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ALLERGIC DESENSITIZATION BY THE INTRADERMAL ROUTE

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The subcutaneous route is and has been used almost universally for the past 50 years for the administration of pollen and other extracts in allergic desensitization procedures. The intradermal* method, however, is the one almost exclusively used in South Africa.

Following upon my recent description[1] of patients who are sensitive to bee stings, in whom effective desensitization had been achieved by the use of gradually increasing strengths of whole bee extract administered by the intradermal route, I have received numerous enquiries for details of this method. It is aimed here to describe the principles, procedures and techniques involved and, not the least, to make better known the advantages of this eminently satisfactory and safe method of desensitization.

There is considerable experimental and clinical justification for immunization *via* the skin. According to Kahn[2] the antigen-localizing capability of the cutaneous tissue is approximately 10 times as great as that of skeletal muscle and is evidently a highly important defensive mechanism against micro-organisms; furthermore, the skin has a reaction-capacity for allergens above that of most other tissues.[3] Rappaport[5] referred to the many authenticated experiments which emphasized the importance of the skin as an active immunologic organ and was of the opinion that the skin of atopic patients contains specific reaginic antibodies in all epidermal cells. Tuft[6] thought that the skin was an extremely important immunologic organ participating very actively in antibody production and that, in certain infectious diseases (small-pox, chicken-pox, measles, and scarlet fever), cutaneous antibody formation was the means by which immunization of the whole body was brought about. He explained the marked antibody response which he uniformly obtained with the intradermal administration of mixed typhoid vaccines as resulting from a local tissue stimulation of the cells of the reticulo-endothelial system, which were particularly abundant in the skin, and, in part also, to a slower absorption of antigen which allowed for local fixation of a larger amount of antigen —and thus for a greater local stimulation of antibodies. In a review of the evidence for the immunologic importance of the skin, Sulzberger[7] concluded that the skin was probably the organ principally concerned in the mechanism of immunologic protection and of allergic alteration. Walzer[8] also regarded the skin as one of the most valuable organs of the body in its immunizing properties. Müller and Corbitt[10] showed that the effect of insulin injections upon the blood-sugar content of the normal rabbit varied with the route of administration and was markedly increased by the employment of the intradermal route. They thought that the degree and period of effectiveness did not depend upon the rapidity of resorption, but upon a hitherto unknown factor which was probably related to the action of the involuntary nervous system—a property seemingly inherent in the skin rather than in the subcutaneous tissue or in the body fluids. Elaborating on this 'special function' of the skin, they pointed out that 0·1 ml. of aolan, a non-specific lactalbumin preparation, was an effective stimulant of the involuntary nervous system if given intradermally, but that no measurable change occurred in the organs controlled by this system after the administration of the same quantity of this agent by other routes. Smith[11] described the intradermal injection as essentially an intralymphatic injection which produced effective antigenic stimulation of the lymph node, an easily accessible and clinically useful site.

The use of the intradermal route for purposes of immunization has been frequently reported in connection with the administration of a variety of antigenic substances—diphtheria,[12,13] scarlet fever,[14,15] mumps,[16] typhoid fever,[17-19] influenza,[20-26] tetanus,[27] poliomyelitis,[28] and rabies.[29]

The beginnings of desensitization *via* the skin are seen in the work of Le Noir *et al.*[30] who reported 5 instances of sensitization to certain foods in which the application of the specific substance to the skin induced a general anaphylactic reaction either immediately or after an interval of 1—24 hours. This suggested to them the possibility of accomplishing desensitization by repeatedly eliciting the skin reaction. Similarly, Vallery-Radot and Blamoutier[31] held that the repeated application of minute quantities of the incriminated protein, merely for a *diagnostic* reaction, was a simple and harmless procedure for desensitizing against asthma, urticaria, and eczema. Thommen[9] noted a 'somewhat common experience'—that the acute symptoms of patients were often definitely alleviated as the result of the intradermal *tests* before any subcutaneous therapeutic injections were given.

Phillips[32] reported the relief† of hay fever by intradermal injections of pollen extracts. He based the use of this method on the fact that tuberculin and vaccine had been given intradermally and also that hay-fever patients benefited by intradermal pollen *tests*. He reported complete relief in 2 patients desensitized intradermally, one pre-seasonally and one co-seasonally; and from 1924 he systematically employed

* The terms 'intradermal' and 'intracutaneous' appear to be used synonymously in the literature; and, in this paper, either word will be used in relation to injections *into* the skin. In the references however, the quoted author's own terminology is adhered to.

