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Reinterpretation of the Dick Test: Role of Group A Streptococcal Pyrogenic Exotoxin

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Because of the association of the group A streptococcal pyrogenic exotoxins (SPEs) with erythrogenic toxin used in the classical Dick test, the involvement of the SPEs in production of erythematous skin reactions was assessed. Unless they had been presensitized, young adult rabbits failed to show skin reactions after intracutaneous challenged with SPEs. Rabbits presensitized to purified protein derivative exhibited enhanced skin reactivity when given purified protein derivative plus SPE C; the enhancement was neutralized by antiserum to SPE C. Rabbits sensitized to bovine serum albumin showed extensive red rash development resembling scarlet fever rashes when given bovine serum albumin containing SPE C. Desquamation occurred 5 to 10 days after injection. Animals sensitized to one SPE type showed enhanced skin reactivity to challenge with homologous or heterologous SPE types, indicating the presence of a cross-reactive determinant within the SPE molecules. Repeated challenge of SPE-sensitized animals with homologous toxin resulted in concomitant antitoxin production with reduction of the enhanced skin reactivities, until typical delayed-hypersensitivity skin reactions remained. The data indicate that, in addition to the toxic reaction previously described, SPEs enhance Arthus and delayed-hypersensitivity skin reactions. It follows that erythrogenic toxin represents the enhancement of acquired skin reactivity to streptococcal antigens by one or more SPE types. Therefore, the Dick test measures SPE-enhanced hypersensitivity to streptococcal products.

As originally described, the Dick test was used to identify individuals with susceptibility to scarlet fever (8). When broth culture filtrates from erythrogenic toxin-producing group A streptococci were injected intracutaneously into susceptible persons, erythematous and edematous skin reactions developed by 24 h after injection. Antitoxin neutralized the reactions (8). Persons with sufficient circulating antitoxin did not develop positive skin responses, and they were therefore not considered susceptible to scarlet fever (8).

Unlike the Dicks (8), who thought the erythematous rash resulted from a direct (primary) toxic effect, others have emphasized the role of delayed hypersensitivity (secondary toxicity) in the reaction (3-5, 9, 13-15, 17, 18, 22). The importance of age in developing scarlet fever (17) is consistent with the delayed-hypersensitivity concept. Scarlet fever is not observed in infants and becomes more prevalent only after repeated streptococcal infections. Rantz et al. (18), after testing a large number of men of military age, determined that positive Dick tests were infrequent in men from geographical areas with low incidences of streptococcal infections. These investigators concluded that the Dick reaction probably resulted from previous exposure, and therefore was the result of acquired hypersensitivity.

The work of Kim and Watson also implicated delayed hypersensitivity in development of skin reactivity (14, 15). They proposed that group A streptococcal pyrogenic exotoxins (SPEs) contained primary toxic moieties which enhance hypersensitivity developed by the host to secondary toxic parts of the molecules. The primary toxicity has other effects on the host, including pyrogenicity (14, 20, 23), enhancement of lethal shock and myocardial damage (14, 20, 21), and alterations of the immune system (2, 6, 7, 10-12), and this moiety of the molecules confers serological specificity. It was proposed also that the secondary toxic part may be shared by all three SPE types (15).

This study was undertaken to elucidate the role of SPE in the development of the erythrogenic toxin rash, and therefore to define erythrogenic toxin more fully. Also, the SPEs were tested for a shared determinant which confers delayed hypersensitivity and which, once developed, can be enhanced by a primary toxicity.

MATERIALS AND METHODS

All reagents and glassware used for toxin preparation and biological assays were maintained pyrogen free.

Bacteria. The NY-5 strain (type 10/12) of group A streptococcus came originally from Rebecca Lancefield of the Rockefeller Institute, New York, and was used for production of SPE types A, B, and C. Strain T18P (19, 23) was used for production of partially purified (EtOH-2) and highly purified SPE C. The T18P strain does not produce SPEs A and B. Cultures were maintained in the lyophilized state in the presence of whole, defibrinated fresh rabbit blood.

