IMMUNOLOGICAL STUDIES ON PATIENTS DEVELOPING URTICARIA ASSOCIATED WITH PENICILLIN THERAPY*

J. LAMAR CALLAWAY, M.D. AND SHERWOOD W. BAREFOOT, M.D.

From the Division of Dermatology and Syphilology of the Department of Medicine, Duke University School of Medicine, Durham, North Carolina

It is not uncommon for patients receiving penicillin to develop urticaria. In most instances this reaction is quite severe and persistent. Keefer and associates (1) have reported fourteen instances in 500 patients, and Lyons (2) twelve instances in 209 patients treated with penicillin. Whether the urticarial responses are due to penicillin *per se* or to the incorporated impurities can not be ascertained until crystalline and absolutely pure penicillin is available. Feinberg (3) found that patients who showed positive skin tests to various extracts of *penicillia* gave negative skin tests to penicillin. Therefore, it would seem that there is not necessarily a cross sensitization between the spore and its products.

The findings in urticaria assumed to be due to penicillin cast some doubt on whether or not these reactions are produced by a true antigen-antibody reaction. Several investigators have tried to establish such a relationship with varying results. Lyons (2) was unable to demonstrate positive skin tests or circulating precipitins in patients who developed urticaria associated with penicillin therapy. In a patient who had not had urticaria, but who displayed a tuberculin-type of skin test to crystalline sodium penicillin, Welch and Rostenberg (4) were unable to demonstrate precipitins in the patient's serum. With some samples of penicillin tested for precipitins with this patient's serum a fine precipitate developed, but this was also demonstrated with normal control sera. Passive transfer tests were negative with this patient's serum. Later the same authors (5) tested 144 individuals who had not had prior contact with penicillin and found 5% to exhibit a positive reaction of the tuberculin type when tested with crystalline penicillin sodium intracutaneously. Passive transfer antibodies could not be demonstrated. In four of these subjects in whom hypersensitivity to penicillin was not present at the outset, but who exhibited reactions of the Arthus type following repeated intradermal injections of penicillin (this phenomenon did not occur following subcutaneous and intramuscular injections of penicillin), they were unable to demonstrate either passive transfer antibodies or serum precipitins.

In a case of urticaria associated with penicillin therapy, Criep (6) reported a positive intracutaneous test, positive passive transfer tests, and precipitins to penicillin, but anaphylactic antibodies were not demonstrated. Barker (7) reported a case of urticaria associated with penicillin therapy with the patient

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exhibiting a positive intracutaneous test to penicillin; and also a patient with dermatitis venenata attributed to penicillin who showed a positive patch test to penicillin.

Kolodny and Denhoff (8) performed intradermal tests in 124 patients who had been treated with penicillin and obtained positive reactions in 21 instances, 7% of which were delayed reactions. Clinical penicillin reactions did not recur consistently in all patients subsequently given additional therapy. The time interval between courses of penicillin bore no relationship to the incidence of clinical reactions in these patients.

McGuire (9) has recently reported a case which seemed to demonstrate a localized sensitivity to extragenous impurities incorporated with penicillin. The patient developed a contact dermatitis at the application site of an ointment containing crude penicillin. This reaction was associated with a disseminated "id". Subsequently, patch tests to the crude penicillin were positive at the site of the original contact dermatitis but negative on other parts of the body. Patch tests with purified penicillin were negative at the site of the original contact dermatitis. Passive transfer tests with blister fluid removed from the area of the contact dermatitis suggested a transfer of antibodies, but were negative with serum obtained from the "id" lesions.

McClosky and Smith (10) feel that they have demonstrated penicillin sensitization in guinea pigs. From their experiments, conclusions were drawn that the antigen-antibody combination is present but lacks permanency and is more readily reversible than in the case of anaphylactic reactions following bacterial or protein sensitization.

Often the course of urticaria associated with penicillin therapy is very bizarre. It may occur at the beginning, several days after institution, or several days after the termination of therapy. As an example of the bizarre cases sometimes seen, the following example is described. A patient with primary syphilis received 2,400,000 units of penicillin over a period of $7\frac{1}{2}$ days. On the 5th day of treatment a severe generalized urticaria appeared. The urticaria subsided soon after the course of penicillin had been completed. One month later the patient suffered a cutaneous relapse and was again given penicillin. During the first three days of therapy, he experienced severe urticaria which subsided in spite of the fact that penicillin was continued. He was then free from urticaria for three days although he was given no treatment for the urticaria, after which the urticaria recurred and persisted until the course of penicillin had been completed. Intracutaneous skin tests were negative to two penicillin preparations with identical lot numbers as those which he received during the two courses of penicillin therapy.

