THE IMMEDIATE WHEAL AND THE 24-48 HOUR TUBERCULIN TYPE EDEMATOUS REACTIONS TO TRICHOPHYTIN*

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INTRODUCTION

In 1930, Sulzberger and Kerr (1) reported a case giving an immediate wheal reaction to trichophytin, in which they demonstrated circulating antibodies by passive transfer. And in 1932 Sulzberger and Wise (13) reported that the usual 48-hour tuberculin-type reaction to trichophytin can often be reduced by repeated intracutaneous injection of trichophytin while the rarer urticarial response remains essentially unchanged after repeated injections.

Both the more unusual urticarial reaction to trichophytin and the relationship between this response and the common 48-hour tuberculin-type trichophytin reaction have received considerable attention and study. The urticarial response has thus far been observed under the following conditions:

a) atopy (2, 3)
b) *Trichophyton rubrum* infections (4, 5, 6, 7, 8, 9)
c) recurrent erysipelas-like eruptions (10, 11, 12)
d) patients under treatment with trichophytin (13).

As far as the nature of and relationship between the two forms of allergic response are concerned the present studies are presented as fully supporting the following concepts expressed by Sulzberger in 1948 (14):

"In one patient of a large series Dr. Rudolf L. Baer and I produced *three different types of specific sensitization to one and the same simple chemical,* namely, eczematous sensitivity, urticarial sensitivity and tuberculin type sensitivity, all to picryl chloride. All three of these were produced by one type of exposure, i.e. intracutaneous injections of the chemical.

In all experimental sensitizations, be they with foreign sera, with "biologic" allergens or with simple chemicals, it is *usually easier* to produce papular responses of tuberculin-type than the urticarial type of sensitivity. The latter as a rule appears in a far smaller percentage of subjects; and even in these often only after more prolonged and intensive application of the sensitizing procedure. There is still another fundamental difference in these two types of response: the degree of *tuberculin type sensitivity can often be reduced* by specific injections while the urticarial form does not commonly respond to specific measures."

OBSERVATIONS

A. *Conditions Under Which Wheal Reaction To Trichophytin Occurs*

In the search for cases showing the immediate wheal reaction to trichophytin, more cases of *Trichophyton rubrum* infections were tested than of *Trichophyton*

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mentagrophytes, and more allergic cases than non-allergic. 1/10 cc. of trichophytin 1/30 (Lederle) was injected intradermally into the ventral surface of the forearm, and the reaction was read twenty minutes later and forty-eight hours later. The control was isotonic saline. A reaction which showed an area of edema of over 1 centimeter in diameter, when read at twenty minutes, was considered a positive immediate wheal. The majority of the reactions were larger than this,

TABLE 1

Immediate wheal reaction to trichophytin

CASE	ALLERGIC HISTORY	DURATION OF TINEA	PAPULE	IMMEDIATE REACTION	CAUSATIVE AGENT
1	Yes	7 years	No	Yes	*T. rubrum*
2	Yes	2 years	No	Yes	*T. rubrum*
3	Yes	4 mos.	No	Yes	*E. floccosum*
4	Yes	?	No	Yes	*T. rubrum*
5	Yes	10 years	No	Yes	*T. rubrum*
6	No	25 years	No	Yes	*E. floccosum* & *T. rubrum*
7	No	4 years	No	Yes	*T. rubrum*
8	No	10 years	No	Yes	*T. rubrum*
9	No	18 years	No	Yes	*T. rubrum*
10	No	5 years	No	Yes	*T. rubrum*
11	No	15 years	Yes	Yes	*T. mentagrophytes*

TABLE 2

Reactions following repeated injections of trichophytin

CASE	ALLERGIC HISTORY	DURATION OF TINEA	INITIAL REACTION		FINAL REACTION		CAUSATIVE AGENT	NUMBER OF INJECTIONS
			Papule	Wheal	Papule	Wheal		
1	No	9 years	Yes	No	No	No	*T. rubrum*	18
2	No	8 years	Yes	No	No	No	*T. rubrum*	6
3	No	?	Yes	No	No	No	*T. mentagrophytes*	9
4	No	5 years	Yes	No	No	No	*T. mentagrophytes*	5
5	No	6 years	Yes	No	No	No	*T. rubrum*	5
6	No	5 years	Yes	No	No	Yes	*T. rubrum*	7
7	No	15 years	Yes	Yes	No	Yes	*T. mentagrophytes*	19
8	No	13 years	Yes	Yes	No	Yes	*T. rubrum*	23
9	Yes	5 years	Yes	No	No	Yes	*T. rubrum*	4
10	Yes	6 years	Yes	No	No	Yes	*T. rubrum*	5
11	?	5 years	Yes	No	No	No	*T. mentagrophytes*	4
12	Yes	8 years	Yes	No	No	No	*T. mentagrophytes*	4

and displayed pseudopods. A papule measuring over 5 millimeters in diameter, forty-eight hours after the injection, was considered a positive tuberculin type of reaction. This type of reaction will henceforth be referred to as a papule. A careful personal and familial allergic history was taken, and results of this investigation are shown in table 1.

