

PENICILLIN ALLERGY AND DESENSITIZATION

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ALLERGIC reactions to penicillin are a serious problem of increasing magnitude. To date, the physician must still rely upon a complete carefully obtained history as the major indication of possible potential reactors. As will be discussed later, skin tests and other immunologic procedures have not solved this problem. From a clinical standpoint, this problem is further complicated by the ability of some patients previously intolerant to penicillin to receive it without difficulty at a later date.

At times, the occasion may arise when penicillin should be given, despite an authenticated past history of abnormal reactions to this drug. Such a problem in a patient with immunologic evidence of penicillin reactivity did confront us. The following report contains the detailed clinical and immunologic studies in this case and summarizes our general experiences with penicillin allergy.

CASE REPORT

A 27-year-old woman, with congenital heart disease, was admitted to the Buffalo General Hospital because of fever of one month's duration. She had been taking oral "prophylactic" penicillin daily until 2 months prior to the hospital admission when generalized urticaria occurred 10 minutes after ingestion of a 250,000 unit tablet. The urticaria responded readily to antihistamines. Penicillin was discontinued and no other antibiotic therapy was given. No further hives occurred. Sulfonamides had caused fever several times in the past and were, therefore, specifically withheld.

Blood cultures taken on the first and second hospital days contained about 80 colonies per milliliter of an alpha hemolytic streptococcus and confirmed the provisional clinical diagnosis of subacute bacterial endocarditis. In view of this severe septicemia, penicillin was recommended as the necessary and most effective therapy.

The status of the patient's suspected penicillin allergy became most important. Intradermal skin tests with aqueous penicillin G suspended in normal saline revealed the following reactions:

<i>Penicillin</i> -----Units/ml.	<i>Skin Reaction</i> (1+ - 4+ scale)
100	++
1,000	+++
10,000	+++
Control-Saline	0

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The direct hemagglutination test for penicillin antibodies, as described by Ley¹ and modified slightly,* was weakly positive.

After thorough consideration of the relative risks involved, a course of "penicillin desensitization" was outlined, with the hope that large therapeutic doses could subsequently be safely administered. The schedule was started and maintained in the absence of any adverse reactions (Table I). All injections were given intramuscularly in the deltoid muscle.

TABLE I. DRUG AND DOSAGE OF DESENSITIZATION PROCEDURE

TIME	CRYSTALLINE PENICILLIN G UNITS (1 M IN DELTOID)	EPINEPHRINE HCl 1:1000 (C.C.)	DIPHENHYDRAMINE
0		0.3	50 mg. (intramuscularly)
30 min.	100	0.2	
1 hr.	1,000	0.2	
1 hr., 30 min.	10,000	0.2	
2 hr.	100,000	0.2	
2 hr., 30 min.	1,000,000	0.2	
3 hr. and every 3 hr. thereafter			50 mg. (oral)
6 hr., 30 min. and every 6 hr. thereafter	1,000,000	0.2	

Twenty-four hours after the onset of therapy, the intramuscular injections were switched to the buttocks. Antihistamines and epinephrine were discontinued after 8 days and 9 days of therapy, respectively. Four million units of procaine penicillin administered intramuscularly were continued for 6 weeks with no ill effects.

The patient became afebrile after 2 days of therapy and all later blood cultures were sterile.

Intradermal skin tests with up to 100,000 units of crystalline penicillin G per milliliter were repeated on the seventh, tenth, and twenty-first days after the onset of therapy and were all completely negative. Skin-sensitizing antibodies against penicillin in the patient's serum were not detectable, either prior to or throughout the course of penicillin therapy. The hemagglutination reaction became much stronger, reaching a titer of 1:64 antiserum dilution. This titer subsequently dropped, but the hemagglutinating antibody was detectable throughout the hospital course (Table II).

TABLE II. HEMAGGLUTINATION TITERS FOLLOWING ONSET OF PENICILLIN THERAPY

DAY	TITER
0	2
4	2
7	4
10	16
14	64
16	32
21	32
26	16
34	16
40	8
1 year	0

*Hemagglutination Method.—Eight cubic centimeters of citrated O Rh negative blood was added to a 200,000 unit vial of aqueous crystalline penicillin G. After incubation at 37° C. for one hour, the vial was placed in the refrigerator and allowed to stand at least 24 hours before usage.