From the foregoing, it is evident that to date it is an unsettled question as to whether or not penicillin induces antibody formation in man. We have studied five patients who developed urticaria associated with penicillin therapy for evidences of the presence of penicillin antibodies and have obtained the following data:

CASES STUDIED

Four of the patients (1, 2, 3, and 4) who were used in this study were among those included in a previous report (11), on the efficacy of Benadryl.

Case 1: A 17 year old white female was given 20,000 units of sodium penicillin every three hours for sixteen days for "pneumonia". Subsequent studies revealed that she had a primary atypical pneumonia, and the penicillin was discontinued. There were no apparent clinical benefits from the penicillin.

Two days after penicillin was discontinued, a mild urticaria developed. Three days later, the urticaria became severe and at this time the patient was started on 50 milligrams of Benadryl four times daily. Within four hours after this treatment was started, she was free from itching and within three days the urticaria had completely subsided.

A review of her past history revealed that she had never previously had urticaria nor any allergic manifestations. There was no history of allergic stigmata in her family.

Case 2: A 44 year old white man had physical and spinal fluid findings indicative of tabes dorsalis. His syphilitic infection has been present for twenty-two years. Although his antisyphilitic treatment had been inadequate, his blood serologic tests for syphilis were negative.

Two days after completing a course of sodium penicillin therapy consisting of 50,000 units intramuscularly every three hours for eighty doses (total of 4,000,000 units), he developed a severe generalized urticaria. He experienced immediate relief with 50 milligrams of Benadryl four times daily. After two days the drug was discontinued for twenty-four hours, and there was an immediate exacerbation of the urticaria. Benadryl was again resumed and he was free from urticaria after three additional days of this therapy.

He had never previously had urticaria nor any other allergic tendencies, and there was no history of allergy in his family.

Case 3: A 42 year old white female received 20,000 units of penicillin every three hours for seven days because of hidroadenitis axillaris. Two days after the penicillin was discontinued, she developed severe generalized urticaria. She was immediately started on 50 milligrams of Benadryl four times a day. After three days the dosage was increased to 300 milligrams each day because of persistence of urticarial lesions. Having received Benadryl for five days, she was completely free from urticaria although she was extremely drowsy while on this therapy.

There was no history of urticaria nor other allergic stigmata in the patient or her family.

Case 4: A 21 year old white female developed urticaria after having received 20,000 units of sodium penicillin intramuscularly every three hours and daily instillations of a solution of sodium penicillin into an empyema cavity for two weeks. After two days of urticaria, she was started on Benadryl, 50 milligrams four times daily with almost immediate relief. The penicillin therapy was continued for two weeks during which she remained free from urticaria except when the Benadryl was temporarily stopped for 2 days after having received the drug for five days.

Case 5: A 26 year old white male physician was admitted to the hospital because of severe impetigo of the face of four days duration. He was started on wet dressings and cremolin containing 500 units of sodium penicillin per cc. locally. He also received 10,000 units of sodium penicillin intramuscularly every three hours. On the fourth hospital day the penicillin was increased to 20,000 units every three hours. The impetigo responded satisfactorily to treatment but on the eighth hospital day, the patient developed a severe generalized urticaria with marked angioneurotic edema of the hands and feet. This subsided within five days following the administration of as much as 400 mgms. of Benadryl daily supplemented by 25 mgms. of ephedrine sulphate by mouth three times daily and occasional subcutaneous injections of 2 cc. of adrenalin in oil.

Four months previous to admission he had received intramuscular penicillin for 6 days for an acute exacerbation of bilateral chronic mastoiditis and otitis media.

Two years previously the patient developed acute urticaria while receiving sulfadiazine for an acute sinus infection. For several months previously he had been treated with insufflations of sulfadiazine powder into the auditory canals for bilateral chronic otitis media. There had been no other allergic stigmata.

His father is said to have developed asthma while on sulfonamide therapy although he had no history of respiratory difficulty before or after sulfonamide therapy.

IMMUNOLOGICAL STUDIES

Blood was obtained from all five patients within 24 hours after the urticaria had completely subsided. At the same time, the patients were tested to sodium penicillin by the intracutaneous method.

