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ALLERGIC REACTIONS TO PENICILLIN

A PANEL DISCUSSION

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Dr. Rose.—The panel of experts who will discuss the subject and answer any questions are Dr. Sheppard Siegal and Dr. William Sherman, of New York, Dr. Irving Schiller, of Boston, and Dr. William Boger, of Philadelphia.

Dr. Sherman, will you open the discussion by describing the common manifestations?

Dr. Sherman.—I am going to start off by reviewing very briefly some of the common reactions, most of which are already very familiar to you. Probably the commonest type of reaction to penicillin, which occurs certainly in 1 or 2 per cent of all patients receiving penicillin, is the delayed urticarial type or what is often spoken of as the "serum-sickness" type of reaction. I think the term "serum-sickness" type is very applicable because it certainly can imitate practically all of the usual features of a reaction to heterologous serum. Like ordinary serum-sickness, it varies in severity from a relatively mild and brief urticaria to an extremely severe illness which may last for several weeks. The predominant feature is urticaria and angioneurotic edema. It is rather characteristic that the palms and the soles of the feet are likely to be involved by the urticaria. Associated with the urticaria, in the majority of cases, there is arthralgia and swelling of the joints, particularly the small joints of the hands and feet, often a really typical arthritis of these joints. Many of these patients have fever. The fever may be negligible in a mild case or it may be as high as 105° in a severe case. As you can see, all of this description exactly fits ordinary serum-sickness and the two conditions are so similar that if a patient with some injury has received tetanus antitoxin and penicillin simultaneously, the reaction may

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be such that one is hard put to say which of the two agents has been the cause. Like serum-sickness, this type of reaction has a characteristic incubation period of five to perhaps fourteen days. I would not attempt to say what is the longest possible incubation period, but certainly anything up to two weeks is not unusual. As in serum-sickness, we assume that this delayed reaction and incubation period indicate that the patient is developing sensitivity as a result of the administration of the drug. Fig. 1 illustrates a few

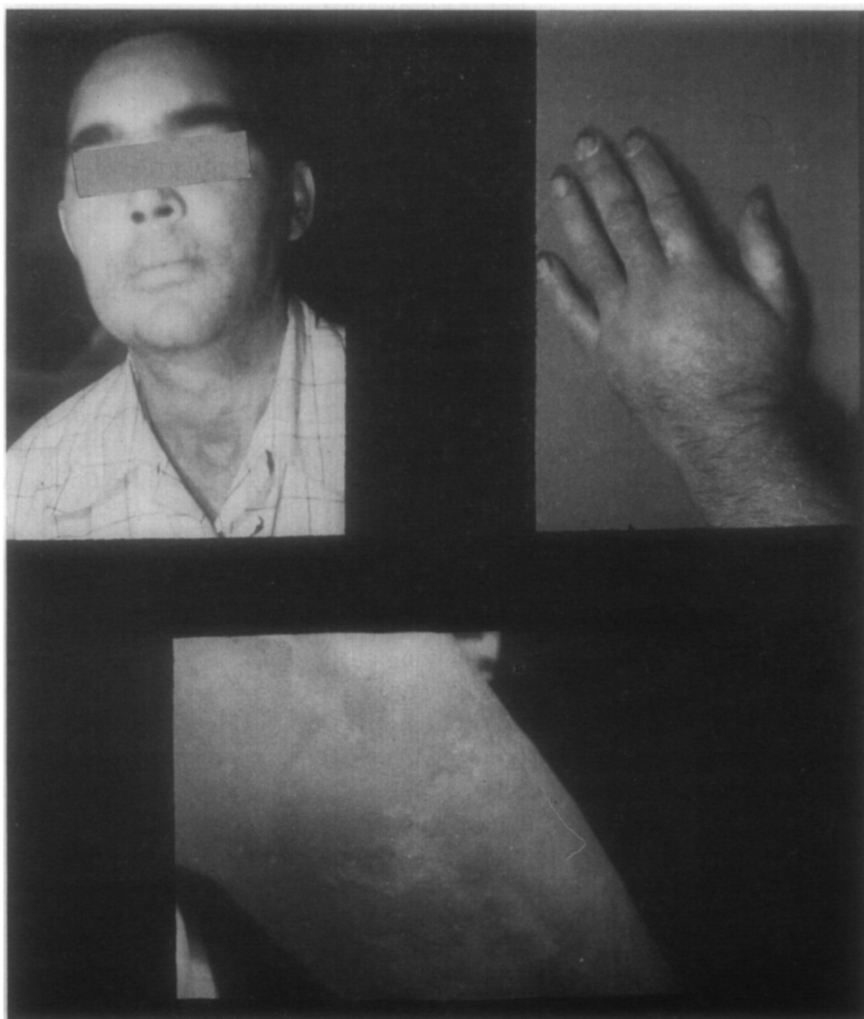


Fig. 1.—Serum-sickness type of reaction to penicillin manifested by edema of the face, swelling and stiffness of fingers, and confluent urticaria of trunk and limbs.