An aliquot of "penicillinized" cells was withdrawn, washed three times in buffered saline, pH 7.2, and made up to a 3 per cent suspension. One tenth milliliter of these cells was added to 0.3 ml. of the patient's sera prepared in serial dilutions. After 15 minutes of incubation at room temperature, the tubes were lightly centrifuged and the agglutination read directly.

Following the patient's hospital discharge, penicillin was discontinued. About 2 months later, oral penicillin was again prescribed by another physician because of tonsillitis. Ten minutes after the first tablet, generalized urticaria recurred. Epinephrine promptly relieved this exacerbation. The tonsillitis was effectively treated with erythromycin.

One year after her hospitalization, the patient was re-examined. She was asymptomatic and had received no further penicillin. Intradermal tests using up to 200,000 units per milliliter of penicillin G were negative. The hemagglutination titer was also negative.

ADDITIONAL EXPERIMENTAL OBSERVATIONS

Sera obtained from other patients with suspected penicillin allergy were examined for the presence of hemagglutinating and skin-sensitizing antibodies. Direct skin tests with aqueous penicillin (up to 10,000 units per milliliter) were also performed on some patients.

The results of direct skin tests and passive transfer tests following various types of penicillin reactions are recorded in Table III. A large percentage of positive reactions were found.

TABLE III. RELATIONSHIP OF THE TYPE OF CLINICAL REACTION AND THE PRESENCE OF PENICILLIN SKIN-SENSITIZING ANTIBODIES

	DIRECT SKIN TEST*		PASSIVE TRANSFER TEST	
	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
Anaphylactoid	3	1†	3	0
Urticaria	2	2	8	5
Serum sickness	1	0	1	0
Maculopapular rash			0	2

*Four patients were tested by both methods. Two patients with urticaria and one patient with a serum sickness-like reaction had both positive direct and passive transfer tests. One patient with urticaria had negative direct and passive transfer tests.

†This patient had an anaphylactoid reaction several years prior to testing.

A hemagglutinating antibody was demonstrated in the sera of 23 of 76 patients with suspected penicillin reactions. Seven of 133 sera obtained from patients receiving large parenteral doses of penicillin without any evidence of an adverse clinical reaction were positive. Ninety-nine random blood bank sera were all negative. The hemagglutination titers in both groups were essentially comparable. Our results and those reported by Harris and Vaughan² are compared in Table IV.

TABLE IV. INCIDENCE OF PENICILLIN ANTIBODY, COMPARING RESULTS WITH THOSE REPORTED BY HARRIS AND VAUGHAN

PATIENTS	INCIDENCE OF POSITIVE HEMAGGLUTINATION	
	PRESENT AUTHORS	HARRIS & VAUGHAN
Probable reactions	23/76	6/16
Receiving penicillin*	7/133	3/307
Random "normal" sera	0/99	0/167

*Our group consisted of adult patients receiving several million units of penicillin parenterally daily. Harris and Vaughan's group were children receiving oral prophylactic penicillin.

The results of hemagglutination tests following various types of penicillin reactions are summarized in Table V. Fifteen of 45 patients with urticarial

reactions and 4 of 11 patients with anaphylactoid reactions had hemagglutinating antibodies. In our experience, patients developing serum sickness-like reactions, maculopapular rashes, and several other miscellaneous reactions were less likely to have positive hemagglutination reactions.

TABLE V. COMPARISON OF THE TYPE OF CLINICAL PENICILLIN REACTION WITH THE PRESENCE OF HEMAGGLUTINATING ANTIBODIES

TYPE OF REACTION	PRESENT AUTHORS	HARRIS & VAUGHAN ²	HEGGIE ³
Urticaria	15/45	1/4	18/53
Serum sickness	0/5	2/2	
Maculopapular rash	1/5	1/6	
Anaphylactoid	4/11		
Miscellaneous*	1/5		

*One patient receiving penicillin developed asymptomatic eosinophilia, up to 60 per cent, and had a positive hemagglutination titer. The four negative reactions in this group were in patients who, after penicillin, had the following symptoms: exacerbation of asthma, generalized pruritis, a lupus erythematosus-like reaction, and generalized angitis.

Comparison of the presence of hemagglutinating antibodies and skin-sensitizing antibodies revealed no definite relationship (Table VI).

