

Mechanisms of clinical desensitization in urticarial hypersensitivity to penicillin

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A patient with known urticarial penicillin allergy and an immediate positive skin test to penicilloyl-polylysine (PPL) had subacute bacterial endocarditis which necessitated high daily intravenous doses of penicillin G (PG). Changes occurred during treatment with penicillin in the titers of both penicilloyl-specific skin-sensitizing antibodies and IgG antibodies. An initial drop of skin-sensitizing and IgG antibodies was followed by a rise in titer of these antibodies. Two mechanisms are thought to have played a role in preventing a severe reaction during the treatment with penicillin: total utilization of skin-sensitizing antibodies and protection by IgG "blocking" antibodies.

Despite its adverse effects, penicillin remains the drug of choice in the treatment of syphilis, gonorrhea, streptococcal throat infections, and subacute bacterial endocarditis. Particularly in the latter, penicillin may be lifesaving and must very often be given despite the possibility of an adverse reaction. Anaphylaxis is the most serious potential adverse reaction and is a real hazard, particularly in patients with positive immediate skin tests to antigens derived from penicillin.^{1, 2}

The patient whom we are about to describe posed this very dilemma. He had subacute bacterial endocarditis requiring treatment with penicillin yet was known to have had clinical allergic reactions to penicillin. Positive immediate skin tests to penicilloyl-polylysine (PPL) placed him in the category of being disposed to have an accelerated or late urticarial reaction following treatment with penicillin,³ but immediate reactions have been reported when such patients have a low titer of IgG hemagglutinating antibodies,⁴ as was the case in this patient. Special precautions were therefore taken to avoid or at least minimize a potential adverse reaction. Subsequently, only a mild urticarial

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reaction occurred in the first few days of treatment despite the fact that 40 million U. of penicillin G (PG) were given intravenously daily for 6 weeks. Repeated direct skin testing, passive transfer tests, and hemagglutination-antibody studies enabled us to follow the changes in antibody titers in great detail. The results suggest that the procedure of administering gradually increasing doses of penicillin led to the clinical loss of sensitivity through the combination of utilization of the skin-sensitizing antibodies present and production of extremely high titers ($>1/64,000$) of "blocking" IgG antibodies.

CASE REPORT

A 26-year-old Caucasian male schoolteacher with subacute bacterial endocarditis was admitted to New York University Hospital on Nov. 27, 1968. Past history revealed that in 1954, at the age of 12, he had had rheumatic fever with damage to the heart valves. At that time he recalls having been treated with penicillin intramuscularly and having developed urticaria. Subsequently, he took penicillin by mouth daily, without any adverse reaction, until the age of 21.

In November, 1963, he was admitted to Bellevue Hospital with subacute bacterial endocarditis and was treated with 20 million U. of PG intravenously daily for 35 days. During and after this course of treatment, he had several attacks of urticaria of moderate intensity. Urticaria was noted on the fourth, fifth, and sixth days of treatment and again 8 days after discontinuation of treatment. Furthermore, on the tenth day of treatment, he developed a severe serum-sickness-like reaction with urticaria, angioedema, arthralgia, and fever. Skin tests performed during the acute phase of the serum-sickness-like reaction with PG, 2×10^{-2} M, and with PPL, 6×10^{-6} M, were negative. Studies for hemagglutinating antibodies were nonrevealing. However, in 1963, the hemagglutination test used was less sensitive than that of 1968. Between 1963 and 1968, the patient received no penicillin and took sulfonamides by mouth for prophylaxis against recurrent infection.

On admission to University Hospital in 1968, repeated blood cultures were positive for alpha hemolytic streptococci sensitive to penicillin. Penicillin therapy, therefore, was deemed highly important.

Schedule for initiating penicillin treatment

Penicillin therapy was started on Nov. 29, 1968. The patient was premedicated with 50 mg. of diphenhydramine, orally. Subsequently, at 20 to 30 minute intervals, he received injections of PG first intradermally, then subcutaneously and intramuscularly, and finally intravenously. Table I summarizes the desensitization schedule and shows that the starting

Table I. *Schedule for administration of penicillin for desensitization for Patient N. L.**

<i>Concentration of PG†</i>	<i>Volume</i>	<i>Route</i>	<i>Approximate dose</i>
1,000 U./ml.	± 0.005 ml.	i.d.	5 U.
5,000 U./ml.	± 0.005 ml.	i.d.	25 U.
25,000 U./ml.	± 0.005 ml.	i.d.	125 U.
50,000 U./ml.	0.01 ml.	i.d.	500 U.
50,000 U./ml.	0.1 ml.	i.d.	5000 U.
50,000 U./ml.	0.1 ml.	s.c.	5000 U.
50,000 U./ml.	1 ml.	s.c.	50,000 U.
50,000 U./ml.	1 ml.	i.m.	50,000 U.
100,000 U./ml.	1 ml.	i.m.	100,000 U.
200,000 U./ml.	1 ml.	i.m.	200,000 U.

