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Original Articles

FATAL AND NEAR-FATAL PENICILLIN ANAPHYLAXIS

THREE NEW CASES WITH A NOTE ON PREVENTION

SHEPPARD SIEGAL, M.D., ROGER W. STEINHARDT, M.D.,
AND ROBERT GERBER, M.D., NEW YORK, N. Y.

THAT penicillin may occasionally be a dangerous and even fatal drug should be known to the profession. In terms of direct toxicity the extraordinary antibiotic efficacy of this drug appears to have been matched by its innocuousness and as a result it is being used very freely. Allergic reactions have constituted the sole toxic manifestation attendant upon its administration.

For the most part the allergic reactions to penicillin have not been severe, being chiefly manifested by episodes of urticaria. However, more marked and serious reactions have been the subject of increasing by frequent reports. These have ranged from the complete serum sickness syndrome to instances of purpura with clear evidence of visceral improvement.[1, 2] More dangerous still are instances of exfoliative dermatitis, which may go on to fatal termination. In such cases autopsy may reveal an inflammatory reaction affecting the smaller veins and arteries.[3] Similar but even more extensive vascular lesions have been encountered at post-mortem examination in cases characterized by bullous purpura and fever.[4] Penicillin must therefore be added to the growing roster of chemotherapeutic agents which can initiate a widespread vascular reaction which may prove fatal even in this day of potent hormonal therapy.

The least known but most dangerous allergic reaction to penicillin is anaphylactic shock. Only a single fatal case of this kind has thus far been published, by Waldbott[5] in 1949. Nonfatal collapse reactions have been noted by several observers.[6, 7, 8, 9] In recent months Curphey[10] has presented two as yet unpublished fatal cases with complete autopsy data.

In the present paper are presented one case of death apparently due to penicillin hypersensitivity and two cases of unequivocal anaphylactic shock due to penicillin. It is certain that other similar cases have been unreported.[11] Even in the light of untold numbers of penicillin injections given without serious damage, these increasingly frequent observations of anaphylactic shock should serve as a warning.

From the Adult Allergy Clinic, The Mount Sinai Hospital.
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CASE REPORTS

CASE 1.—S. C., a 67-year-old white woman, had bronchial asthma for several years. This was perennial and characterized by marked mucoid bronchorrhea. She had been studied completely from the allergic point of view elsewhere and had been found sensitive on skin tests to ragweed, plantain, feathers, kapok, and house dust. However, the major causative factor in her asthma was thought to be chronic sinus disease. Sinus x-rays showed thickened membrane. Her asthma was accentuated after upper respiratory infections. For this reason she had been treated with many antibiotics and had been given repeated injections of penicillin. To none of these had she shown any sign of intolerance. She was definitely allergic to aspirin which aggravated her asthma.