Nine of the cases were caused by *T. rubrum*, two by *Epidermophyton floccosum*, and one by T. *mentagrophytes*. Five of the patients had a positive atopic history, and in four of these *T. rubrum* was the infecting agent. Case # 11 had a re-

current erysipelas-like eruption of the right leg. Not all cases with atopy and dermatophytosis gave an immediate reaction (see table 2).

In each case there was present one of the three factors noted by others as being associated with the wheal reaction: history of atopy, *T. rubrum* infection, or recurrent lymphangitis. As the cases were selected, this is not evidence that a wheal reaction may not occur in other types of cases, or that it is more frequent with *T. rubrum* than with *T. mentagrophytes*, or in allergic than in non-allergic individuals.

B. *Induction of Wheal by Intradermal Injection of Trichophytin*

Sulzberger and Wise (13) noted the development of the wheal while giving repeated injections of trichophytin in treatment of dermatophytids.

To substantiate this observation, repeated injections of trichophytin (Lederle) were given intradermally once a week to patients who had a typical papule in reaction to trichophytin 1/30. 1/10 cc. was given per injection, and isotonic saline was used as a control. In the first few cases, weak dilutions of trichophytin were used, but later only 1/30 dilutions were employed. Injections were continued until a wheal appeared, or until the papule ceased to appear.

In all 12 cases, the papule ceased to appear after from four to twenty-three injections. Three of the patients developed a wheal; 2 of these had a positive atopic history. Cases 7 and 8 had a combined reaction initially, i.e., a wheal followed by a papule. Their history of atopy was negative. Following a large number of injections in these cases, only the wheal appeared. In 7 cases, the disappearance of the papule was not preceded or accompanied by a wheal. Compared to the control, however, most of these individuals had a positive immediate reaction, manifested by an area of central edema of less than 1 centimeter, and a large flare several centimeters in diameter. There was an intense exacerbation of this reaction four to six hours later in 5 of these cases.

DISCUSSION

The wheal and papular reactions were formerly regarded as distinct types of sensitivity due to different chemical antigens. But Sulzberger's opinion as to the possibility that single allergens can sometimes cause these different responses has been quoted (14). Zinsser (15) states that there are two types of hypersensitiveness in the guinea pig injection with bacteria. One is the typical anaphylaxis, in which protein material of the bacterial cell is concerned. This reaction develops late and can be reproduced by injection of dead bacterial material. The second is the tuberculin type of reaction, which is a hypersensitiveness to non-protein constituents. Tillett and Francis (15), however, demonstrated that when the pneumococcus polysaccharides were injected into patients *convalescing from pneumonia*, an immediate wheal reaction was obtained, whereas the nucleoprotein of the pneumococcus gave a tuberculin type of reaction.

More recently, evidence has been brought forward that the wheal and the papule represent different degrees rather than different kinds of allergy. Like Sulzberger, Dienes (16) presented experimental results to demonstrate that the

tuberculin type of reaction represents the early stage and the immediate reaction the late stage in the development of the sensitization process. He concludes that the factors determining these two types of reaction are extremely complicated, but at least one of these relates to time.

Jones and Mote (17) used normal rabbit proteins injected intradermally. Repeated injections were made in humans, the first reaction to appear being of the tuberculin type. After a few more injections, the immediate wheal type of reaction appeared, followed by the tuberculin type. If injections were continued, only the immediate wheal reaction appeared. Simon and Rackemann (18) confirmed the previous experiment using injections of guinea pig serum in humans.

Landsteiner and Jacobs (19) sensitized guinea pigs with p-chlorobenzoyl chloride. The animals showed the tuberculin type of reaction on the skin, and typical anaphylactic shock, following intravenous injection of the same compound. They conclude that the two types of allergic manifestation are closely related conditions.

Spink (20) observed that within a few days after the onset of the invasive stage of trichinosis, the trichinella skin test became positive, and that at this stage it was of the tuberculin type. On the average of seventeen days after onset of periorbital edema and myalgia, the papule disappeared. A positive skin test to trichinella antigen thereafter was represented by a wheal. This reaction persisted for months or years.

