval was 19 months, the second only 13 months.

At the first relapse (in winter) the gradual recurrence of diarrhea was accompanied by the appearance of nasal polyps. For convenience, these were removed and have not recurred. It is now considered preferable to give this patient a boosting hyposensitization every six months. A total of 17 doses have been given in eight years. The patient has preferred to continue the long-established, pre-seasonal courses of injections for his hay fever and there was no need to dissuade him.

Discussion

Enzyme potentiated hyposensitization has been developed from a clinical procedure which was initially successful.[6] By 1967 a blind trial had already shown a statistically significant result: the method was used to treat hay fever patients and the effect was evaluated by intranasal provocation with grass pollen extract. These results were never published because it soon became obvious that many batches of β glucuronidase would not potentiate hyposensitization.

Animal experiments were undertaken in order to overcome this problem and the findings have been published.[1,2,3,4] The subsequent development of a formulation of β glucuronidase suitable for clinical use was carried out in trials with hay fever patients, the effects of treatment again assessed "blind" by intranasal provocation. These results have also been published.[3,4]

Throughout the time which has elapsed since 1966 it has been possible to find batches of commercially produced β glucuronidase which were effective hyposensitizing agents by empirical testing in the clinic. By this means maintenance treatment has been available when required to the many patients who were successfully hyposensitized in the first 18 months of work. Since then patients treated during trials have also been offered maintenance, and it has been impossible to refuse the hyposensitizing treatment to the many other severely ill patients who have been referred to the clinic.

As a result more than 2,000 patients have been treated by enzyme potentiated hyposensitization and more than 10,000 doses have been given. Follow-up has been as exhaustive as possible. This has established the safety of the new method of hyposensitization and

also its efficacy in a wide variety of clinical conditions which in the past could only be treated by palliative drugs or surgery. Nevertheless this experience has been gained using suboptimal formulations of β glucuronidase and formal clinical trials would have been premature.

The patients referred to in this paper were treated during this time but it is opportune to publish this account now for two reasons. Firstly because the effectiveness and safety of enzyme potentiated hyposensitization in these cases illustrate how the method will extend the therapeutic capability of the allergist. Secondly because the effects of hyposensitization in patients with acute food allergy are sufficiently objective to make a placebo group superfluous.

The first four patients discussed in this paper would develop tingling and swelling of their lips and tongues immediately they made contact with small particles of the foods to which they were allergic. These reactions would start so quickly that the patients rarely swallowed any of the offending foods. It is generally acknowledged that in such patients attempts at hyposensitization by injections of food extracts may be dangerous. The value of enzyme potentiated hyposensitization is demonstrated by the fact that all these patients were enabled to eat foods which previously upset them. This was achieved by a relatively small number of out-patient treatments which caused no troublesome reactions. (In the interests of safety it should be pointed out that patients known to develop anaphylaxis after prick testing to foods have not been included in this series.)

The fifth patient described suffered from a colitic reaction to milk. The immediacy and viciousness of the reaction were unusual. The patient had recognized quickly that milk provoked his symptoms. The severe disease which would have developed had he been of lesser intelligence might have resembled ulcerative colitis, a condition which can be provoked by hypersensitivity to milk.[8]

Maintenance treatment is often unnecessary but was continued for each of the patients described here in the form of one further hyposensitizing dose every four months. In this series, the shortest total period of treatment was 24 months, the longest eight years. Only one patient has been followed up for fewer than four years.

The mechanism by which hyposensitization has been produced in these patients is still uncertain and work on this question will be undertaken. Nevertheless, whatever the immunological mechanism involved, enzyme potentiated hyposensitization has already shown itself to be an effective form of therapy. Its immediate safety is greater than that of conventional hyposensitizing injections and after nine years of use there have been no unwanted long-term effects.

Two of the patients reported here developed nasal polyps when they ate foods ad lib, to which they had previously been severely hypersensitive, but at times when their enzyme potentiated hyposensitization needed boosting. The later disappearance of the polyps in patient 4 should dispel the idea that enzyme potentiated hyposensitization caused them. It is a pity that patient 5 elected to have an operation without giving his polyps a chance to shrink with further hyposensitization. Nevertheless these cases nicely illustrate the role of food hypersensitivity in the aetiology of nasal polyposis.

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TEN YEARS FROM NOW

"These ten years will be filled with opportunities and challenges that can only be hinted at. We are at the frontier, for example, of a new age of personal health and medicine. We will find ourselves in the paradox that as the age of effective man is lengthened and his energy and wisdom increased, the retirement age gets lower and lower. It may be in this reservoir that selling in America will find its ultimate answer for effective manpower to meet this awesome challenge.

"Within these ten years the wide variety of new drugs will increase the capacity of everyone. The antibiotics have already killed infection; the cortisones will smash fatigue and the relaxers will suppress anxiety, but only man can create purpose. And it is the search for purpose which will be the ultimate goal of this incredible new enterprise."

Leo Clerne
Ten Years from Today. November, 1956