of the characteristic features of this type of reaction—massive and often confluent urticaria involving often a large part of the body surface, edema of the face, particularly about the eyes, and swelling of the hand, including particularly the small joints of the fingers. This picture could equally well be one of serum-sickness due to heterologous serum.

Of the various types of penicillin which have been used, crystalline penicillin and procaine penicillin seem to produce essentially the same form and incidence of urticarial reactions. However, one type of penicillin, penicillin in beeswax and oil, produced an unusual incidence of this type of reaction, often associated with severe reactions at the sites of injections. Fig. 2 shows the arm of a patient who had received one injection of penicillin in oil and wax in the left deltoid region about nine days before the photograph was made. The main feature shown in this illustration is a large local reaction at the site of the injection. With penicillin in oil and wax, there are two differences from the procaine penicillin and the crystalline penicillin: first, the incidence of sensitization is much greater, which we may assume is due to the fact that the oil and wax act as adjuvants increasing the tendency to sensitization. Second, the absorption of antigens from the site of injection is much delayed so that when sensitization occurs, the local reaction is very great.



Fig. 2.—Local reaction occurring eight days after injection of penicillin in oil and wax into left deltoid region.

Fig. 3 shows a side view of the same patient and one of the interesting features is that over the site of injection is not only a large edematous swelling but a localized area of vesicular dermatitis. In other words, this patient is showing two distinct types of reactions at the same time, the dermatitic type and the urticarial type. Such local reactions are very much less common with procaine penicillin than with penicillin in oil and beeswax.

Another relatively common type of reaction, which is less often seen nowadays with procaine penicillin than formerly, is what has been known as the "id" type of reaction which, at least superficially, resembles an attack of epidermophytosis involving particularly the interdigital spaces, the groin

and flexion creases. This type of reaction characteristically occurs early in the course of treatment with an incubation period of a few hours to not more than one day. The reaction is characterized by redness, oozing, and itching. It has been suggested repeatedly that this type of reaction represents a cross reaction in a patient who, because of a previous fungus infection of the skin, has a local sensitization to fungus products, which gives a cross reaction with penicillin. It has been pointed out that patients showing this type of reaction are very likely to show positive reactions to skin tests with trichophyton or oïdiomycin. However, so many patients show reactions to these fungus antigens that we are unable to use these tests as a criterion for treatment; otherwise, we would needlessly omit using penicillin in many cases.



Fig. 3.—Local reaction to injection of penicillin in oil and wax showing vesicular lesion superimposed upon subcutaneous edema.

A third common type of reaction is dermatitis medicamentosa, a relatively nondescript generalized rash, which may be macular or papular, quite similar to what may be seen after the sulfonamide drugs, phenobarbital, or numerous other agents. This type of reaction varies tremendously in severity. It may be very mild and not infrequently treatment has been continued, in spite of the occurrence of the reaction, with relatively little difficulty. Certain of these nondescript rashes, which we lump together as dermatitis medicamentosa, may become increasingly severe and progress to a serious and disabling exfoliative dermatitis which may persist for a long time after the penicillin is discontinued.

The fourth common type of penicillin reaction is contact dermatitis due to topical application of penicillin, usually in the form of penicillin ointment. This is a typical vesicular contact dermatitis with the usual features. The sensitization is usually developed in the course of one to two weeks after the first contact with the ointment, so that it is practically never an immediate reaction in the patient who has not previously been exposed. This type of reaction is illustrated by Fig. 4, showing a patient who had a small area of follicular infection in the bearded part of his face and was given penicillin ointment to apply. He applied it regularly and, after a week or so, the area of irritation spread. He kept applying more and more as the reaction spread so that what started as a small area about the size of a dime came to involve the entire neck and lower face. The rash was now of the vesicular type quite similar to poison ivy, a typical contact dermatitis.

