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DELAYED REACTIVITY TO BACTERIAL AND VIRAL EXTRACT(S) IN DIFFERENT DERMATOSES

G. Rajka

From the Department of Dermatology, Karolinska sjukhuset, Stockholm, Sweden

Abstract. Delayed reactivity was investigated in 177 patients having various dermatoses, treated with bacterial extracts (tuberculin, strepto-staphylococcal extract, Schick test solution) and with mumps vaccine. In the eczema group, failing reactivity was only found in some doubtful cases where the diagnosis later proved to be atopic dermatitis. This is in accordance with earlier studies showing a decreased delayed reactivity in the latter. A non-reactivity to delayed allergens was also found—as expected—in some cases of malignant lymphoma and sarcoidosis, and in cases of acne conglobata. This was in contrast to normal reactivity of acne juvenilis and pyodermic cases and points to the possibility of immunologic changes in acne conglobata (cystic acne). Hyperreactivity was in general found in the vasculitis group; in this relation, 2 cases of aphthosis Touraine are discussed. The diagnostic value of delayed reactivity in various dermatoses is in general limited. Delayed reactivity may, however, be of pathogenic interest in relation to certain dermatoses.

In previous reports, delayed reactivity to certain bacterial/viral extract(s) (tuberculin, pyococcal extracts, diphtheria toxin, mumps vaccine) was investigated in patients with atopic dermatitis (AD) and decreasing reactivity was found (28, 29). In another work (30) decreased delayed reactivity to bacterial/viral antigen(s) was shown in aged persons, i.e. in 97 patients of a geriatric clinic aged over 69 years as well as in 20 patients of the same age class with diagnosed (prostatic, mammary, colonic and pulmonary) cancer.

The present investigation is a study of the delayed reactivity to bacterial/viral extract(s) in patients with various skin diseases and between 20–60 years of age. The possibility that the results may give some diagnostic aid was considered.

MATERIAL AND METHODS

177 patients with the following skin diseases were investigated: 48 patients with various types of eczematous dermatitis, 7 with mycotic eczemas, 33 with psoriasis, 10 with chronic urticaria, 15 with palmoplantar pustulosis, 13 with various types of cutaneous vasculitis (including 2 cases of aphthosis Touraine), 10 with different pyodermas or acne vulgaris, 6 with acne conglobata (cystic acne), 5 with prurigo and pruritus, 2 sarcoidosis, 7 with malignant lymphoma and mycosis fungoides, 1 with oral candidiasis and 20 with various other dermatoses.

These patients were given the following extracts intracutaneously (0.1 ml in the arms):

1. (*a*) Tuberculin (National Swedish Bacteriological Laboratory, 0.1 mg).
   (b) In several cases PPD strength 1 (0.02 μg)/or 2 (5 μg) was also administered. In 17 cases both strengths as well as tuberculin 0.1 mg were injected.
2. Streptococcal extract. The dose given corresponded to 50 million organisms.
3. Combined staphylovaccine (National Swedish Bacteriological Laboratory). Polyvalent vaccine prepared from heat-killed bacteria of about 12 hospital strains, several of these were of phage type 80–81. The dose given consisted of 0.15 U of alpha-toxoid and 6 million organisms. Merthiolate 0.01% was added as a preservative.
4. Mumps vaccine $1:10^2$. Preservative: ethylmercurithiosalicylate 0.01%.
5. Schick test solution (National Swedish Bacteriological Laboratory). Control: Schick control solution (National Swedish Bacteriological Laboratory).

Physiological saline was, furthermore, used as control. Reactivity to the preservatives were checked in several cases.

The delayed reactions were recorded at 48 hours but read also at 24 and 72 hours. Their grading was recorded as positive if the sum of the largest perpendicular dimensions of the papule was more than 12 mm. Reactions over 20 mm were registered as + +, etc.

RESULTS AND COMMENTS

Table I summarizes the absence of delayed reactivity (non-reactivity, negativity) in the patient material. Absent delayed reactivity was found in relatively few cases. For practical reasons the re-

Table I

Patient material (total cases, disease type)	No. of cases lacking delayed reactivity to bacterial/viral extract(s)
48, eczematous dermatitis	1[a]
33, psoriasis	0
15, palmoplantar pustulosis	0
13, various cut. vasculitis	0
10, chronic urticaria	2
10, pyoderma/acne vulgaris	0
7, mycotic eczema	1[a]
7, malignant lymphoma group	3
6, acne conglobata	4
5, prurigo/pruritus	2[b]
2, sarcoidosis	2
1, candidal granuloma	0
20, other dermatoses	0
177	15

[a] Later diagnosed as possible atopic dermatitis.
[b] Later diagnosed as atopic dermatitis.

sults are commented on according to the extracts and to respective disease categories.