TABLE VI. RELATIONSHIP OF THE PRESENCE OF SKIN-SENSITIZING AND HEMAGGLUTINATING ANTIBODIES

SKIN TEST	HEMAGGLUTINATION TITER	
	POSITIVE	NEGATIVE
Positive 15	7	8
Negative 9	3	6

Passive transfer studies were done using sera from 3 patients who had skin-sensitizing antibodies which developed following penicillin G therapy. Sensitized sites on normal recipients were challenged with three types of penicillin. The results are found in Table VII. Penicillin G and sodium dimethoxyphenyl penicillin* produced wheal erythema reactions with all three sera. Potassium phenethicillin reacted with two of three sera.

TABLE VII. PASSIVE TRANSFER STUDIES OF THE PENICILLIN REAGIN

SENSITIZING ANTISERUM	CHALLENGING ANTIGEN	REACTION
FN	Penicillin G	+
FN	Potassium phenethicillin*	++
FN	Sodium dimethoxyphenyl penicillin†	+
JT	Penicillin G	++
JT	Potassium phenethicillin	++
JT	Sodium dimethoxyphenyl penicillin	++
MR	Penicillin G	+
MR	Potassium phenethicillin	0
MR	Sodium dimethoxyphenyl penicillin	+

The challenging doses were penicillin G and potassium phenethicillin—10,000 units per milliliter, and sodium dimethoxyphenyl penicillin—100,000 units per milliliter.

*Syncillin, Bristol Laboratories, Syracuse, N. Y.

†Staphicillin, Bristol Laboratories, Syracuse, N. Y.

Inhibition of patient E. B.'s hemagglutination reaction with various types of penicillin was also done (Table VIII). All of the various penicillin preparations showed inhibiting ability.

*Supplied by Bristol Laboratories, Syracuse, New York.

TABLE VIII. RESULTS OF INHIBITION OF HEMAGGLUTINATION BY VARIOUS TYPES OF PENICILLIN

ANTIGEN DILUTION	# 1	# 2	# 3	# 4	# 5	# 6
Undiluted	0	0	0	0	0	0
1-2	0	0	0	0	0	0
1-4	+	+	0	0	0	0
1-8	+	+	0	0	0	0
1-16	++	+	0	0	+	+
1-32	++	+	0	0	+	+
1-64	++	+	0	+	++	+
1-128	++	++	+	++	++	+
1-256	++	++	+	++	++	++
0	++	++	++	++	++	++

0.1 ml. of inhibiting antigen incubated for 3 hr., with 0.5 c.c. of antisera, day 14, diluted 1:20. 0.1 c.c. of a 3 per cent suspension of red cells coated with penicillin were then added. Following 15 min. incubation, the tubes were centrifuged and the suspensions read.

- #1 Penicillin G, 100,000 U./ml.
 #2 Penicillin O, 100,000 U./ml. (Cer-O-Cillin, Upjohn Co., Kalamazoo, Mich.).
 #3 Penicillin V potassium, 100,000 U./ml. (V-Cillin K, Eli Lilly Co., Indianapolis, Ind.).
 #4 Penicillin V 100,000 U./ml. (V-Cillin, Eli Lilly Co., Indianapolis, Ind.).
 #5 Potassium phenethicillin, 100,000 U./ml. (Syncillin, Bristol Laboratories, Syracuse, N. Y.).
 #6 Sodium dimethoxyphenyl penicillin, 1,000,000 U./ml. (Staphcillin, Bristol Laboratories, Syracuse, N. Y.).

DISCUSSION

The greatest experience with desensitization procedures has been with individuals allergic to foreign sera. Prior to the availability of antibiotics and the widespread use of active immunization programs, products made from horse serum were a major therapeutic tool. There often was nothing else to offer patients, and consequently the problem of horse serum sensitivity was more serious and more common than it is today. The method of desensitization used to prevent anaphylaxis in animals was adapted as the model for human work. The experience with human desensitization to horse serum has been reviewed in detail by Ratner.⁴ The most common approach has been the use of small, gradually increasing, parenteral doses of horse serum, given at short intervals. Theoretically, gradual neutralization of circulating or cellular antibodies is thus accomplished. This method has proved successful in some patients. However, it must be undertaken with great care, as severe reactions and fatalities have occurred.

A second approach to desensitization in animals is the use of a single large injection of antigen. Apparently reactions can be inhibited by antigen in great excess. This method has not been attempted in humans. However, there are some data to suggest that excessively large doses of horse serum produce fewer incidences of serum sickness than doses under 100 ml.⁴

Very little information is available about conversion of positive immediate skin tests following desensitization procedures.