*This is not necessarily a recommended procedure for desensitization for patients with all forms of penicillin allergy.

†Given at approximately 20 minute intervals.

dose of 5 U. of penicillin was increased gradually to approximately 200,000 U. per injection. During this procedure, no adverse reactions were noted. Thirty minutes after the last intramuscular injection of 200,000 U. and approximately 4 hours after the first dose of 5 U., 30 million U. of PG in 1,000 ml. of 5 per cent glucose solution was started intravenously at a rate of 40,000 U. per minute. After 4 hours, approximately 9 million U. of PG had been given. By the second day, the dose was increased, and a continuous intravenous drip of 40 million units of PG daily was then maintained for a total of 38 days.

Skin test

The patient was repeatedly tested with PPL, 6×10^{-5} M, and with PG, 2×10^{-2} M. Approximately 0.005 ml. was injected intradermally in the deltoid region. Reactions were read after 20 minutes for wheal and flare, as previously described.³

Passive transfer tests

These tests were done according to standard technique in a human volunteer with the use of a 24 hour latent period. Transfer of serum to a *Macaca mulatta* monkey was done in addition. The animal was anesthetized with Seronyl, 1.5 ml. intramuscularly, and 0.1 ml. of sera was injected intradermally into the abdominal and flank skin. Following a 24 hour latent period, the identical sites were challenged with approximately 0.01 ml. of PPL, 6×10^{-5} M. Controls were performed with saline and challenged similarly.

Hemagglutination tests

Assays for IgG and IgM penicilloyl-specific serum antibodies were performed as previously described.³ Sera were drawn repeatedly during the first 4 days and at approximately weekly intervals thereafter.

RESULTS

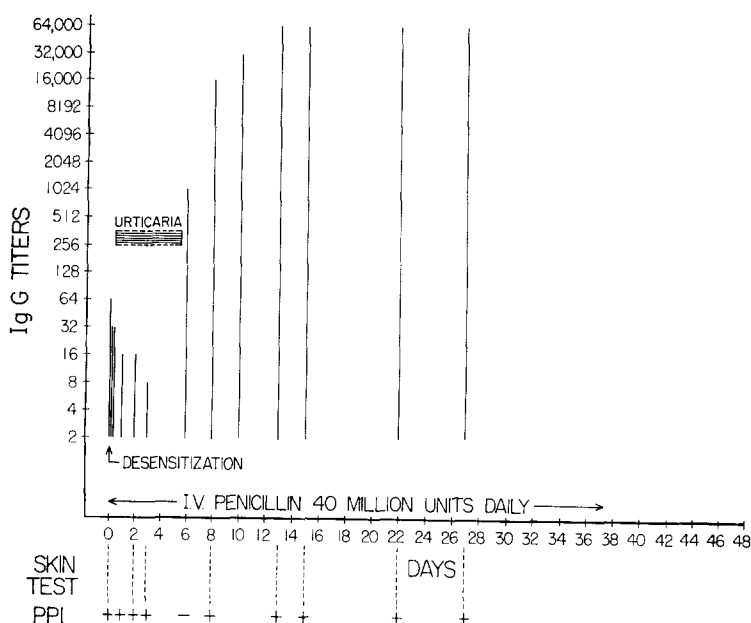
Clinical course

The patient tolerated gradual initiation of penicillin therapy without adverse effect until after 8 hours, when he had received approximately 9 million U. of penicillin and developed several urticarial lesions on the trunk and thighs. The intravenous drip was continued, but its flow rate was decreased, and 50 mg. of diphenhydramine was administered orally. The urticaria subsided within one hour. At about this time, it was noted that there was a pronounced decrease in skin test reactivity to PPL, although the test had not become completely negative. Mild urticaria recurred over the next few days but cleared completely on the sixth day. Fig. 1 correlates the doses of penicillin administered with changes in the clinical status and in the hemagglutinating antibody titers. He was last seen 5 months after hospitalization and was considered to be clinically free from bacterial infection and feeling well.

Skin tests

Skin tests with PG were always negative.* The tests with PPL, however, showed interesting variations (see Table II). The skin test was strongly positive 48 hours before initiation of therapy and showed a 20 mm. wheal and 40 mm. flare. On the next day, immediately before therapy was begun and after the patient had received 50 mg. of diphenhydramine orally, the patient showed

*The "minor determinant" antigenic derivatives of penicillin¹ were not available in time for testing.