† To most writers 'relief' implies control of symptoms in the pollen season by co-seasonal therapeutic desensitization. Sometimes the reference is to pre-seasonal prophylactic desensitization before the occurrence of symptoms, and sometimes this distinction is not made clear.

the intradermal method with 2 or 3 injections a week on about half the patients treated co-seasonally. Satisfactory results, which he described as 'monotonously successful' were obtained in more than 91% of the patients, the relief being usually experienced at or before the seventh day of treatment. He stated[33] that the special advantages of this method were the low dosage required and the promptness of relief of symptoms. Duke[34] tried Phillip's intradermal technique and obtained complete relief in a remarkably short space of time in every patient treated during the season. For this reason, and because the local superficial reaction permitted a ready decision upon the size and time for a subsequent dose, he thought that this would be the method of choice. Thommen[9] used the intradermal method of desensitization with results decidedly superior to those obtained by the subcutaneous method. Similarly, Anderson[4] obtained satisfactory desensitization in 84% of his patients. Waldbott and Ascher[35] found no difference in therapeutic response from either intradermal or subcutaneous injections, but conceded that the intradermal method was of greater service as a gauge for further treatment because of the more distinct appearance of the wheal. Hansel[36] summarized reports from physicians to the effect that satisfactory relief in hay fever could be obtained by the co-seasonal method of treatment given by the intracutaneous or subcutaneous route or by both routes. He recommended that whenever possible the co-seasonal type of therapy should be preceded by a series of about 10 injections, either intracutaneously or subcutaneously, before the onset of the season. Rockwell and Rockwell[37] thought that subcutaneous injections gave good results, but had the disadvantage that the amount of reaction was not always apparent until a too severe reaction had occurred, whereas the reaction from the intradermal injection, however slight, was always visible in patients with positive skin tests.

THE USE OF THE INTRADERMAL METHOD OF DESENSITIZATION IN SOUTH AFRICA

Seasonal Pollen Allergy

Investigations into the causes and treatment of seasonal hay fever in South Africa were originally carried out by Pirie,[38] formerly of this Institute. He initially employed and advised others to use the subcutaneous method of desensitization until the intradermal method of Phillips came to his notice, when he was impressed with the results in the cases on which this was tried. He thereafter advocated the intradermal desensitization technique for pre-seasonal desensitization in hay fever and favoured the scheme of a pre-seasonal course of intradermal injections followed by injections at 7—10-day intervals throughout the season. He confirmed the advantage that Phillips had claimed for this method and added that such treatment could be started at any time either before or during the hay-fever season; that reactions were clearly visible and easily gauged, and dosage could be suitably regulated by the reaction; and that a course of treatment was usually shorter, the results better, and the risk of aggravating hay fever or of giving an anaphylactic shock by overdosage was practically nil.

More than 20 years ago when I took charge of the Allergy Department of this Institute, I had to decide whether to recommend the intradermal method or to advise the adoption of the generally used subcutaneous method. After considerable clinical and laboratory investigations I concluded that the continuance of desensitization by the intradermal route, both prophylactically and therapeutically in hay fever, was fully justified, and I have accordingly fostered this method assiduously so that it is now, with few exceptions, the method employed in South Africa.

Seasonal pollinosis in South Africa[39] is almost entirely summer hay fever or asthma caused by grass pollen present in the atmosphere from October to March. The pollens of the compositae are sometimes clinically significant more especially in florists, gardeners, and others coming into close contact with plants of this group. Not infrequently trees (mainly plane, oak, and poplar) cause symptoms when they pollinate in spring (August—October), and occasional cases of cypress (*Cupressus* spp.) pollinosis[40] occur from May to October. Ragweed (*Ambrosieae* spp.) and other weeds of importance in the United States of America play no part in respiratory allergy in South Africa.

Experience over the years has amply confirmed the effectiveness of the intradermal method of prophylactic desensitization in pollen allergy. A recent analysis of answers to a questionnaire sent to physicians in the 'grasslands' of South Africa, where summer hay fever caused by grass pollen is common, revealed undoubted benefit to the great majority of the patients. In the control of manifestations of hay fever in the season, the method employed therapeutically has proved very satisfactory since symptoms are generally alleviated after relatively few (3—12) injections of grass-pollen extract. It is wise, therefore, to encourage desensitization in the season if the patient presents himself at that time.

Non-Seasonal Allergy

The procedures of desensitization by the intradermal route have been further studied and developed to the present stage where the employment of this route can now confidently be advised for prophylaxis in any allergic condition where desensitization is indicated. Intradermal desensitization is successfully carried out in non-seasonal respiratory allergic conditions with extracts of animal hairs, feathers, house dust, air-borne fungi and the other commoner substances responsible for symptoms. Such desensitization has also been accomplished in cases of sensitivity to the inhalation of dust from wood,[41,42] cereal grains[43] and lucerne,[44] and also to the effects of bee[1,45] and wasp stings.