In addition, there is still great doubt that desensitization can be accomplished in atopy. Ratner⁴ reviewed a case reported by Alexander⁵ and described this as "the only instance of the successful administration of large amounts of serum to a genuine 'horse asthmatic' of which I am aware." It has been

shown that the naturally occurring reagin differs from the artificially induced reagin occurring with serum disease.⁶ Thus, the nature of the reagin may be important in determining successful response to desensitization. This, of course, might also be related to the degree of sensitivity, as most "horse asthmatics" are extremely sensitive individuals.

Several reports of desensitization to drugs have been recorded. Corcoran,⁷ in 1938, successfully and rapidly desensitized a diabetic patient who had had generalized urticaria from insulin. Prior to the desensitization procedure, the patient had immediate skin reactions to beef, hog, and sheep insulin. Small, gradually increasing doses of insulin were given about every 15 to 30 minutes. After 15 hours, the patient was able to tolerate 40 units administered intravenously. Subcutaneous insulin evoked no real reaction following desensitization. Peck and associates⁸ reported successful desensitization of several patients who had had urticarial and erythematous vesicular allergic reactions to penicillin. This was accomplished slowly, by giving parenteral penicillin thrice weekly in gradually increasing doses. One of their patients had markedly positive delayed skin reaction to penicillin, which became negative following desensitization. One case of successful oral desensitization was also described.

O'Driscoll⁹ reported successful desensitization of a nurse who developed swelling of her eyelids when handling penicillin. Penicillin was given intramuscularly in increasing daily doses. Antihistamines were "helpful" in preventing reactions. A patch test was markedly positive prior to desensitization. Afterward, an intradermal test was apparently equivocal, being reported as the same as the control. The nurse returned to work and was able to handle penicillin without difficulty.

An experience similar to ours was reported by Balme and Dormer.¹⁰ Their patient had subacute bacterial endocarditis due to *Streptococcus viridans* and had an anaphylactoid reaction to a first dose of intramuscular penicillin. Subsequently, an immediate reaction was elicited by testing with subcutaneous penicillin. Attempted treatment with another antibiotic was unsuccessful. Two months after the anaphylactoid reaction, desensitization was attempted. Antihistamines were given with small, increasing doses of parenterally administered penicillin. Only slight urticaria occurred after the first two injections. By the sixth day, antihistamines were stopped and full doses of penicillin were tolerated successfully for 6 weeks. No follow-up skin tests were reported. Vallery-Radot and co-workers¹¹ also reported a successful desensitization experience handled in the same manner.

Prevention of penicillin reactions with concomitant administration of antihistamines has been suggested by several investigators.^{12, 13} On the other hand, Seiple and co-workers,¹⁴ in a controlled study of over 4,500 patients, could find no evidence of decreased reactions with the use of antihistamines. In another large, well-controlled study, Mathews and colleagues¹⁵ also found that both oral and parenteral antihistamines did not effect the reaction rate to penicillin. However, the incidence of immediate urticarial reactions (as our patient experienced) was significantly reduced by added antihistamines. Coleman and Siegel¹⁶ showed that antihistamines failed to prevent contralateral passive trans-

fer reactions, and, hence, concluded that these drugs would be unlikely to prevent anaphylactoid reactions to penicillin.

The action of epinephrine in reducing capillary permeability and affording immediate relief in the treatment of urticaria is well known. It could well have played a major role in the success of the desensitization procedure in our patient.

Successful prophylaxis of delayed type penicillin reactions by the use of adrenal corticosteroids has been reported.¹⁷ There is very little available information concerning the effect of steroids upon immediate or anaphylactoid reactions. However, most animal experiments indicate that steroids have no effect upon the induction of anaphylaxis.¹⁸ Also, the occurrence in allergic patients of immediate direct skin reactions, which are mediated by reagins, is not influenced by prior steroid administration. Thus, the evidence suggests that adrenal steroids would have little value as prophylactic therapy of the immediate type of drug reactions.

Attempts have been made to define the immunologic mechanisms responsible for the variety of allergic manifestations caused by penicillin. In particular, a skin-sensitizing antibody and a hemagglutinating antibody, as measured by the method of Ley, have received much attention.