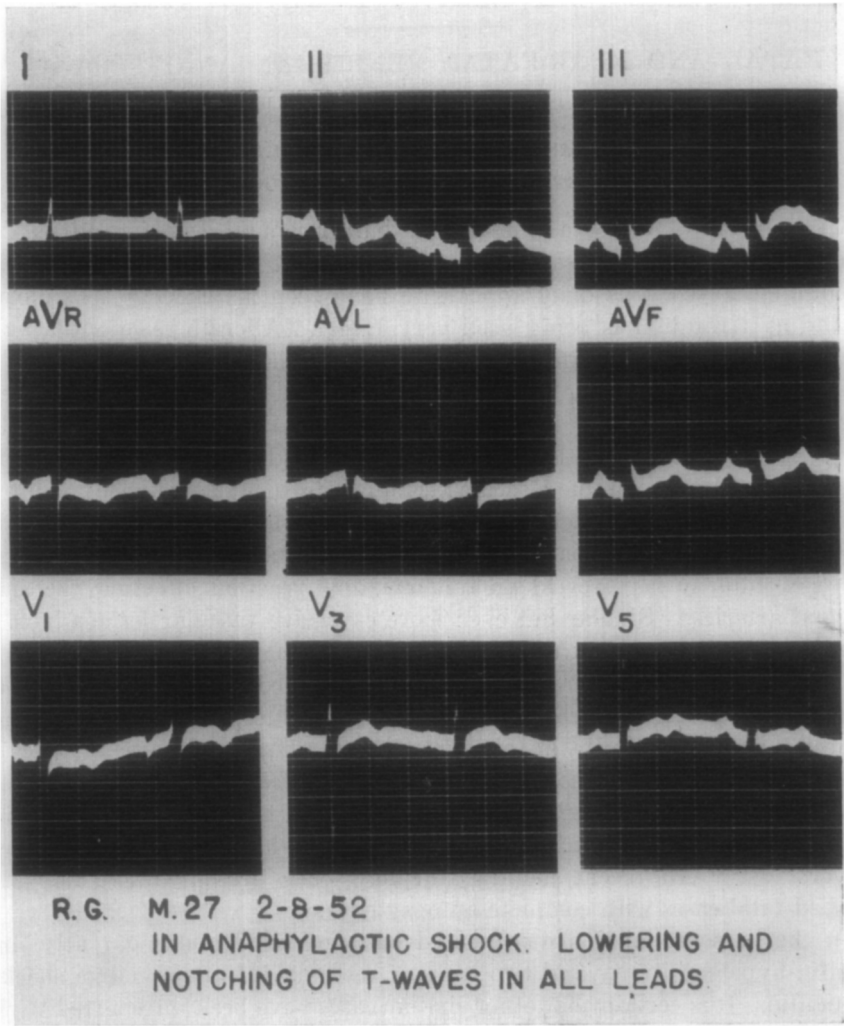


Fig. 1.—Case 2.

Apart from the asthma this patient was in good health. She had never had angina or any other evidence of heart disease. She had had no phlebitis, nor any indication of disease affecting the veins of her legs. Her blood pressure was 110/70. Electrocardiograms were

within normal limits. Complete blood count, blood glucose, nonprotein nitrogen, and cholesterol gave normal results.

On Oct. 25, 1951, she visited her physician while having rather severe asthma. Her temperature was 100° F. She was found to have acute follicular tonsillitis. She was therefore given an intramuscular injection of 300,000 units of aqueous procaine penicillin into the buttock. Within thirty seconds she complained of a strange taste in the mouth, tightness in the chest, and inability to breathe. Before epinephrine could be given she became extremely cyanotic and her labored respirations ceased. On auscultation there were no heart sounds. Intracardiac injection of epinephrine and artificial respiration were of no avail.

Acute toxicity tests carried out by the manufacturer with the penicillin from the vial used for the treatment of this patient were negative. An autopsy was not performed.

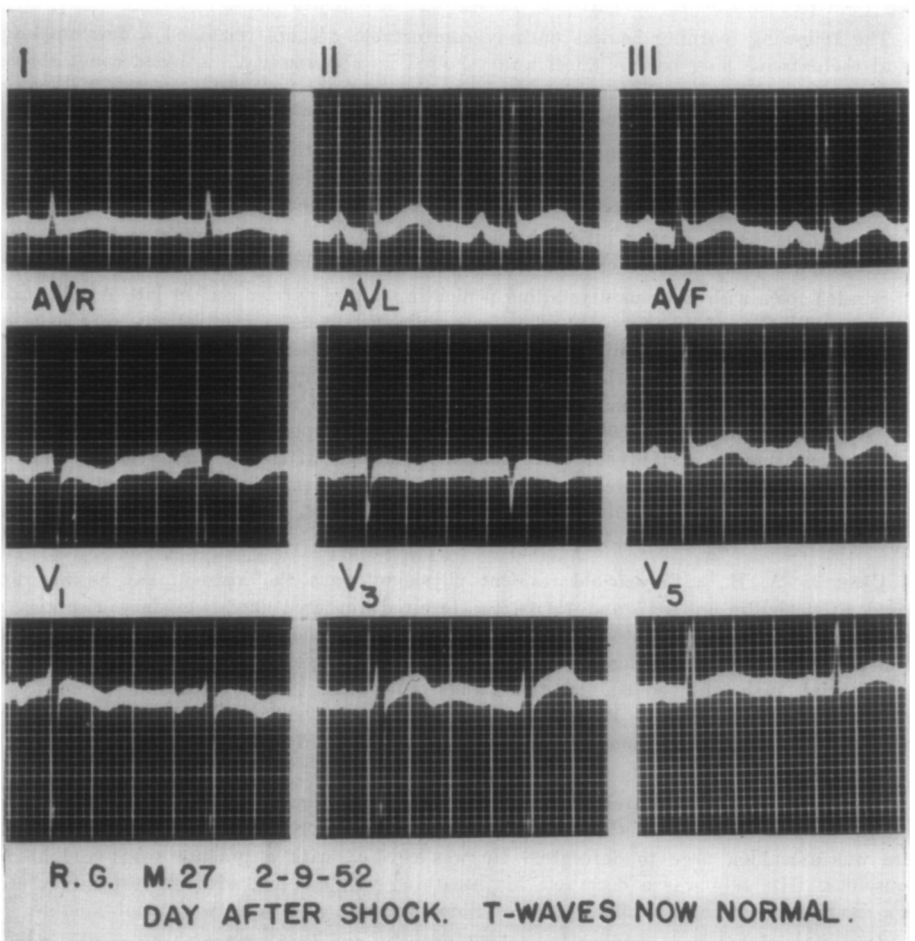


Fig. 2.—Case 2.