Toxin preparation. SPEs were obtained from cell-free culture supernatant fluids of streptococci grown in a beef-heart dialysate medium (14, 23). Toxins were purified using differential precipitation with −20°C ethanol and resolubilization in acetate-buffered saline, followed by preparative thin-layer isoelectric focusing (1, 14, 19, 23). SPE types A and C thus obtained required approximately 0.1 μg of protein per kg given intravenously to rabbits to produce a 0.5°C average fever response 4 h after injection (1MPD-4). SPE type B consisted of a pool of B (pI 8.0) and B (pI 8.4).

Animals. American Dutch belted rabbits weighed from 1.0 to 2.0 kg.

Immunizations. Hyperimmune antisera to SPEs and bovine serum albumin (BSA; Pentex, Miles Laboratories Inc., Kankakee, Ill.) were prepared in rabbits. For use in skin test experiments, animals were sensitized to SPE types A, B, and C by administering 125 μg of toxin emulsified in Freund complete adjuvant (containing killed *Mycobacterium tuberculosis* H-37Rv) subcutaneously on days 0 and 14. Rabbits were sensitized to BSA by subcutaneously administering to each animal 1 mg of protein emulsified in Freund incomplete adjuvant on days 0 and 14. Rabbits were considered sensitized when a small local Arthus reaction could be elicited after challenge using 350 μg of BSA. Animals were sensitized against purified protein derivative (PPD) using subcutaneous injections of Freund complete adjuvant on days 0 and 14. After two injections, rabbits showed weak delayed-hypersensitivity skin reactions when challenged intracutaneously with 250 test units of PPD (Mantoux; Connaught Laboratories Ltd., Willowdale, Ontario, Canada; batch CT68).

Skin testing. Rabbits were skin tested using antigen injected intracutaneously, 0.1 ml per animal, in phosphate-buffered saline (0.005 M phosphate buffer, 0.15 M NaCl, pH 7.0). Test doses were: SPEs, 50 μg; BSA, 350 μg; PPD, either 250 or 25 test units. For development of passive local Arthus reactions, 350 μg of BSA mixed with antiserum to BSA in slight antigen excess was administered intracutaneously to nonimmune animals. Antigen and antibody were mixed immediately before injection. Neutralization of SPE enhancement of skin reactivity was accomplished by adding 10 μl of hyperimmune antiserum to 0.1 ml of injection mixture.

RESULTS

Initial studies were directed towards more clearly defining erythrogenic toxin. Rabbits are not a natural host for group A streptococci and were therefore used to test for direct toxicity by the SPE as manifested in the development of erythematous skin reactions. Nonsensitized rabbits failed to develop positive Dick reactions after intracutaneous challenge with SPEs (Table 1). The data indicate that direct toxicity alone by the SPEs was not responsible for development of erythematous skin reactions.

Unlike nonsensitized rabbits, animals presensitized to the SPEs exhibited significant skin test reactions after challenge with homologous toxin (Table 2). The skin reactions obtained were not typical delayed-hypersensitivity responses, but were intensely red with some edema. Representative examples of rabbits used in Tables 1 and 2 are shown in Fig. 1A and B. The animal shown in Fig. 1A was not sensitized, whereas that in Fig. 1B was presensitized to SPE C. Both animals were challenged with homologous toxin. Subsequent challenge of the same rabbits (from Table 2) 1 week later with homologous SPE resulted in typical delayed-hypersensitivity reactions in several of the animals (Table 3). The reaction sites were edematous and yellow to orange in color. The overall reaction diameters decreased significantly compared to those presented in Table 2. The level of significance for the differences between first (Table 2) and second (Table 3) challenges of sensitized animals is indicated in Table 3. Together, the data presented in Tables 2 and 3 suggest that SPEs enhanced acquired skin reactivity to themselves, and that this enhanced reactivity was neutral-

TABLE 1. *Lack of skin test reactivity of rabbits without prior sensitization to SPE*

SPE type[a]	No. of rabbits tested	Skin reaction diameter (mm)[b]
A	5	0
B	5	0
C	15	0

[a] Dose: 50 μg administered intracutaneously in 0.1 ml.
[b] Average diameter after 24 to 48 h.