THE SIGNIFICANT REACTION AS A GUIDE TO DESENSITIZATION BY THE INTRADERMAL ROUTE

Desensitization by the intradermal route becomes a simple matter if the principle is followed that the occurrence of a *significant* reaction after any injection implies that desensitization is proceeding.

A *significant* reaction is represented by a well-defined, clearly visible wheal, generally with pseudopodia, 1—2 cm. in diameter appearing 5—15 minutes after an intradermal injection.

In desensitizing by the intradermal route, therefore, the aim should be to obtain a *significant* reaction after each and every injection.

With this principle as a guide it is obvious that desensitization may be commenced at any time and under any circumstances provided that the dose (size/strength) of extract producing a significant reaction has been established for the patient. Thus, in pollen sensitivity pre-seasonal desensitization may safely be followed by co-seasonal desensitization

because the dose producing the significant reaction is known at the time. For the same reason desensitization may conveniently be commenced during the pollen season. Further, if for any reason perennial desensitization with 'maintenance doses' of extracts has been interrupted (e.g. the patient has left the district temporarily or has been suffering from an unrelated illness, etc.), it may readily be resumed at any time after once again determining the dose (size/strength) of extract now required to produce a significant reaction.

RECOMMENDED METHOD OF DESENSITIZATION BY THE INTRADERMAL ROUTE

Outline of Procedures

The desensitization procedures by the intradermal method involve:

(*a*) The determination of the initial dose of the extracts to be employed, i.e. the smallest dose (size/strength) required to produce a *significant* reaction on intradermal injection.

(*b*) Systematic desensitization thereafter with gradually increasing doses until the full strength (1 : 1) extract is reached, aiming with each injection to obtain a *significant* reaction.

(*c*) Continuing with 'maintenance' injections of the full strength (1 : 1) extract at increasing intervals of time to maintain the state of hyposensitization acquired.

Details of Techniques and Procedures

1. *Preparation of Extracts*

Watery extracts of pollens and other allergens are prepared in the usual way with buffered saline solutions (Coca's, Evan's, etc.). Stock extracts are prepared according to the weight/volume relationship of allergen to extracting fluid. These are for convenience referred to as 'full strength' (1 : 1) extracts from which dilutions are made as required for intradermal desensitization. Determinations of protein nitrogen or other 'unitage' are not made.

2. *Treatment Sets for Intradermal Desensitization*

Treatment sets for desensitization purposes are, for convenience, prepared for each patient in a series of 5 graduated standard strengths of extracts in 2 ml. rubber-capped bottles:

1 : 1,000, 1 : 100, 1 : 10, 1 : 2, 1 : 1.

If the patient is previously known to be highly sensitive (clinically) to a specific substance, the treatment set may consist of a series of extracts weaker than the above, commencing, for example, with 1 : 10,000, 1 : 100,000, or even greater dilutions.

3. *Determination of the Initial Dose*

The dose (size/strength) for the initial injection will depend upon the degree of the patient's sensitivity to the graduated extracts in the set, and is readily determined by a series of intradermal injections of 0·05, 0·1 and 0·2 ml. of each strength of extract, commencing with the weakest at intervals of 5—15 minutes until a *significant* reaction appears. In most patients the significant reaction appears with the 1 : 100 strength, although the occasionally more highly-sensitive persons may react to the 1 : 1,000 strength extract.

4. *Desensitizing Injections*

The volume of an intradermal injection does not exceed 0·25 ml. A fresh area of skin is selected for each injection to ensure a brisk local response and the next injection should be given not sooner than 24 hours thereafter by which time the previous reaction will have faded.

Injections for desensitization are given daily or every other day with the weaker extracts (1 : 1,000 or 1 : 100) and 2 or 3 times a week with the stronger extracts (1 : 10, 1 : 2, 1 : 1).

The aim with each and every injection is to obtain a wheal 1—2 cm. in diameter. As long as that occurs desensitization is proceeding and there is no need to increase size of dose or strength of extract, even though the same dose (size/strength) is repeated a number of times. When, however, the reaction wheal tends to become smaller, the dose-size or extract-strength or both are systematically increased so that the required significant reaction constantly appears.