**Fig. 1**

Antibody changes during desensitization of a penicillin-sensitive patient.

Table II. *Changes in direct skin test responses to PPL*

Therapy	Time	Test dose (PG)	Skin test response (mm.)		
50 mg. benadryl p.o.	-48 hr.	100 U. i.d.	4+	20W	40F
	-5 hr.				
	-4 hr.	10 U. i.d.	2+	7-8W	35F
	-3 hr.	50,000 U. s.c.	2+	6W	30F
30 mU. PG i.v. drip	-2 hr.	50,000 U. i.m.	1+	5W	15F
	0		1+	5W	15F
	7 hr.	10 U. i.d.	trace	4W	0 F
40 mU. PG i.v. drip	24 hr.	10 U. i.d.	trace	4W	0 F
	6 days	10 U. i.d.	0		
	14 days	10 U. i.d.	2+	9W	20F
	38 days	10 U. i.d.	4+	20W	60F

a 7 mm. wheal and 35 mm. flare in response to skin testing with PPL. Within the first 12 hours after starting treatment, the test became gradually less positive. At 12 hours, the reaction was barely detectable (4 mm. wheal, 5 mm. flare). On the sixth day of treatment, the skin test with PPL had become completely negative. On the fourteenth day, the skin test was again distinctly positive (10 mm. wheal, 20 mm. flare), and at the conclusion of treatment with PG on the thirty-eighth day, it had become even more strongly positive (20 mm. wheal, 60 mm. flare). On Day 155, 5 months after the start of therapy and approximately 4 months after the discontinuation of therapy, the skin test with PPL was still positive.

Hemagglutination tests

Hemagglutinating antibodies were penicilloyl specific, as shown by hapten inhibition studies with excess penicilloyl-propylamine. With the use of 2-mercaptoethanol, antibodies were shown to be IgG. However, the method does not readily permit detection of small amounts of IgM in the presence of large amounts (approximately 50 to 100 μ g per milliliter or greater) of IgG. A blood sample taken after hospitalization, but before any skin tests had been done, revealed the presence of IgG antibodies of low titer (1:8). The titer was 1:64 2 days after initial skin testing. During the first 3 days of penicillin therapy, the IgG titer gradually dropped to 1:8. A rapid and striking rise of the titer to 1:1,024 was noted first on the sixth day after therapy was begun. By Day 13 the level was greater than 1:64,000, where it remained throughout the patient's hospital course. The last follow-up on Day 155 showed a hemagglutination titer of 1:256 IgG.

Passive transfer tests

Passive transfer tests confirmed the absence of skin-sensitizing antibodies on the sixth day of treatment, while serum drawn on the forty-eighth day, 10 days after completion of therapy, gave a positive passive transfer reaction.

DISCUSSION

The word "desensitization" has been used with several meanings in immunologic studies.^{1, 6, 7} From the clinical viewpoint, desensitization refers to a procedure in which a patient with penicillin allergy receives gradually increasing dosages of penicillin, which makes it possible for him to subsequently receive the full dose without developing a serious allergic reaction. Many prefer the term hyposensitization, since what is sought is a state of tolerance to the intended full dosage, without necessarily bringing about a complete loss of sensitivity. In our case, for example, clinical desensitization was not complete at all times as evidenced by the intermittent attacks of urticaria. While we feel that the term hyposensitization would be preferable, we follow common usage and employ the term "desensitization."

From the immunologic viewpoint, however, desensitization in the strict sense denotes either the complete loss of skin-sensitizing antibodies or the production of blocking or neutralizing antibodies in sufficiently high titers to be capable of binding all available antigen or a combination of both mechanisms. It is this aspect of desensitization which we have attempted to study in detail in our patient. In contrast to the many clinical observations and recommendations, little work has been done in regard to the mechanisms involved in desensitization, except for that of Levine¹ and Voss.⁸

Voss described 4 patients with a history of penicillin allergy and positive skin tests to PPL who tolerated penicillin therapy for 3 to 6 weeks after its initiation with gradually increasing dosages. In one case, there was no change in skin test reactivity or hemagglutination antibody titer (IgG 1:16,000). In the 3 other cases, the IgG antibody titer fell in the first days to a low level, and urticaria developed. Subsequently, there was a rise in IgG antibody with

disappearance of the urticaria. Direct skin tests with PPL became completely negative in 2 of the 3 patients and decreased in intensity in the other after 4 weeks of therapy. During the "clinical desensitization," the skin tests remained positive.