W. Jadassohn (21) adequately demonstrated that the dermatophytes produce multiple antigens. They have group-specific and species-specific antigens. Whether a single antigen, or multiple ones, are involved in the production of the immediate and the tuberculin types of skin reaction to trichophytin is not known. The frequency of the urticarial reaction in *T. rubrum* infections might suggest a species-specific antigen as the cause of this reaction. Against this is the fact that the immediate wheal has been noted in individuals where only *T. mentagrophytes* or *E. floccosum* were present (2, 22, and this paper). It is conceivable that a combined infection existed and that *T. rubrum* was overlooked. This was found to be true in Case 6, table 1, where only *E. floccosum* was isolated initially. Later *T. rubrum* was cultured. Also against the assumption of a *T. rubrum*-specific antigen is the fact that the immediate wheal may be produced artificially in some individuals by repeated injections of an extract made from *T. mentagrophytes*.

Observation already mentioned indicates that the atopic background, species of fungus (*T. rubrum*), recurrent lymphangitis, and the repeated injection of trichophytin, are factors which help determine the development of the urticarial type of sensitivity.

Thompson (23) noted a more persistent reaction to trichophytin where lymph stasis or edema were present. Naide (24) and Thompson (23) found a much greater response to trichophytin tests in legs involved with phlebitis or venous thrombosis. In our case of recurrent erysipelas-like eruption, a thrombosis of the greater saphenous vein preceded the onset of the lymphangitis. Naide suggested that due to trapping of the antigen by venous disease, there might have been

more time for the antigen to act. Also, edema and dystrophic skin might produce a more persistent dermatophytosis. Thus it is conceivable that stasis and dermatophytosis may be the sole cause of this disease, or that bacterial lymphangitis with the production of lymph stasis could produce the necessary time and degree elements for the development of the urticarial type of sensitivity to trichophytin.

All the factors previously enumerated, with the exception of the atopic group, tend to prolong the period of sensitization and to give a constant supply of antigen. This indicates that time is one of the important factors in the production of this type of sensitization. This would explain the observation of this reaction in individuals having *T. rubrum* infections, as this fungus frequently produces a *persistent*, chronic, recalcitrant dermatophytosis. Its presence in individuals with the asthma-hay fever complex might be due to the fact that these individuals produce reagins with great facility.

Circulating antibodies have been demonstrated in patients showing the immediate wheal reaction, and are presumably present in all cases. Also, Marcussen (2) showed that if trichophytin is reinjected after the disappearance of the wheal in Prausnitz-Kustner experiments on patients with a normal papular reaction, this results in a natural tuberculin type of reaction, whereas in the passive transfer test, a wheal is produced but no papule. The papule cannot be passively transferred. This suggests the working hypothesis that in the process of sensitization, fixed tissue antibodies are first produced and are, therefore, not passively transferrable by means of serum. Later, circulating antibodies are developed in addition, as demonstrated by positive Prausnitz-Kustner reactions. Union between antigens and humoral antibodies results in a wheal with partial or complete utilization of the antigen, trichophytin. In the latter case, no tuberculin type of reaction will be observed following the wheal. If some antigens remain after the production of the wheal, these can unite with the tissue antibodies and produce a papule. In this event, there is a combined type of reaction—both a wheal and a papule from a single injection of trichophytin.

In addition to the typical immediate wheals, a type of reaction was observed which we found difficult to classify. In 2 cases, the injection of trichophytin was followed at first by an area of edema less than 1 cm. in diameter (negative by our standards), surrounded by a flare. This subsided in about thirty minutes, but four to six hours later there appeared at the site of injection an edematous, tender swelling 2 cm. or more in diameter, with a large flare. This persisted for twelve hours or more. Three other patients described even more intense reactions of this nature which we did not observe. Whether these differed basically from the immediate wheal reaction, we could not be certain, but they did differ in their delayed appearance, prolonged course, and severity. We have not heretofore seen reactions of this type described. The only similar reaction noted was the Foshay reaction (25, 26), but here serum with antibodies is injected, rather than antigens.

SUMMARY

1. As previously reported by others, urticarial reactions to trichophytin were observed in patients with *T. rubrum* infections, in patients with a history of

atopy, and in patients with recurrent lymphangitis. No one of these factors was constantly present.

2. In confirmation of previous studies by Sulzberger and Wise and others, the tuberculin type of sensitivity was abolished in all of the 12 patients given intradermal injections of trichophytin.

3. The urticarial type of sensitivity was not abolished by such injections in 2 patients who showed it before treatment, and it developed in 3 additional patients at about the time their tuberculin type of sensitivity disappeared.

4. An intense edematous type of somewhat delayed reaction was observed during the course of immunization in some cases.

5. The present findings confirm the opinion that time and a constant supply of antigen are likely to be important factors in the production of the wheal reaction to trichophytin.

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