TABLE 2. *Enhanced skin reactivity of rabbits presensitized to SPE and challenged with homologous toxin*

SPE type[a]	No. of rabbits tested	Skin reaction diameter (mm) ± SE[b]
A	7	39 ± 5.0
B	5	29 ± 2.4
C	4	40 ± 4.0

[a] Dose: 50 μg/0.1 ml injected intracutaneously.
[b] Average diameter after 24 h ± 1 standard error of the mean (SE).

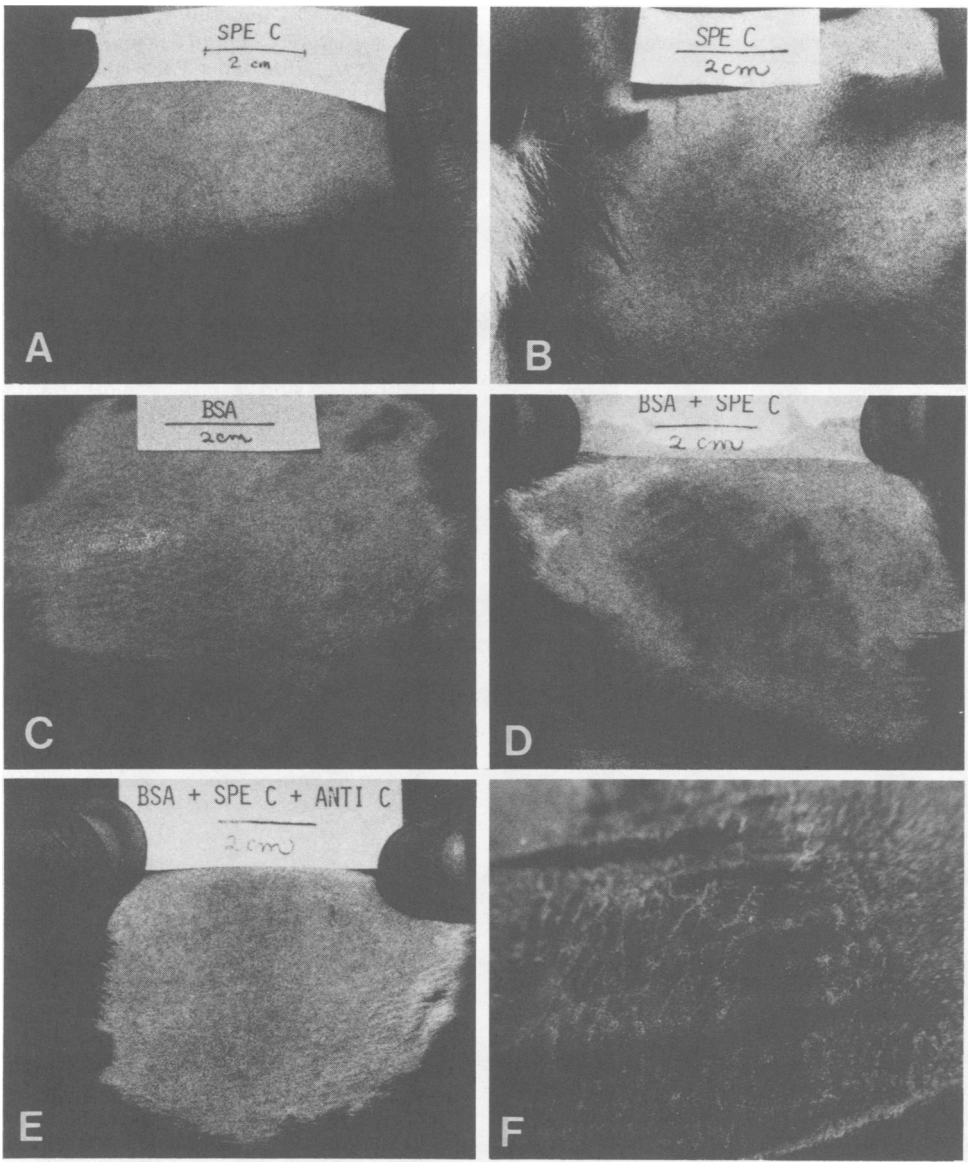

FIG. 1. *Skin reactivity of rabbits challenged with SPE C alone or in combination with BSA or BSA plus antiserum to SPE C. (A) Rabbit unsensitized and challenged intracutaneously with SPE C; (B) rabbit presensitized to SPE C and challenged with homologous toxin; (C) rabbit presensitized to BSA and challenged with BSA; (D) rabbit sensitized to BSA and injected with SPC C plus BSA; (E) rabbit sensitized to BSA and challenged with SPE C, BSA, and antiserum to SPE C; (F) rabbit sensitized to BSA and injected with SPE C plus BSA.*

ized by antitoxin, which increased with repeated injection of homologous toxin until only delayed-hypersensitivity reactions were expressed.

The SPEs were tested for capacity to enhance hypersensitivity reactions developed against unrelated proteins in rabbits. Animals presensitized to PPD showed significantly enhanced skin reactivity on one flank when challenged with PPD plus SPE C, compared to the other side, which received PPD alone (Table 4). SPE C alone given to PPD-sensitized animals did not elicit skin test responses. The enhanced skin reactivity on the flanks receiving PPD plus SPE C was most dramatic when the low dose of PPD was used: 22-mm average diameter, compared to 0 mm when PPD alone was used. Rabbit hyper-