CASE 2.—R. G., a 27-year-old resident physician, awoke on Feb. 8, 1952, with sore throat which persisted throughout the day. Toward evening he stopped at the emergency ward for an injection of 300,000 units of aqueous procaine penicillin intramuscularly. Three minutes later while carrying on a telephone conversation his voice became husky and he had to clear his throat repeatedly. Then he felt lightheaded and this was followed abruptly by a severe sensation of pressure across the entire chest. He had an anesthetic feeling in

the back of his throat and a sense that his "larynx was about to close off." He was overcome by extreme weakness but was able to seek refuge in the neighboring electrocardiographic department. The sensation of chest constriction increased in intensity, his face became swollen and intensely pruritic, and he was covered with a cold sweat. He had severe nausea, repeated retching, and an urge to defecate. The acute phase of the attack lasted perhaps fifteen minutes.

Objectively, there was marked puffy swelling of the eyes, lips, and of the soft tissues of the neck. Slight cyanosis was present. A few fine râles with an occasional wheeze could be heard at the lung bases. His heart sounds were feeble, his pulse unobtainable, and blood pressure 50/30. In response to subcutaneous epinephrine and oral Pyribenzamine his edema subsided and his color improved.

An electrocardiogram taken during the shock reaction revealed lowering and notching of the T-waves in all leads, indicative of myocardial involvement (Fig. 1).

The following morning he was entirely comfortable. There remained a few crackling râles at the extreme lung bases. Chest x-ray showed no abnormality. A blood count showed no abnormality. Electrocardiographic examination now showed reversion of the T-waves to normal (Fig. 2).

His history as to previous exposure to penicillin was that he had received the drug by injection several times over a three-year period, without ill effects of any kind. The last previous penicillin injection was four months before the shocking dose.

His history as to allergy included some hay fever in the fall season and a tendency to dermographia present since childhood. His mother had light urticaria.

Scratch tests with aqueous crystalline penicillin G were carried out in late April, beginning with a dilution of 10 units per ml. Tests with increasing concentrations were negative until one was made with penicillin, 10,000 units per ml. After fifteen minutes there was a 2-3 plus reaction consisting of a 15 mm. wheal with moderate erythema of 20 mm. The control tests showed only a 2 to 3 mm. wheal and scarcely visible erythema. Scratch tests with aqueous procaine penicillin, 300,000 units per ml. and with 2 per cent procaine were negative. Passive transfer tests, carried out more than two months after the anaphylactic reaction, gave negative results on two recipients. For these tests penicillin G was used in 20,000 units per ml. concentration. Direct intracutaneous tests with ragweed and timothy pollens and animal danders gave strongly positive reactions.

CASE 3.—A. B., a 27-year-old resident physician, gave the history that he was first exposed to penicillin in 1947 and thereafter received repeated intramuscular injections of aqueous penicillin without untoward effect. In late 1949 he had his first reaction when within a few minutes following an injection of aqueous crystalline penicillin he developed an urticarial rash and edema of the hands and feet. This responded promptly to Pyribenzamine. In January, 1950, he was again given 50,000 units of penicillin intramuscularly and was almost immediately seized with marked dyspnea, likewise responding to an oral antihistamine.

Two months later, in March, 1950, he received an injection of 100,000 units of crystalline penicillin intramuscularly. Within thirty seconds he was overcome with a sense of collapse. There was a sudden urge to defecate. He was covered with a profuse sweat and he fell unconscious. His skin was a deep red, his breathing was labored, with an inspiratory crow and a cough productive of frothy sputum. Blood pressure and pulse were unobtainable.

Oxygen by inhalation, epinephrine subcutaneously, and Pyribenzamine by mouth induced relief of respiratory distress within ten minutes. Following recovery, nausea and extreme weakness persisted for several hours and there was residual dizziness for a brief additional period.