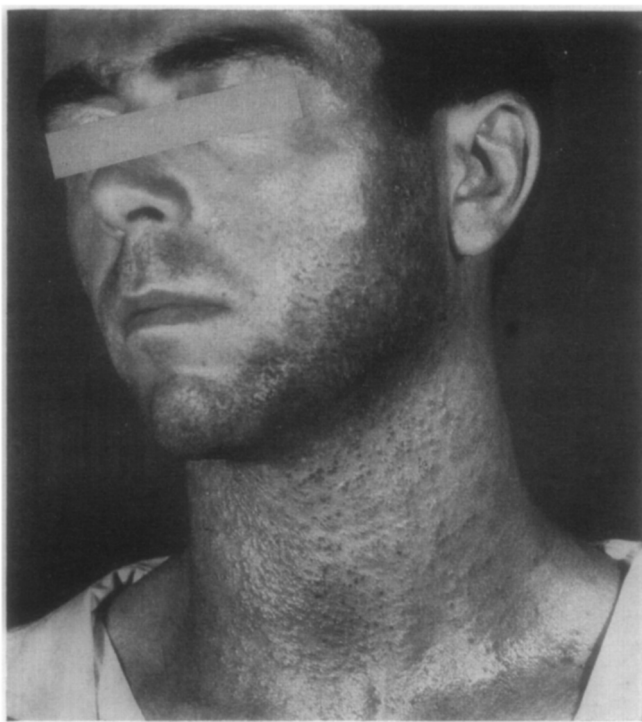


Fig. 4.—Contact dermatitis due to penicillin ointment.

Dr. Rose.—Dr. Sherman has just outlined the common types to you. I am now going to ask Dr. Boger, unless there are any further comments from the panel, to talk about the more infrequent manifestations of penicillin reactions.

Dr. Boger.—A good beginning point for the discussion of the rare and rather serious reactions to penicillin is a slide that Dr. Schiller was kind enough to bring along. This female patient (Fig. 5) shows an extensive

purpura, and Dr. Schiller advises that the patient's purpura was nonthrombocytopenic in nature. Others have observed purpura due to sensitivity to penicillin that has been accompanied by thrombocytopenia. The manifestation of purpura serves to emphasize the role of vascular permeability in the development of various of the rare sensitivity phenomena. Some of the commoner manifestations, itching, urticaria, and rashes, that have just been described can be explained, at least in part, by vascular permeability. It is an easy step in our thinking to go from the purpura just shown to an occasional microscopic and even gross hematuria if one conceives a purpuric type of lesion in the kidney due to penicillin sensitivity. Vascular permeability and damage to small blood vessels can be involved as an explanation of the arthritis and hydrarthrosis that are seen in cases of penicillin hypersensitivity classified as serum-sickness. In rare cases of serum-sickness the

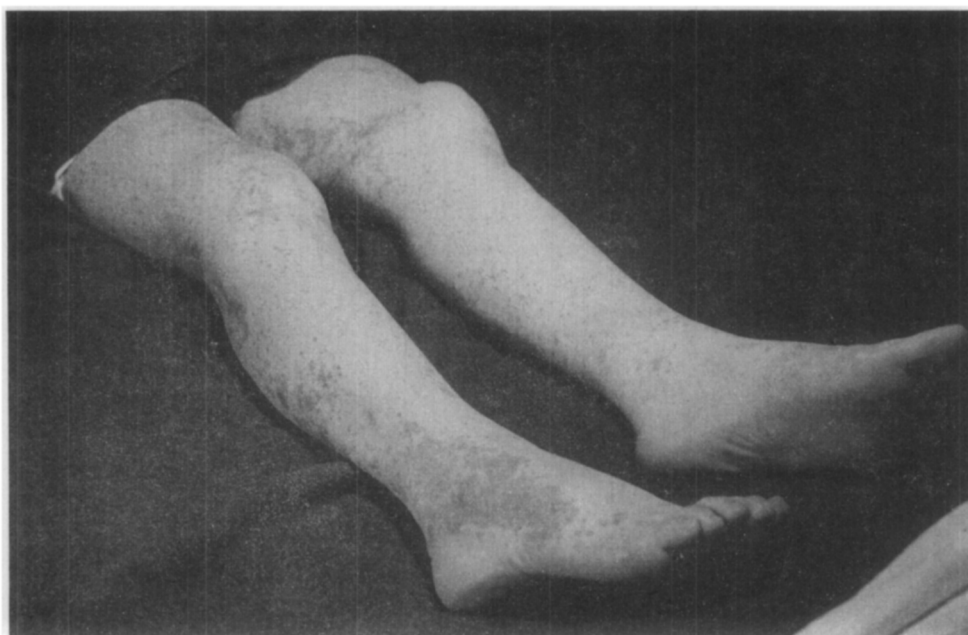


Fig. 5.—Purpuric eruption following the administration of penicillin.