TABLE 3. *Skin reactivity of rabbits presensitized to SPE and challenged with homologous toxin*

SPE type[a]	No. of rabbits tested	Skin reaction diameter (mm) ± SE[b]	Significance (*P*)[c]
A	7	19 ± 5.5	<0.008
B	5	12 ± 6.0	<0.02
C	4	15 ± 2.0	<0.02

[a] Dose: 50 μg/0.1 ml injected intracutaneously.
[b] Average diameter after 24 h ± 1 standard error of the mean (SE).
[c] *P* values were determined using paired *t*-test analysis of data presented in Table 2 and this table.

TABLE 4. *Skin reactivity of rabbits to PPD, enhanced by SPE C*

Skin test material	No. of rabbits tested[a]	Skin reaction diameter (mm) ± SE[b]	Significance (*P*)[c]
PPD (25)[d]	12	0	<0.001
PPD (25) + SPE C[e]	12	22 ± 2.3	
PPD (250)	5	14 ± 1.0	<0.001
PPD (250) + SPE C	5	33 ± 2.5	
PPD (250) + SPE C	5	23 ± 4.5	<0.02
PPD (250) + SPE C + Anti C	5	8 ± 3.8	

[a] Rabbits were presensitized to PPD.
[b] Average skin test diameter ± 1 standard error of the mean (SE).
[c] *P* values were determined using paired *t*-test analysis of control and experimental reaction diameters.
[d] Numbers in parentheses refer to test units used for challenge.
[e] SPE C concentrations were 50 μg/0.1 ml.

immune antiserum raised against SPE C effectively neutralized the enhanced skin reactivity to PPD (Table 4); typical delayed-hypersensitivity reactions to PPD remained.