This patient had no clear-cut history of allergic disturbances previously. He was, however, aware that he sneezed readily on exposure to house dust and "caught cold" easily. This was usually promptly benefited by antihistamines. He had neither hay fever nor bronchial asthma and he recalled having urticaria briefly on one occasion only many years ago. There had been no other evidence of drug allergy. His family history was positive for

allergy in that one sister has marked summer and fall hay fever and another had a near-fatal reaction to diphtheria antitoxin. His mother had penicillin urticaria.

No attempt was made to test this patient directly with penicillin. Passive transfer tests, carried out two years after the anaphylactic shock, gave negative reactions to crystalline penicillin G, 20,000 units per ml. Direct and passive transfer tests with pollen extracts were negative.

DISCUSSION

Only a single case of fatal penicillin anaphylaxis has been published thus far. In 1949, Waldbott[5] reported upon a 39-year-old female patient with asthma whose fatal reaction followed an intramuscular injection of 50,000 units of aqueous crystalline penicillin. Within minutes she complained of a strange taste in the mouth, tightness in the throat, and generalized itching. There was facial flush, extreme cyanosis, collapse and death. She had been treated with penicillin previously without any untoward reaction whatsoever.

In March, 1952, Curphey[10] presented a report on two cases of fatal anaphylaxis following penicillin in two patients with bronchial asthma. One patient died within five minutes after receiving aqueous procaine penicillin intramuscularly and at autopsy the chief finding was that of voluminously distended lungs with marked dilatation of the alveoli. These findings were consistent with the picture of "guinea pig anaphylaxis," as has been reported previously in other instances of fatal human anaphylactic shock.[12] His second patient died within ten minutes after an injection of penicillin and streptomycin combined. At autopsy the most noticeable finding was that of extensive mucoid exudate in the smaller bronchi and alveoli. In neither case was there found any other cause of death.

If we add Case 1 of the present report, it is striking that all four fatal cases of penicillin anaphylaxis were in patients with bronchial asthma. Of great practical import too is the fact that one of them had exhibited only questionable indication of previous penicillin allergy, and in the other three there was not the slightest hint of possible fatal anaphylaxis.

Since autopsy was not obtained in two of the cases it cannot be stated beyond any doubt that some other cause of sudden death was not present. Nonetheless, the fatality directly after injection, the accompanying asthma, and the manner of exitus all point strongly to true anaphylactic death.

Although other antigenic components such as procaine or streptomycin cannot be completely excluded as possible causative factors in two of these cases, the penicillin itself appears to be the most probable cause. This conclusion is considerably strengthened by the observations made in the nonfatal cases to be discussed.

Four nonfatal anaphylactic reactions to penicillin have been described previously. Burleson's[7] patient reacted to aqueous crystalline penicillin, mixed with procaine, with sudden dyspnea, generalized pruritus, and collapse. An immediate intracutaneous test with penicillin gave a positive reaction, whereas that to procaine was negative. Everett's[8] patient twice underwent severe shock inasmuch as penicillin was not at first recognized to be the causative agent. The first reaction followed the instillation of 30,000 units of aqueous crystalline

penicillin G solution into the maxillary antrum. Facial flush, dyspnea, wheeze, collapse, and unconsciousness supervened. Three months later intramuscular procaine penicillin in peanut oil induced an identical reaction. This patient had received penicillin by instillation into the antrum and by injection repeatedly in the previous four years without incident. He was not asthmatic and apparently not atopic.

The patient reported by Irwin and associates[9] was, as in Case 2, and Case 3 of the present report, a physician. Again parallel with Case 3, he failed to heed a previous immediate reaction to penicillin. After a three-week interval he was given procaine penicillin in oil and in thirty seconds felt a generalized sensation of heat, with scrotal itching and dyspnea, and went into collapse. He was subsequently scratch-tested with crystalline penicillin, 1,000 units per ml. in aqueous solution, and reacted with a huge zone of whealing and erythema. A similar test with procaine was negative. Passive transfer tests were positive in one recipient, negative in two others.

All six cases of nonfatal anaphylactic shock, including the two here first reported, were almost certainly due to penicillin itself, and not to accompanying procaine or vehicle. Two of these patients had experienced previous immediate reactions to penicillin which should have served as a warning of possible anaphylactic sensitivity. The patient described by O'Donovan and Klorfajn[6] had penicillin contact dermatitis, and reacted with collapse to an injection of penicillin.