Levine¹ performed both skin tests with PPL and PG and hemagglutination tests for IgG and IgM penicilloyl-specific antibodies. His group distinguished 2 meanings of the word "desensitization" relative to penicillin: (1) complete loss of skin-sensitizing antibodies prior to initiation of full dosage of penicillin which is achieved by gradually increasing dosage of antigen, and (2) gradually increasing dosage of antigen without severe allergic reactions. This latter is a clinical definition. Review of the literature shows that clinical desensitization has been successful many times.^{1, 4, 6-8}

In our patient the titer of skin-sensitizing antibodies gradually became lower with treatment as indicated by weaker skin tests reactions, and on the sixth day after desensitization, they were no longer detectable by skin tests or passive transfer. Depletion of skin-sensitizing antibodies by antigen is a likely explanation for this phenomenon. This finding differs from previous reports^{1, 8} where the skin tests changed only after 4 weeks of intensive penicillin therapy and might be considered as true desensitization, since the skin test reaction decreased in intensity even within the first few hours after beginning treatment with penicillin. Probably by the same mechanism, IgG antibody titers promptly and progressively decreased from 1:64 to 1:8 early in penicillin therapy.

The reappearance of skin-sensitizing antibodies 8 days after desensitization and start of therapy is probably best explained as a secondary response following administration of antigen. It is noteworthy that this renewed presence of skin-sensitizing antibodies was not accompanied by any adverse clinical reactions. This is presumably due to the fact that at that very time very high titers of IgG "blocking" antibodies ($>1:64,000$) were present. This is similar to the cases of Voss and associates,⁸ although the titer was lower in their cases (1:4,096) and dropped subsequently to 1:256 within 2 weeks. Such a blocking or neutralizing role has been previously suggested for IgG penicillin antibodies in the penicillin allergy system; i.e., these protective antibodies can delay clinical reactions, alter clinical manifestations into less severe forms, or even completely abolish adverse reactions.^{1, 3, 4, 8} The mechanism of this protective action is thought to be a competition for antigen with skin-sensitizing antibodies. This blocking activity of the IgG antibodies is, of course, not limited to the penicillin system and has been thought to exist in atopic patients after desensitization procedures, e.g., with ragweed.⁹ A similar mechanism has recently been described in a case of urticaria due to insulin.¹⁰

Among the unresolved questions is whether the high titers of IgG, which "protect" against adverse reaction to penicillin, could also interfere with the antibiotic action of the drug by removing it from its intended sites of action on bacteria. In this connection, it should be noted that our patient took an unusually long time (14 days) to defervesce.

However, our results support the role of IgG as a blocking antibody and

indicate that knowledge of penicillin skin test and hemagglutination test results may be of clinical usefulness as a guide to the management of patients with clearly known penicillin allergy who, nevertheless, require treatment with this drug.

REFERENCES

1. Levine, B. B., Redmond, A. P., Voss, H. E., and Zolov, D. M.: Prediction of penicillin allergy by immunological tests, *Annals New York Acad. Sc.* **145**: 298, 1967.
2. Parker, C. W., Shapiro, J., Kern, M., and Eisen, H. N.: Hypersensitivity to penicillinic acid derivatives in human beings with penicillin allergy, *J. Exper. Med.* **115**: 821, 1962.
3. Levine, B. B., Redmond, A. P., Fellner, M. J., Voss, H. E., and Levytska, V.: Penicillin allergy and the heterogeneous immune responses of man to benzylpenicillin, *J. Clin. Invest.* **45**: 1895, 1966.
4. Fellner, M. J., Levine, B. B., and Baer, R. L.: Immediate reactions to penicillin, *J. A. M. A.* **202**: 908, 1967.
5. Levine, B. B., Fellner, M. J., and Levytska, V.: Benzylpenicilloyl-specific serum antibodies to penicillin in man. II. Sensitivity of the hemagglutination assay method, *J. Immunol.* **96**: 719, 1966.
6. O'Driscoll, B. J.: Desensitization of nurses allergic to penicillin, *Brit. M. J.* **2**: 473, 1955.
7. Reisman, R. E., Rose, N. R., Witebsky, E., and Arbesman, C. E.: Penicillin allergy and desensitization, *J. ALLERGY* **33**: 178, 1962.
8. Voss, H. E., Redmond, A. R., and Levine, B. B.: Clinical detection of the potential allergic reactor to penicillin by immunologic tests, *J. A. M. A.* **196**: 679, 1966.
9. Lichtenstein, L. M., Norman, P. S., and Winkenwerder, W. L.: Antibody response following immunotherapy in ragweed hay fever: Alpyral vs. whole ragweed extract, *J. ALLERGY* **41**: 49, 1968.
10. Reisman, R. E., Dolovich, J., Schnatz, J. D., Yagi, Y., and Arbesman, C. E.: Immunologic studies of insulin allergy and resistance, *J. ALLERGY* **43**: 169, 1969. (Abst.)