SPE C also enhanced Arthus reactions to an unrelated protein. Rabbits actively immunized against BSA showed greatly enhanced skin reactivity after challenge on one flank with BSA plus SPE C, compared to BSA alone on the opposite side (Table 5). After challenge with BSA alone, Arthus reactions were obtained with maximal edema occurring in approximately 8 h. The flanks receiving BSA plus SPE C, however, showed extensive edematous and erythematous skin reactions which persisted for at least 48 h and desquamated 5 to 10 days after injection. The reactions obtained after challenge with BSA plus SPE C most resembled scarlet fever rashes. The rabbit shown in Fig. 1C and D typifies the types of skin reactions obtained after challenge with BSA and BSA plus SPE C. The animal shown received BSA alone on one flank (Fig. 1C) and BSA plus SPE C on the other side (Fig. 1D). A representative example of desquamation as a result of challenge with BSA plus SPE is shown in Fig. 1F. Administration of antiserum to SPE C together with BSA plus SPE C resulted in neutralization of the enhanced reactivity (Table 5; Fig. 1E). Enhancement of passive local Arthus reactions by SPE C is shown in Table 6. The reactions obtained, although significant, were not as pronounced as those from animals actively immunized to BSA and subsequently challenged. The data presented in Tables 4 to 6 demonstrate the potential of SPE to enhance both delayed and Arthus-type hypersensitivity reactions to unrelated antigens. Therefore, the erythrogenic toxin may represent SPE-enhanced skin reactivity to other antigens, or to the SPEs themselves, to which the host has acquired hypersensitivity.

The SPEs were then tested for capacity to enhance hypersensitivity reactions to other SPE types. By immunizing with one SPE type and then challenging with the others, it was possible to test for a common core part shared by all the SPEs, as proposed earlier (15). All animals used in this study were challenged with homologous SPE until typical delayed-hypersensitivity skin reactions were obtained. EtOH-2 SPE C (200 μg/0.1 ml) was used in place of purified SPE C

TABLE 5. *Skin reactivity of rabbits to BSA, enhanced by SPE C*

Injection material	No. of rabbits tested[a]	Avg skin reaction diameter (mm) ± SE[b]	Significance (*P*)[c]
BSA	11	7.5 ± 3.2	<0.001
BSA + SPE C[d]	11	52.0 ± 5.0	
BSA + SPE C	6	40 ± 6.0	
BSA + SPE C + Anti C	6	15 ± 5.5	<0.001

[a] Rabbits were presensitized to BSA.
[b] SE, Standard error of the mean.
[c] *P* values were determined using paired *t*-test analysis of control and experimental reaction diameters.
[d] SPE C concentrations were 50 μg/0.1 ml.

TABLE 6. *SPE C-enhanced passive Arthus reaction development in rabbits*

Injection material	No. of rabbits tested	Avg skin reaction diameter (mm) ± SE[a]	Significance (*P*)[b]
Complex[c]	12	16.7 ± 1.3	<0.008
Complex + SPE C (50 μg)	12	25 ± 1.4	

[a] SE, Standard error of the mean.
[b] *P* value was determined using paired *t*-test analysis of reaction diameters.
[c] Complex consisted of BSA mixed immediately before injection with rabbit antiserum to BSA.

for skin testing to control for potential cross-immunization against trace ampholytes possibly carried along from toxin purifications. Rabbits sensitized to any of SPE types A, B, and C showed positive skin reactions when challenged with heterologous toxins (Table 7), whether highly purified or EtOH-2. The reactions obtained, again, were typical of enhanced skin reactivity rather than those of delayed hypersensitivity. The skin reactions were neutralized using antisera to the challenge toxin; typical delayed-hypersensitivity reactions remained. The data indicate that the SPEs share a determinant to which delayed hypersensitivity could be developed. Once hypersensitivity was acquired, a serologically specific primary toxicity could enhance skin reactivity.

DISCUSSION

In this study the SPEs failed to produce skin test reactions upon primary injection into nonsensitized rabbits. The inability to invoke a skin reaction is consistent with research indicating that host-acquired hypersensitivity is required for development of the scarlet fever rash (3–5, 9, 13–15, 17, 18, 22). The data suggest that primary toxicity alone, as proposed by the Dicks (8), is not responsible for rash development.