In Burleson's[7] case there was only questionable evidence of previous penicillin allergy. In the remaining two cases there was nothing whatsoever to serve as a warning that a state of anaphylactic sensitivity to penicillin had been induced.

PREVENTION

Despite the apparent rarity of dangerous reactions to penicillin it is our contention that these experiences call for far greater circumspection in the use of penicillin than is the current practice. It appears probable that penicillin anaphylaxis is on the increase as more and more persons attain a high level of sensitization through repeated exposure to the drug. It would therefore seem the wiser course to avoid needless hypersensitization of patients through indiscriminate use of this antibiotic.

1. For many minor respiratory infections which are mostly viral in nature, no specific antibiotic is available and chemotherapy should be avoided altogether. When penicillin is distinctly the drug of choice oral preparations should be used more frequently in mild to moderate infections. It has been emphasized increasingly that for such conditions one or two 200,000 unit tablets three times daily often comprises effective therapy.[13, 14] While sensitization may occur as well by the oral route, the occurrence of anaphylactic shock should thus be reduced and anaphylactic death possibly prevented altogether. Immediate drug fatalities of this type almost never occur after oral administration but are not too rare after parenteral injection.[15] It is for this reason that Feinberg[16] stated: ". . . it is incumbent upon the conscientious physician to observe the strict rule that nothing that is effective by mouth should be given by injection."

2. Before administering or prescribing penicillin a careful history should be elicited as to its previous administration and the occurrence of any reaction. An accurate history should also be taken as to both personal and familial allergy, particularly as to bronchial asthma.

Anaphylactic shock to penicillin need not be feared in patients who have never been exposed to the drug previously. Some confusion may exist on this score because some individuals have latent penicillin sensitivity presumably based upon pre-existing dermatomycosis. The initial exposure to penicillin in such patients may elicit a cutaneous reaction of the "id-like" erythematovesicular type, but has not been known to cause anaphylactic shock.

Anaphylactic shock has thus far been observed after single injections of penicillin in patients intermittently treated and not during a course of continuous therapy. This appears analogous to the common experience with animal anaphylaxis where adequate spacing of antigen injections greatly enhances the likelihood of inducing shock.

In evaluating the history of previous penicillin allergy the physician should distinguish sharply between the common *delayed* reactions on the one hand and the uncommon *accelerated or immediate reactions* on the other. The delayed reactions occur typically after an incubation period of seven to twenty-eight days, are often mild and characterized by some or all of the elements of the serum sickness syndrome. For the most part these are associated with only a transient period of sensitization and such patients often tolerate a subsequent course of penicillin without difficulty.[17, 18] In sharp contrast, the accelerated and immediate reactions come on within a matter of minutes or hours, or at most a day or two after penicillin. Immediate reactions tend to be more violent, but even though such a reaction may be mild, its timing should serve as a warning that penicillin sensitivity is present and anaphylactic shock a distinct probability. A possible exception to this rule is the "id-like" erythematovesicular reaction which may appear within twenty-four hours after penicillin treatment. The morphology of this eruption and its typical hands-feet-groin distribution should readily differentiate it, a matter of practical importance, as such sensitivity is apparently not indicative of an anaphylactic danger.

Apart from the immediate and accelerated allergic reactions to penicillin certain other forms of penicillin allergy are more likely to be associated with severe degrees of sensitivity. Thus a history of exfoliative dermatitis or a purpuric reaction indicates the need for special care. Patients with a contact allergy to penicillin, as seen particularly in doctors and nurses, should not be treated with the drug as they may react dangerously. Moreover, it should be noted that regardless of the character of reaction to penicillin, patients who have had more than a single episode of penicillin allergy should be treated with caution. Last, it must be understood that the absence of any previous allergic reaction to the drug by no means precludes the possibility of anaphylactic sensitization. Indeed, several of the patients here reported or referred to had had no previous untoward reaction to the drug.

3. Skin tests with penicillin may be helpful in the prevention of anaphylaxis. Experience is thus far too limited to present a definitive evaluation but the

observations made in Case 2 of the present report, in the case reported by Irwin and associates,[9] and in Burleson's[7] case suggest that anaphylactic sensitivity to penicillin may in some cases be associated with a positive immediate skin test. This is in contrast with most forms of drug allergy in which negative skin tests are the rule.