joint symptoms persist for three and four months and we have followed several such patients. Indeed, the syndromes that have been described under the designation of "collagen diseases" are being reported as due to penicillin sensitivity. It has taken a number of years to develop the full picture of penicillin reactions, but it also took a number of years, during which the sulfonamide drugs were employed, to show that erythema nodosum was a mild manifestation and periarteritis nodosa the ultimate. That fatal arteritis can result from the administration of sulfonamide drugs has been amply confirmed and we are beginning to hear of obliterative arteritis and generalized periarteritis nodosa due to penicillin. There are those investigators who

claim to be seeing photosensitivity and even lupus erythematosus due to penicillin. Personally, I have not seen such a case, but perhaps one of the other panel members can speak more familiarly on this point. Angioneurotic edema with obstruction to the airway is uncommon but distressing; exfoliative dermatitis, syncope, collapse, and death are not common but they have all been reported. It seems reasonable to suggest that all the phenomena of drug sensitivity, including the gamut of symptoms assigned to the various collagen diseases, will be shown, sooner or later, to be due to hypersensitivity to penicillin.

The practice of introducing penicillin intrathecally should be mentioned. When the nervous system is exposed directly to penicillin in a quantity as little as 50,000 units, severe convulsions can result.¹² This is due to direct chemical irritation and has nothing to do with allergy. Death has been caused by the intrathecal administration of larger doses of water-soluble penicillin and, consequently, there is an increasing trend away from this mode of administration of the drug.

All of the rare reactions to penicillin have not been reviewed for I think any phenomenon that has been observed in connection with hypersensitivity can be observed in connection with penicillin administration. We have tried to emphasize some of the more serious and rare complications in the hope of avoiding the use of penicillin, or any other drug, if it is not indicated.

Dr. Rose.—You will see that as we progress the reactions become more severe. We will now ask Dr. Siegal, therefore, to say something of the anaphylactic and fatal cases which appear to be on the increase.

Dr. Siegal.—Penicillin anaphylaxis, it seems to me, is becoming a more frequent problem to which we will have to give very serious attention. As an indication of this may I point out that in the past fifteen months 15 cases of penicillin anaphylaxis were published, and, of these, 6 were fatal. By contrast from 1946 to 1951, there were only six cases reported with but one fatality.* Moreover, in the past year or so I know of nine unreported cases occurring in the area of New York and vicinity alone, and, of these, four were fatal. Several of these recent cases, reported or unreported, have been reactions to crystalline penicillin G and in others where aqueous suspension of procaine penicillin was used all the evidence incriminates penicillin rather than procaine. On January 31 of this year there were published in the *Journal of the American Medical Association*¹ six cases of anaphylactic collapse from penicillin, one of which was fatal. Most recently, my attention was called to a report of anaphylactic death from penicillin taking place on board a ship of the United States Navy.²

At the May meeting of the New York Allergy Society in 1952, I first reported three cases of penicillin anaphylaxis, later published in *THE JOURNAL*

*In view of the more frequent use of penicillin it is difficult to say whether or not this greater number of reported anaphylactic reactions actually represents an increased incidence. All cases reported as having this type of reaction have been patients who have received previous courses of penicillin. As the use of penicillin increases, obviously more patients will receive second and third courses of the drug.