I. *Different Extracts*

Tuberculin reactivity

Tuberculin reactivity was often absent in our patients. 56% of the patients reacted to 0.1 mg tuberculin, whereas 46% did not. There was a tendency to positive response among persons 30–40 years of age, whereas younger (20–30 years) showed more negativity. The most likely explanation for this fact was that natural immunity was lost more slowly than the artificial BCG-immunisation, which is obligatory during the first postnatal days of life in Sweden (checked after 3 months, and if negative, repeated; as well as often being checked even later on). Furthermore, in persons older than 40 years, there was a trend to negativity. It is well known that tuberculin reactivity after BCG mostly (19) runs parallel with BCG allergy, and according to several observations, often diminishes after some years, e.g. if checked during adolescence.

In 17 cases (9 with eczematous dermatitis, 2 psoriasis, 2 pyoderma, 4 other dermatoses), all three tuberculoproteins were injected. There was greatest reactivity to PPD strength 2; if the reactivity to tuberculin 0.1 mg was considered as 100%, the ratios were: to PPD 0.02 μg: 72% and to PPD 5 μg: 212%. According to Jillson (16), PPD strength 1 corresponds to the applied tuberculin dose. This type of parallelism was found in all but one case, furthermore in 3 out of the 17 cases reactivity could be observed only to 5 μg PPD.

The reaction to 0.1 mg tuberculin was 60 mm in 1 case (of erythema nodosum). The reactions to tuberculoproteins run mostly parallel with other allergens. However, due to the above-mentioned relatively short duration of BCG (tuberculin) reactivity, it is difficult to evaluate the non-reactivity to tuberculin in our series as a sign of general alteration of the delayed reactivity.

Streptococcal extract

The reactions were mostly moderately positive and parallel to, especially, staphylococcal "allergen". Sometimes small pustules were seen at the injection site; the lesions were, however, always sterile. This phenomenon is already described in relation to vasculitis (5). Furthermore, one has impression that the delayed reactivity to some samples showed minor variations, but a quite good correlation was found between different samples by checking on the same individual.

Staphylococcal extract

The delayed reaction to this extract was in general relatively strong positive. Extreme reactivity was found in 3 patients:

ÅB, palmoplantar pustulosis, 65 mm;
JL, hypostatic ulcer (age: 46 years), 52 mm;
LS, lupus vulgaris, 60 mm (tuberculin reactivity, as other allergens were here moderately positive).

Mumps vaccine

With three exceptions, all patients showed a reactivity to this extract and therefore it may be assumed that in addition to immunologic response in adult age (39) the reactivity includes response to primary irritation. There were, in general, relatively strong reactions to mumps vaccine, in 1 case (SI eczematous dermatitis): 50 mm. In previous studies non-reactivity was found to the same concentration in half of 16 patients with AD.

Schick test solution

In general, moderately delayed reactivity to (the irritant effect of) diphtheria toxin was seen. Con-

trols were negative except in 1 case, in which pseudopositive ("allergic") reaction was observed to heat-inactivated diphtheria-toxin.

Intensity of reactivity during readings

According to general observations the strongest reactions in this series were seen after 48 hours, although in the majority of the cases no larger difference was found between readings at 24 and 48 hours. However, some contradiction in their time-curve was seen in relation to staphylococcal and mumps vaccines based on 34 cases (if more than 6 mm differences were noted):

	Staphylococcal vaccine	Mumps vaccine
No difference between 24/48 hour readings	25 cases	17 cases
Decreased reactivity 24/48 hour readings	9 cases	3 cases
Increased reactivity 24/48 hour readings	0 cases	14 cases
	34 cases	34 cases

No reaction to physiologic saline or to preservatives was found in the series.