Penicillin skin testing has thus far been done with aqueous solution of penicillin G, and it is this solution which should be employed for the purpose of detecting the anaphylactic state. There is no published experience with tests made with procaine penicillin, which may release penicillin too slowly to induce an immediate reaction on scratch test (Case 2). Penicillin G solution has the disadvantage of being unstable at room temperature and even under refrigeration loses both potency and antigenicity within a week. However, 100,000 unit vials of powdered, dry crystalline penicillin G can be kept at hand in the doctor's bag, in offices, and in hospitals specifically for use in skin testing.

For routine use a scratch test is safest as the intracutaneous test may rarely induce shock.[19] Crystalline penicillin G, 10,000 units per ml. in distilled water, should be used and the reaction read at twenty minutes. A positive test may be missed if the reading is done too soon. The positive reaction consists in a definite wheal and flare. Such a test would serve as a crude screening procedure of particular value for: (1) patients who have had repeated previous administration of penicillin; (2) those who have a history of a previous reaction to penicillin, especially if recent or if unusually severe; (3) for atopic individuals and particularly for the asthmatic patient. When convenient, immediate intracutaneous tests with aqueous penicillin may also be carried out if the scratch test has proved negative.

It cannot be emphasized too strongly, however, that negative skin tests do not rule out penicillin allergy or anaphylaxis. It is therefore safer to avoid penicillin therapy in patients with a history of an immediate or accelerated reaction to penicillin despite negative skin reactions. When there has been a previous delayed reaction to penicillin of the usual type it is often wise to administer preliminary smaller doses of penicillin, perhaps[18] 5,000 to 10,000 units, before giving the full therapeutic amount.

In instances in which the overriding consideration is the urgent need for penicillin despite a strong suspicion of anaphylactic sensitivity, a series of trial injections of penicillin in ascending dosage might be indicated. The initial dose would be from 20 to 50 units given subcutaneously into the upper extremity, injections being repeated at intervals of one-half to one hour, with the hope that eventually a dose of therapeutic value would be attained. Whenever the risk of anaphylactic reaction is to be taken it need hardly be emphasized that a syringe filled with aqueous solution of epinephrine must be at hand as well as an injectable solution of antihistamine and a tourniquet. Such a procedure is best carried out in the hospital.

The delayed penicillin intracutaneous test, performed with 0.1 ml. of aqueous solution, 10,000 to 20,000 units per ml., and read at twenty-four to forty-eight hours, is not discussed here. Although much the most commonly positive of all penicillin skin tests, it has little place in the prevention of

anaphylactic reactions. Its area of usefulness and its limitations have been described previously.[18]

4. The technique of penicillin injection deserves critical appraisal in the effort to avoid anaphylaxis. Injections, especially the first of a series, should be given into the outer aspect of the upper arm rather than into buttock or deltoid, so that if necessary a tourniquet, ready at hand, may be applied proximal to the site of injection. Accidental intravenous injection should be avoided by the routine measure of tugging on the plunger and observing whether there is blood in the syringe before actual administration.

In discussing the prevention of anaphylactic shock from other substances, Waldbott[20] suggested that the first few drops of solution be injected, followed by a forty-five second pause before the remainder of the dose is given. This seems sensible in that the potentially fatal reactions may become evident within this period (Case 3). Epinephrine should be directly at hand whenever a penicillin injection is to be given.

The precautions just outlined are intended particularly for the care of asthmatic and atopic persons and for any patient who gives a history of penicillin allergy. Nonetheless, all may benefit from greater caution in the use of the antibiotic.

SUMMARY

1. One death and two cases of nonfatal anaphylactic shock due to penicillin are described.

2. The fatality occurred in a patient with bronchial asthma. Three other known deaths attributable to penicillin anaphylaxis have also occurred in asthmatics.

3. Two of these patients, including the one with a fatal reaction, had received penicillin many times before without indication of allergy. The third patient responded previously with immediate reactions to penicillin which went unheeded as a warning of anaphylaxis.

4. A direct scratch test with aqueous crystalline penicillin was positive in one case, whereas similar tests were negative with aqueous procaine penicillin and 2 per cent procaine. Passive transfer tests were negative.

5. Detailed precautions are suggested toward the prevention of penicillin anaphylaxis, particularly for asthmatic and penicillin-allergic persons. The avoidance of the indiscriminate use of penicillin, particularly by injection, is emphasized. The value of a systematic inquiry as to previous penicillin treatment and reactions as well as of the general allergic status is stressed. Certain refinements in the method of penicillin injection are suggested. The technique and interpretation of preliminary penicillin skin tests are discussed.

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