OF ALLERGY.³ Two of these were hospital residents who reacted with severe shock, to crystalline penicillin G in one case, to procaine penicillin G in the other. There was reason to believe that both were atopic individuals, one being a hay fever sufferer. Whereas fortunately they recovered, the third patient, a 67-year-old asthmatic woman, had a fatal reaction to an intramuscular injection of 300,000 units of aqueous procaine penicillin. She almost immediately felt a strange taste in her mouth, complained of inability

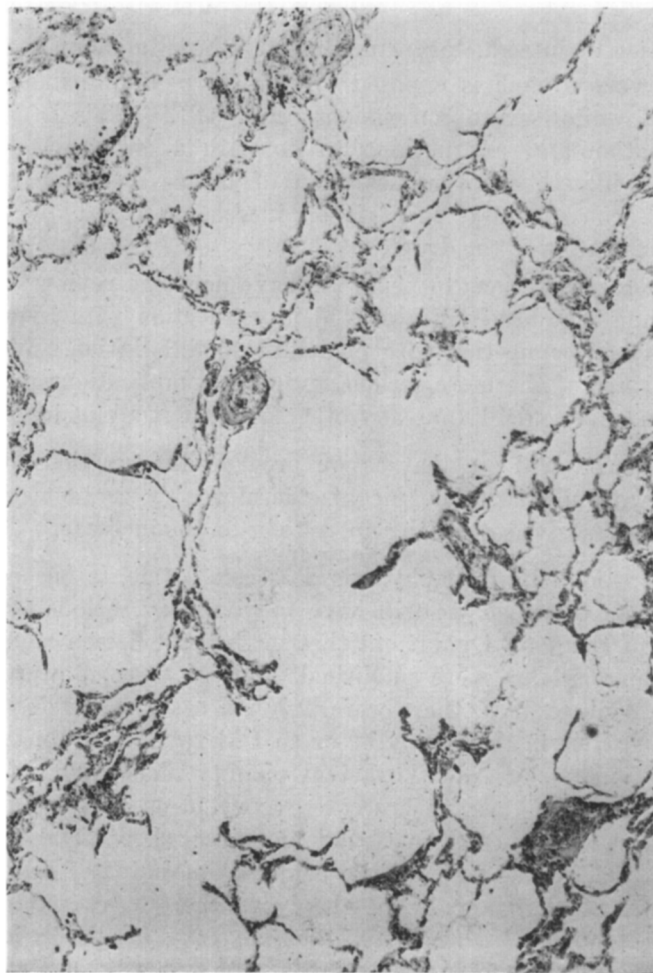


Fig. 6.—Penicillin anaphylaxis in an asthmatic patient. Acute pulmonary emphysema showing distended alveoli.

to breathe, promptly became unconscious, and was in collapse. She was dead in the doctor's office before anything could be done. Autopsy was not performed. It is important to note that two of the three patients gave no history of a previous reaction to penicillin, while the third had previous reactions which were ignored.

Of great interest are two autopsied cases of penicillin anaphylaxis reported by Curphey, Medical Examiner of Nassau County. Both were asthmatics who died in a few minutes following procaine penicillin in one instance and after combined penicillin-streptomycin in the other. At post-

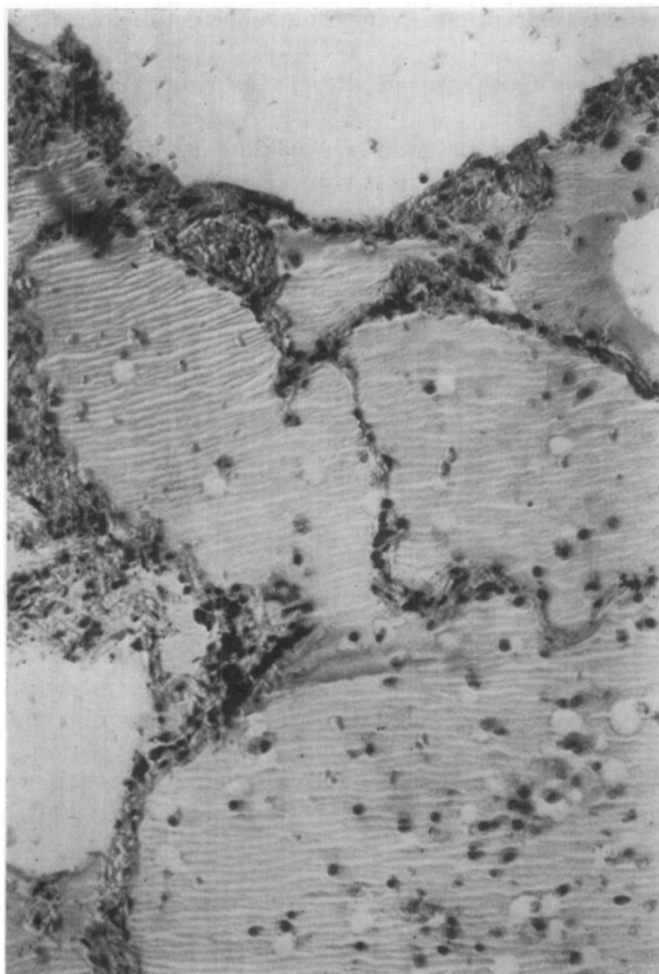


Fig. 7.—Penicillin anaphylaxis in an asthmatic patient. Extensive bronchial and bronchiolar mucoid exudate filling many alveoli.