Investigators have equated SPEs with erythrogenic toxins (13, 16, 24). In this paper the relationship of these two toxins was more fully studied; the SPEs significantly enhance acquired hypersensitivity reactions, both humoral and cell mediated, to either unrelated antigens or homologous or heterologous SPE. It is likely that the SPEs would enhance hypersensitivity reactions developed by the host to a variety of streptococcal products after repeated infections resulting in the erythrogenic toxin (scarlet fever) rash. The enhancement of hypersensitivity by SPEs is neutralized by specific antibody to the SPE and is consistent with reports which demonstrate neutralization of erythrogenic toxin activity (4, 5, 8). Therefore, erythrogenic toxin may be defined more clearly as SPE enhancement of acquired hypersensitivity reactions to streptococcal products, and the Dick test is a measure of SPE-enhanced hypersensitivity to streptococcal products. Since the enhancement of skin reactivity by SPE depends upon acquired hypersensitivity developed by the host to a streptococcal product, erythrogenic toxin should not be equated with SPE. Furthermore, erythrogenic toxin cannot be clearly defined unless the product to which the host was presensitized is known. In light of this, the use of SPE as a single toxic entity is preferred.

TABLE 7. *Skin test cross-reactivity by SPE types A, B, and C*

Sensitizing SPE	Challenge SPE	No. of rabbits tested	Avg skin test diameter (mm) ± SE[a]
A	A	8	19 ± 5.5
A	B	8	48 ± 4.0
A	C[b]	8	41 ± 3.9
B	A	5	31 ± 1.0
B	B	5	15 ± 6.0
B	C[b]	5	40 ± 6.3
C	A	4	35 ± 2.9
C	B	4	34 ± 2.4
C	C[b]	4	21 ± 3.0

[a] SE, Standard error of the mean.

[b] Challenge SPE C dose was 200 μg of EtoH-2 toxin from strain T18P per 0.1 ml.

The ability of the SPEs to enhance hypersensitivity reactions is consistent with other properties of the toxins. They enhance host susceptibility to lethal shock and myocardial damage (14, 21, 23). The immunoglobulin G response to a second antigen is enhanced (10, 12). Also, the toxins enhance anaphylactic shock (S. W. Kayute and D. W. Watson, Bacteriol. Proc., p. 94, 1955). The mechanism by which delayed-hypersensitivity skin reactions are enhanced may relate to the nonspecific lymphocyte mitogenicity of the SPEs (2). As proposed previously, the SPE molecules may consist of two parts, a primary toxicity and a secondary toxicity to which delayed hypersensitivity may be developed (15). The host with delayed hypersensitivity to the secondary toxicity of SPEs or other antigens would be expected to show typical skin test reactivity when challenged with homologous antigen, resulting from lymphokine release by lymphocytes and recruitment of macrophages. An exaggeration of this effect may result when primary toxicity moieties are coadministered with antigen, stimulating release of more lymphokines and enhancing macrophage infiltration.

The enhancement of local Arthus reactions by SPEs appears more closely related to the typical scarlet fever rash. The greatly enhanced skin reaction with erythema may result from a more rapid and extensive infiltration of phagocytic cells and complement components. SPE C previously was shown to alter the permeability of the blood-brain barrier (20) and potentially could alter blood vessel permeability. Preliminary studies indicate that SPEs alter the permeability of vessels, as determined by Evans blue dye accumulation in tissues (unpublished data).

It is interesting that the SPE molecules appear to have two subparts, with the secondary toxic part being shared between SPE types, whereas the primary toxicity is serologically specific. Evidence for a shared determinant was provided previously, in which it was shown that

lymphocytes from guinea pigs sensitive to SPE A showed higher than expected responses to SPE B (2). It was proposed that the response represented a combination of nonspecific mitogenicity due to SPE B and specific cross-reactive mitogenicity induced by the shared determinant. The enhancement of skin reactivity to the shared determinant may be produced by any of the SPE types. Thus, the scarlet fever rash may be elicited during infection by a streptococcal strain producing any SPE type, after the host has been sensitized to the shared determinant or other streptococcal antigens and in the absence of circulating antibody to the serologically specific primary toxicity.

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