Reagins to penicillin have been implicated as causing immediate reactions. Kern and Wimberly¹⁹ stated "that the development of a wheal and erythema constitute a positive test and is indicative of a high degree of sensitivity with real danger of anaphylaxis. It would be dangerous to give penicillin to such a patient." Siegel and Coleman²⁰ concluded, after studying 11 cases of immediate reactions, "all allergic shock reactions to penicillin in our experience, have been upon a reaginic mechanism." However, they point out that the reagins disappeared from the circulation within several months after the clinical reaction. Tuft and Gregory²¹ noted a similar experience. One may wonder if skin sensitivity to penicillin continues to reflect systemic sensitivity.

In large scale penicillin skin testing of normal people, very few positive reactions have been found. Smith²² reported one anaphylactoid reaction in 778 soldiers who had negative tests to penicillin. Johnston and Cazort²³ reported only 7 positive scratch tests in over 7,000 patients tested. They enthusiastically support testing prior to penicillin therapy. Carr²⁴ summed up these results as follows: "Skin tests are apparently valuable in predicting anaphylaxis from penicillin, in that they are seldom negative falsely, although false positive reactions occur."

However, a study by Idsoe and Wang,²⁵ in Formosa, has raised serious contradictory evidence. All patients receiving penicillin were first skin tested. Following penicillin therapy, 22 anaphylactoid reactions occurred. Of these, 16 patients had had *negative* scratch or intradermal tests prior to therapy. Thus, the question still appears unsettled.

In our own limited experience, we have found passive transfer antibodies in 6 of 7 patients following anaphylactoid reactions (see Table III). This confirms reports of several other investigators. Also, 8 of 14 patients following

urticarial reactions and one patient with a serum sickness-type reaction have had skin-sensitizing antibodies.

Failure to transfer passively the penicillin reagin with antisera obtained prior to therapy (and when patient E. B. had a positive direct skin test) may be a quantitative phenomena. As a parallel, we have seen numerous patients, with serum disease following administration of tetanus antitoxin, who retain direct positive skin tests to horse serum indefinitely, although positive passive transfer is temporary.

In recent years, a hemagglutinating antibody to penicillin has been widely investigated. Ley¹ found 25 positive sera of 2,000 examined. All 25 patients had received penicillin and a "minority" had reactions. Watson²⁶ examined 3,000 unselected sera and found 40 positives. These patients were all receiving penicillin and none had had reactions. However, our experience, and that of others, has indicated that this hemagglutinating antibody is more likely to be an indication of penicillin sensitivity. The antibody was found in the sera of approximately one third of patients with probable penicillin reactions. It was present in only about 5 per cent of patients receiving large amounts of penicillin and not found in the large number of "normal" sera which were screened. The hemagglutinating antibody occurred most frequently in patients who had urticarial and anaphylactoid reactions (see Table V). However, only about one third of the patients with these reactions had penicillin hemagglutinating antibodies.

The present work of DeWeck and Eisen²⁷ suggests that it may be the breakdown products of penicillin, as penicillinic acid, which are the active allergens or antigens, rather than penicillin itself. Failure of the various immunologic procedures may thus be due to an inappropriate testing material.

The use of different types of penicillin, particularly those claimed to be "less allergenic," has been recommended as another method of treating sensitive patients. However, our clinical experience has not borne out this claim of lowered allergenicity. Also, our immunologic studies, and those of others, have indicated cross antigenicity of various types of penicillin.²⁸ It is of interest that the two types of penicillin which were claimed to be nonallergenic, penicillin O and potassium phenethicillin were at least as antigenic in the hemagglutination inhibition test as penicillin G, against which the antibodies were formed. Inhibition studies with other penicillin antisera have also shown cross antigenicity of the various penicillin preparations. Therefore, it would seem that, from an immunologic viewpoint, there is limited value in treating sensitive patients with different types of penicillin.

SUMMARY AND CONCLUSION

1. It was possible to give large therapeutic doses of penicillin to a patient who had a history of allergy to penicillin and a strongly positive intradermal skin test by the use of a gradual desensitization program. It is not suggested that this be tried in all patients sensitive to this medication. Attempted desensitization should be reserved for those instances where penicillin is the drug of choice for a seriously ill patient.

2. Reagins were found by either direct skin testing or passive transfer studies in 6 of 7 patients with anaphylactoid reactions. Hemagglutinating antibodies were present in about 33 per cent of patients with either of the above type reactions. There was a poor correlation between the presence of hemagglutinating and reaginic antibodies.

3. Hemagglutinating inhibition tests and passive transfer tests both indicated cross reactivity of various types of commercially available penicillin.

4. There is great need for better immunologic testing in the field of drug allergy. The use of breakdown products of penicillin may shed new light in this direction.

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