mortem the striking findings in the first case were the voluminosely distended lungs of acute emphysema, the so-called "guinea pig" lungs (Fig. 6). In the second case the chief finding was of marked mucoid secretion in the bronchi, shown on microscopic section to extend into the alveoli (Fig. 7).*

I have the distinct impression that with repeated exposure to penicillin through the years, largely by injection, increasing numbers of persons are becoming sensitized to the anaphylactic level. Penicillin can no longer be

*I am grateful to Dr. Theodore J. Curphey for permission to use these photomicrographs.

regarded as largely an innocuous drug. How are we going to prevent these extremely dangerous, even fatal reactions? It seems to me that the following points should be noted:

1. Anaphylaxis occurs only in those who have had penicillin previously, usually on several occasions.

2. Anaphylaxis can occur even though penicillin was well tolerated previously.

3. It occurs more frequently in allergic individuals and is more likely to be fatal in asthmatics.

4. The dangerous and potentially shocking dose is usually the first injection following a prolonged interval since the last exposure to penicillin. This interval has often been one of several months. This is comparable to what is observed in animal anaphylaxis. Therefore, all precautions must be taken for this initial injection. Subsequent successive doses are probably not dangerous.

I would like to suggest certain precautions for the prevention of anaphylaxis:

1. Avoid needless sensitization through the use of penicillin for trivial or doubtful indications. Other forms of chemotherapy may be preferable.

2. For mild infections employ oral penicillin which is certainly less likely to cause fatal reactions.

3. A careful history as to previous penicillin treatment and reactions is important. Previous accelerated and above all immediate reactions are especially significant.

4. Modification of the technique of penicillin injections is an additional precaution. The initial or potentially shocking dose should be given into the arm rather than into the buttock so that a tourniquet may be applied. Avoid scrupulously the possibility of accidental intravenous injections. It may be wise, following an earlier suggestion of Waldbott, to inject the first drop or two, then pause for forty-five seconds before completing the injection, as the really violent reactions may become evident within seconds. Keep epinephrine directly at hand when giving this injection of penicillin.

5. Preliminary skin tests may be helpful in screening out some individuals who may react with anaphylaxis. A simple scratch test has been helpful and should be done routinely. Earlier experience with penicillin skin testing has been with aqueous solution of crystalline G penicillin. More recently, however, aqueous procaine penicillin has been used effectively. In view of the much greater convenience to the general physician, it is suggested that the scratch test may be carried out with the treatment material ready at hand, aqueous procaine penicillin, 300,000 units per cubic centimeter, adding a drop of water at the skin site to prevent too rapid drying. It is best to wait at least fifteen minutes before making a final reading. Intracutaneous tests may be dangerous and are best carried out only after a negative scratch test. A strongly positive skin test reaction should rule out penicillin administration. Since allergy and even anaphylaxis to penicillin may occur in the absence

of a positive skin test, an additional helpful precaution might well be the oral administration of a 50,000 unit penicillin tablet ten minutes before the intramuscular injection.

Dr. Boger.—May I make a comment? The severe and even fatal reactions that are being cited should be viewed in their proper perspective. No one will disagree that penicillin is an allergen with sensitizing potential, but we should not lose sight of the rarity of serious reactions if viewed in terms of the enormous quantity of penicillin that has safely been administered and of the countless number of lives that have been saved. Penicillin is the foremost of the antibiotic agents. Its indiscriminate use is unfortunate and is to be deplored.

Dr. Rose.—Dr. Schiller is going to discuss the use of skin tests because we do want to know what can be done first of all to tell whether a patient is sensitive to penicillin and what we can do about it. I would like to ask Dr. Schiller also to tell something about the interpretation of the skin tests.