II. *Disease Categories*

Eczematous dermatitis; mycotic eczema; prurigo; (Atopic dermatitis)

Of 48 patients with eczematous dermatitis, as well as of 7 cases with mycotic eczema, 1 case of each showed delayed reactivity. The same findings were observed in 2 out of 5 cases, classified after thorough clinical investigations as presumably itching and sequelae to prurigo simplex subacuta. It was assumed that the 4 non-reactors possibly belong to or are equivalent to the clinical group of AD. In this disease the present author has shown that a low-grade reactivity to bacterial/viral extract(s) occurs. It is noteworthy that delayed hyporeactivity was also found in Wiskott–Aldrich-syndrome (1, 2). Clinically, in two of the "prurigo" cases the diagnosis was later changed to AD and this was the strong suspicion even in the two other non-reactors of the eczema/mycotic eczema group. Thus it may be emphasized that if a delayed non-reactivity occurs in patients with eczematous/pruriginous lesions, one should suspect a possible ("correct") diagnosis of AD.

Psoriasis

In psoriatics no special findings in relation to delayed reactivity were found in our earlier studies, when psoriatics (among other categories) were used as controls for patients with AD. Normal delayed reactivity was also found by Landau et al. (20). As to *epi*cutaneous reactivity in psoriatics exemplified by reactivity to sensitizers, in spite of earlier reports on decreased reactivity (9), normal reactivity was found in general (33, 8).

In present series no greater difference in delayed reactivity was found in psoriatics than in other patients. If, e.g., the reactivity to tuberculin and pyococcal extracts (extracts 1–3) were compared, delayed reactivity was observed in 23 of 35 patients with eczema and in 23 of 33 patients with psoriasis.

Urticaria/edema

Of 10 patients with urticaria/edema, 2 showed a non-reactivity in present investigations. Although it is difficult to draw conclusions from this small material, it is assumed that the mechanical washing-off effect (32, 21) or some similar functional factor may occur in the edematous skin in relation of frequent immediate and relatively rare poor delayed reactivity. Increased tuberculin reactions, in 2 cases centrally, were observed in 6 out of 15 patients with chronic urticaria [without active tuberculosis (22)]. In our series, the ratio between tuberculin positivity/negativity was not dissimilar to other patient categories studied.

Acne conglobata/acne-pyoderma group

Whereas in 10 patients with acne juvenilis or different pyodermas (and in 15 patients with palmoplantar pustulosis without manifest psoriasis) no delayed hyporeactivity was found; 4 of 6 patients with acne conglobata (cystic acne) showed total absence of delayed reactivity (and the fifth case reacted only weakly to mumps vaccine). This immunologic alteration found in acne conglobata is further confirmed by improvement after steroids in "antibiotic-resistant" cases. In addition, some cases of acne conglobata were observed, where an acute sepsis-like reaction with fever and leukocytosis over 15,000 occurred and blood cultures gave no information of a possible infectious agent. Thus even in the preliminary stage of observations on acne conglobata it may be stressed that the absence of delayed reactivity, in accordance with above-mentioned observations, points,

to the importance of immunologic changes in this disease.

"Allergic" vasculitis/panniculitis group

In this heterogenous group, it is known that delayed reactivity is, in general, increased, e.g. to streptococcal extract (31, 5). In our series of 11 cases: 3 with erythema nodosum, Weber-Christian panniculitis, and 3 more with pyoderma gangraenosum as well as 1 case each of erythema indurativum and periarteritis nodosa cutanea, mostly, but not always, strong reactions were registered especially to strepto-staphylococcal and mumps vaccines. If delayed reactions to these three extracts were observed, the strongest reactivity was found in 2 cases of erythema nodosum (of which the one was of recurrent type, presumably a borderline case to allergic vasculitis). The two other strong delayed reactions were 1 case of chronic urticaria and an uncertain case of "chronic gingivitis".

Aphthosis Touraine

We have observed 2 cases of aphthosis Touraine, both female patients where recurrent oral aphthae and nodules on the legs were seen. The latter began in the one case 19 years ago and healed after 5 years but recurrent papules have been observed even in recent years; in the other case recurrent nodules have appeared on the legs for 20 years and show histological alterations of type vasculitis and panniculitis (but not of erythema nodosum type). Clinical and laboratory investigations were irrelevant and virus culture from mouth lesions negative. In one of these patients a delayed hyperreactivity was seen, whereas in the other, small, practically negative, reactions were read.