The manufacturer and lot number of the penicillin were known but were different in the case of patients 2 and 5; and were unknown for the other patients. Penicillin made by the same manufacturer and of the same lot number as that which patient 2 received was used for the immunological studies of patients 1, 2, 3, and 4. Patient 5 was studied with penicillin identical with that which he was receiving at the time the urticaria appeared. Serum from a normal, non-allergic individual who had never received penicillin was used as a control in these studies.

RESULTS OF SKIN TESTS

Each of the five patients was given intracutaneously 0.05 cc. of a solution of normal saline containing 20,000 units of sodium penicillin per cc. on the volar surface of the right forearm and a similar amount of normal saline intracutaneously on the volar surface of the left forearm. All of the intracutaneous tests were negative at 30 minutes, twenty-four hours, and forty-eight hours.

PASSIVE TRANSFER TESTS

Nine non-allergic individuals who had never received penicillin were selected for these studies. Two of these individuals were injected intracutaneously on the back with 0.1 cc. of blood serum from each of patients 1, 2, 3, and 4, as well as 0.1 cc. of normal control blood serum and 0.1 cc. of normal saline. Thirty-six hours later each site was injected with 0.1 cc. of normal saline containing 10,000 units of sodium penicillin per cc. There was no reaction at any of the sites within two hours, nor at twenty-four and forty-eight hours.

Two other subjects were tested for the so-called "distant reaction" with blood serum from each of patients 1, 2, 3, and 4 and serum from the control along with normal saline as in the above subjects. Thirty-six hours later the two subjects were given 30,000 units of sodium penicillin intramuscularly into the gluteal muscles. These two subjects were observed for two hours after the penicillin injection and at twenty-four and forty-eight hours and no positive reaction was observed.

Reversed passive transfer tests were employed in two subjects using serum from patients 1, 2, 3, and 4. This technique consisted of giving two injections of 30,000 units of penicillin into the gluteal muscles two hours apart. Two

hours after the second injection of penicillin each subject was injected intracutaneously on the back with 0.1 cc. of serum from patients 1, 2, 3, and 4 and the control along with a similar amount of normal saline. These subjects were observed for two hours, at twenty-four hours, and at forty-eight hours. No positive reactions were observed.

Three other subjects were tested for passive transfer antibodies (one by the Prausnitz-Kuestner reaction, one for "distant reactions" and the third by the reversed passive transfer method) with serum from patient 5 using sodium penicillin of identical lot number and made by the same manufacturer as that which he was receiving at the time the urticaria appeared. The same technical details as described previously were used in the performance of the tests. These studies also gave negative results.

PRECIPITIN TESTS

Precipitin tests were performed with sera from patients 1, 2, 3, and 4, and the control using penicillin identical to that which patient 2 was receiving at the time his urticaria developed. Serum from patient 5 and from the control were tested against sodium penicillin identical to that which this patient had received therapeutically. Serum dilutions of 1–10, 1–100, 1–1,000, 1–10,000, and 1–100,000 were made. Normal saline containing 500, 5,000 and 20,000 units of sodium penicillin per cc. was tested against each serum dilution. In every instance, including the control tests, a fine precipitate was noted at the junction of the serum and penicillin solutions. Welch and Rostenberg (4) have reported a similar experience in the performance of precipitin tests with many preparations and attribute this phenomena to chemical contaminants.

SUMMARY AND CONCLUSIONS

1. Five patients who developed urticaria associated with penicillin therapy were studied for hypersensitivity and for circulating antibodies to sodium penicillin by means of intracutaneous tests, passive transfer tests, (including the usual Prausnitz-Kuestner reaction, "distant reaction", and reversed passive transfer test) and precipitin tests. All intracutaneous and passive transfer tests were negative. The precipitin tests were inconclusive because all dilutions of sera, including those from a control, showed a fine precipitate at the junction of the sera and the penicillin solutions.

2. In two patients (Case 2 and 5), we were able to use in the immunological studies penicillin identical with that which the patients received therapeutically and to which they had reacted clinically. The immunological studies in these patients were in no way different from those in three patients who had received penicillin of which the manufacturer and lot number were unknown.

3. In all instances the urticaria was controlled by Benadryl. Hence, it is assumed that an excessive amount of histamine was present to account for the urticaria, but from the studies reported the urticaria cannot be accounted for on the basis of an antigen-antibody reaction.

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