The number of injections that need to be systematically given is indicated in Table I, but will of course depend on the way the patient has reacted. Sometimes certain doses of particular size/strength may have to be repeated a number of times because of the persistence of a significant reaction after each injection. This should occasion no concern because

TABLE I. OUTLINE OF DESENSITIZATION BY THE INTRADERMAL ROUTE

Strength of extract	*Size of injection ml.*	*Comments*
1 : 1,000	0·05 0·10 0·20	The initial dose for desensitization, as indicated by the *significant* reaction, is generally within this range
1 : 100	0·05 0·10 0·15 *** 0·20 ***	
1 : 10	0·05 *** 0·10 *** 0·15 *** 0·20 ***	
1 : 2	0·05 *** 0·10 *** 0·15 *** 0·20	***Any of these doses may have to be repeated one or more times depending on the persistence of the *significant* reaction
1 : 1	0·10 *** 0·15 *** 0·20 ***	
	'Maintenance' doses	Injections at gradually increasing intervals until an injection is given every 6—10 weeks

desensitization is occurring; and often in such cases the maintenance series of injections may be commenced even before the full-strength extract is reached, i.e. with the 1 : 2 or even occasionally with the 1 : 10 strength extract. But with each and every such injection it is important that a significant reaction be obtained.

5. *Maintenance Injections*

When the patient readily tolerates the full-strength (1 : 1) extract, i.e. responds to it with a significant reaction, the intervals between injections are increased until he is receiving an intradermal injection once a week for a few weeks, once a month for 2 or 3 months, and thereafter once every 6-10 weeks as a 'maintenance' dose to preserve the state of hyposensitization acquired. Indeed the physician will often be able to space the maintenance injections at even longer intervals depending upon the continued well-being of the patient. It is necessary, however, to ensure that a significant reaction is consistently obtained after each and every such maintenance injection. With this use of maintenance injections in pollen allergy the need for subsequent pre-seasonal desensitization injections is obviated.

Reactions

If the principle of aiming for a significant reaction is followed there is no need to anticipate any general or even undue local reactions.

The objections reported to the use of the intradermal route for desensitization have no validity with the techniques recommended and employed by us. Duke[46] and Vaughan and Black[47] referred to 'tissue-scarring' as a complication. Phillips[33] had already in 1933 commented on skin blemishes after intradermal injections and showed that these were from scratching or the intolerance of certain skins to glycerine, which was sometimes used at that time with desensitizing extracts or for the incorporation therein of adrenaline. In our experience scarring never occurs with the use of the usual buffered saline extracts of allergens. Thommen[9] and Rockwell and Rockwell[37] pointed out that the limited amount of extract that could be injected was a disadvantage. The implication in this adverse comment is that relatively large amounts of extracts are necessary for desensitization purposes. In our experience of intradermal desensitization the important matter is not the quantity of extract in each dose or in the total amount injected, but as has been shown, in the production after each injection of a *significant* skin reaction; and for this small amounts only of extract are, in fact, required. This view is supported by Phillips,[33] who had previously stated that the relief was proportionate to the extent and vigour of the local reaction rather than to the quantity of pollen extract administered, as well as by Anderson[4] who emphasized that with the intradermal technique small amounts of pollen extracts were adequate in the treatment of the great majority of patients. Hansel[36] also reported that small amounts only of the extract proved effective, the degree and duration of relief being generally proportional to the size of the wheal as well as to the amount and strength of the dilutions employed.

SUMMARY AND CONCLUSIONS

While the subcutaneous route is almost generally employed for desensitization in allergic conditions, the intradermal method is and has been the method mainly used in South Africa—its history and development are described.

Details are given of the principles, procedures, and techniques at present recommended by us for intradermal desensitization.

Emphasis is placed on the importance of following the principle: that desensitization is occurring if a *significant* reaction follows an intradermal injection and on the necessity, therefore, of always aiming for a *significant* reaction—a wheal 1—2 cm. in diameter, generally with pseudopodia.

Advantages claimed for the intradermal method of desensitization include the following:

(*a*) The superficial local skin reactions after intradermal injections are clearly visible within a few minutes after the injection and provide an adequate guide to the dose (size/strength) of the injection to follow.

(*b*) With the *significant* reaction as a guide, desensitization may be commenced or resumed at any time and under all circumstances, irrespective of season or other contact with the responsible allergen.

(*c*) The amount of extract used for each injection and for the desensitization procedure as a whole is relatively small.

The intradermal method is recommended because of its effectiveness in pre-seasonal and co-seasonal desensitization in pollen allergy and also for its value in prophylactic desensitization with extracts of other allergens responsible for non-seasonal allergic conditions.

With the procedures recommended, this method is noteworthy for the absence of severe local and any general reaction.

A successful outcome from intradermal desensitization may be anticipated where the specific allergens responsible for the condition are clearly defined and used for desensitization and where the recommended procedures are followed.

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