Dr. Schiller.—You are all familiar, I am sure, with the scratch, intracutaneous, and patch tests used to study penicillin sensitivity. Fresh aqueous solutions of penicillin G, or penicillin O if you wish, in a strength of 10,000 units per milliliter are prepared. All tests should be properly controlled using the diluent as the blank solution. We test patients initially by the *scratch method*, for a few serious reactions have been reported following intracutaneous tests. A small drop of the test solution, as well as a drop of the control solution, is applied to the skin and then the skin is scratched through the drop. A positive reaction is characterized by a wheal and erythema which appears within fifteen or twenty minutes, or sooner. The wheal may be pseudopodic, may vary from 10 to even 30 mm. or more in diameter, and itching may be present. This, of course, is compared with the control site, which should appear normal except for perhaps the slight trauma of the scratch. The scratch test, if negative, is followed, in our clinic, by the *intracutaneous test* which is carried out by injecting 0.05 ml. of the 10,000 unit strength intracutaneously. The site is observed for fifteen or twenty minutes and when positive is also a typical wheal and flare reaction. In any case, whether the reaction is positive or negative, the site of the injection is observed for the next forty-eight hours for the appearance of the *delayed positive reaction*. When this occurs, its appearance is similar to a positive tuberculin reaction. Here one sees an erythematous area which may measure from 10 to 20 mm. or more in diameter, frequently raised and indurated and oftentimes studded with papules. The reaction may continue to grow in intensity up to seventy-two hours and then may persist, frequently, for a week or longer, leaving a fading brownish site in its wake. The *patch test* is done by making a solution of 50,000 units per milliliter or 100,000 units per milliliter of penicillin, applied to the skin soaked in a piece of cotton, and read in forty-eight hours. When the reaction is positive, one sees an erythematous area in which vesicles of varying size are present.

Now, what is the clinical significance of these various tests? In spite of the well-known limitations of skin tests and the fact that their reliability is still open to question, we feel that they serve to call attention to possible disastrous effects that may follow the administration of penicillin. A negative reaction certainly does not rule out the possibility of a serious reaction, nor does a positive one indicate that an immediate systemic reaction, or even a reaction of the delayed type, will ensue with penicillin therapy. Nevertheless, we can speculate that had some individuals been skin tested with penicillin and the results given proper consideration, collapse or anaphylactic reactions might have been avoided. A positive scratch test in an individual with a history of having had one or more courses of penicillin or one suggesting an allergic reaction from penicillin certainly is indicative of clinical sensitivity and the likelihood of a severe reaction should penicillin be given. Likewise, the immediate positive intracutaneous test should suggest the existence of a high degree of penicillin allergy. The delayed positive reaction or "spontaneous" penicillin sensitivity, first described by Welch and Rostenberg,^{4, 5} is said to be present in about 4 or 5 per cent of individuals who have never received penicillin. It has been suggested that such sensitivity possibly has developed from subtle exposure to related fungus products or previous fungus infections of the skin. This needs further clarification. The incidence of the delayed reaction is increased in patients who have had penicillin in the past and is much higher in patients who have had penicillin reactions. I am sure that both Dr. Siegal and Dr. Boger will have something to say about this. Patients with the delayed positive type of reaction are not perhaps as likely to have manifestations of the immediate type. If clinical sensitivity develops at all, it would take the form of the more common urticarial or "serum-sickness" type of reaction. Recently we saw a patient who is an exception to this and we will have more to say about this later. So far as the patch test goes, we have had but little experience with it, and I hope that the other members of the panel will have more to say about it. It seems that the patch test is of only questionable value as an index of general penicillin sensitivity.⁶

Dr. Rose.—There is the question, of course, that is always raised with reference to the intradermal test with penicillin. I know of one case where death occurred very quickly following the use of this test in the hands of a capable physician who was trained in allergy. Scratch testing, I believe, is to be preferred; however, I would like to hear further opinions about it.

Dr. Boger.—Pertinent to Dr. Schiller's remarks, we have observed generalized rash and fever from intracutaneous skin tests performed during our comparisons of one penicillin with another. Each test constituted 2,000 units of the penicillin in question and two tests on 4,000 units (approximately 2.5 mg.) produced generalized reactions on an allergic basis.

Dr. Rose.—The technique of skin testing has been described, and a general interpretation given. Skin testing has its limitations, however, and I would like to ask Dr. Sherman to discuss this point.