Aphthosis Touraine (34) is a broader clinical entity which may include the Behçet disease (35) and further combinations e.g. between recurrent aphthae (on basis of vasculitis) and vasculitic alterations chiefly on the legs, as noduli, dermohypodermitis (26, 37, 23). Hyperreactivity to delayed antigens, including physiologic saline, was found in the active stage of Behçet disease (25) and even to antigen prepared from typical lesions [behcetin, (15, 18)]. In 30 cases of recurrent oral aphthae, hyperreactivity to alfa-streptococcal extract, evidenced by extensive reactions frequently measuring up to 4 cm, was observed by Graykowski et al. (13) whereas in another report no delayed hyperreactivity was found in 20 similar cases (18).

All these (and other findings on the beneficial effect of steroids, etc.) point to the similarity in delayed hyperreactivity between the vasculitis group and the presumedly closely related aphthosis Touraine-group.

That we could observe for this group typical hyperreactivity only in 1 of our 2 cases is not necessarily a contrast to the above-mentioned. In another cases of the vasculitic group, where in general strong delayed reactivity was observed, some exception could be registered.

Since infections are frequently suspected as triggers (or allergens?) in cases of cutaneous vasculitis, testing with a "battery" of bacterial/viral extracts may considered as being not without risk. Therefore regular tests with stronger reactors are not recommended in this group. On the other hand, testing with only physiologic saline, which we performed in several cases of vasculitis, was regularly negative. Perhaps testing with streptococcal *or* staphylococcal extracts (in our series showing no greater differences in intensity) instead of several antigens is the best method if one wishes to test this patient group.

Cases with anticipated delayed hyporeactivity

It is well-known that among diseases with dermatological interest, certain types show delayed hyporeactivity. First, the malignant lymphoma group, best represented by Hodgkin's disease, but also including allied diseases (12, 6, 3, 24) should be mentioned. In our series 3, absent delayed reactivity was noted, though not in 2 other cases with inceptive malignant lymphoma. Furthermore, no change in delayed reactivity could be noted in 2 cases of mycosis fungoides, corresponding to other reports (3).

The failing delayed reactivity, in the first place to tuberculin, in sarcoidosis is also well-documented (for references, see 26, 29) and this was the case with 2 sarcoidosis patients in our series. Mucocutaneous candidal granulomatosis is also associated with immune deficiency and delayed non-reactivity (7, 14). In our case, a girl of 19 years with longstanding mucocutaneous candidiasis chiefly localized in the mouth and combined with Turner-syndrome, the applied delayed tests were normal. However, she reacted only very

weakly (6 mm) to mumps vaccine which fact only occurred in patients with AD and in one patient with eczematous dermatitis.

Practical diagnostic value of testing with delayed reactors in dermatoses

For diagnostic purposes the practical value of delayed reactivity is generally limited. This is primarily due to the fact that the diagnosis in many diseases from candidiasis to malignant lymphoma or acne conglobata is made on the basis of clinical, histologic or laboratory findings. In some cases, however, the possible failure of delayed reactivity may be of secondary diagnostic importance, as in sarcoidosis, in certain cases of malignant lymphoma, etc. Although the same considerations are valid in AD, the absence or decrease of delayed reactions in cases with suspected/unclear AD or in unclear closely related diseases such as prurigo subacuta simplex (prurigo with itching) according to present author's findings may be of certain importance for the diagnosis of AD.

Pathogenetic considerations

The failure of delayed reactivity found in malignant lymphoma, in cancer or in sarcoidosis, is of undoubted significance in pathomechanism and is possibly of even basic importance. The author mentions his similar results in AD [possible relation with decreased resistance to certain viruses ? (29)] and those of acne conglobata cited in this report. The decrease/failure in delayed reactivity of the latter (at least to applied extracts) points to pathologically important immunologic changes. The delayed hyperreactivity found in the cutaneous vasculitis group, including the findings on aphthosis Touraine, is assumedly not without significance in causation/elicitation of this disease group. Delayed reactivity to i.c. applied autologous leukocytes (36) or to DNA, nucleoprotein or histone (27, 17) gave mostly positive delayed reaction in SLE although the specific value of this test is debatable (11). Even in advanced disseminating discoid LE cases, such reactions are mentioned (17). Delayed *hypo*reactivity may have significance even in other diseases of dermatologic interest not mentioned here, as in ataxia-telangiectasia (10), lepromatous leprosy (38), in SLE (concerning PPD, 4). In erythema annulare centrifugum, weak trichophitin reaction was observed if injected centrally, but not if applied outside the lesion (18).

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Georg Rajka, M.D.
Department of Dermatology
Karolinska sjukhuset
S-104 01 Stockholm 60
Sweden