Dr. Sherman.—I do not want to take a great deal of time because I think that most of this subject has been covered. I would like to emphasize the fact that a negative reaction to scratch test or intracutaneous test is never a reliable index that the patient is not sensitive, that he or she will not have an immediate reaction, or that a delayed reaction will not occur. As far as the delayed urticarial type of reaction goes, I do not believe that any skin test is of any value. Oftentimes during and immediately after the delayed urticarial reaction, intracutaneous tests, even going up to considerably higher levels than have been mentioned previously, are completely negative. When positive reactions are obtained, they are almost always so small that they are not significantly different from what may be obtained in normal individuals. However, it is obvious, I am sure, to all allergists that in those rare cases where you do get a strong, immediate urticarial reaction to either a scratch or intracutaneous test, you have a very unusual degree of sensitivity and the greatest possible danger if ordinary doses of penicillin are given in spite of them. I do not have anything worth while to say either in regard to delayed reactions to intracutaneous tests or to patch tests.

Dr. Rose.—I know that Dr. Siegal has something further to say about delayed skin reactions and we are going to ask him to tell us about it.

Dr. Siegal.—Quite a few years ago, when we studied the delayed intracutaneous test, we found that among 25 cases of the "serum-sickness" type of reaction, 10 had a positive test of the twenty-four to forty-eight hour type. Subsequently, Risman and Boger⁷ published a series of observations on the several penicillins about which I know Dr. Boger will speak, and in which, incidentally, there is statistically demonstrated the fact that the delayed test does actually indicate the existence of penicillin allergy. Fifty-five per cent of the patients who had a previous reaction to penicillin gave a positive delayed test as compared with only a 10 per cent incidence among those who had penicillin previously but without a reaction.

Dr. Schiller.—Before the subject of skin tests is left, I might mention that for the past three months we have been interested in the incidence of penicillin sensitivity in the allergic population passing through our clinic. Intracutaneous tests were carried out comparing penicillin G and O. Of some 50-odd patients studied, the majority of whom had previously received penicillin, no positive immediate reactions nor delayed reactions were seen. However, when subjects were selected (hospital personnel) for study who had had previous penicillin reactions, the story was quite different. These frequently had immediate or delayed positive cutaneous tests. It seems to us that the incidence of positive penicillin skin tests correlates best with past systemic reactions to the antibiotic.

Dr. Rose.—Since we should try to know something about the basic immunology of the reactions, I would like to ask Dr. Sherman what he would say about that.

Dr. Sherman.—The first thing I would say is that *nothing* is really known about the immunology and that all of the ordinary rules that you might expect to apply seem to be remarkably unreliable in relation to penicillin reactions. Now to go back to what I have spoken of as the “serum-sickness” type of reaction, this so closely resembles serum-sickness due to heterologous serum that anyone might reasonably expect that all the same immunologic mechanisms would be apparent. However, there is, as I have stated, no reliable immediate urticarial reaction to skin tests during or after the reaction. The delayed type of reaction or the immediate intracutaneous test is occasionally positive, but the percentage is not high enough to make it of any great significance as to interpretation. The attempts to demonstrate antibodies of any type in the serum of patients having this type of reaction have been pretty uniformly negative. Whether we attempt to do this by passive sensitization of human skin, by Dale reaction in guinea pigs, or any other method including precipitin, there is no reliable immunologic test for this “serum-sickness” type of reaction, whereas, of course, when the same clinical type of reaction is due to heterologous serum, all of these tests are fairly consistently positive. Now another feature that is very strikingly different in serum-sickness and in the penicillin reactions is that it is only occasionally that the occurrence of penicillin urticaria leads to a persistent anaphylactic type of sensitization in which a subsequent dose will produce an immediate reaction. It happens often enough so that there is certain danger involved, but it is nowhere near as consistently positive as in the case of heterologous serum. It is very common, indeed, to find that a patient who has had one delayed urticarial reaction to penicillin, on the next course of penicillin several months later will have another delayed urticarial reaction with the same incubation period, which would lead you to believe that the patient was again starting to become sensitized with the first dose. However, if such patients are treated the second time the incidence of the delayed reaction is much greater in those who have previously had a delayed reaction. I do not think that there is any doubt at all that the anaphylactic type of reaction Dr. Siegal has described is often associated with positive skin tests and is often associated with a demonstrable Prausnitz-Kustner type of antibody. Without doubt it occurs more often in patients who show a family or past history of allergy so that it is the one exceptional type which appears to fit in with our ordinary concepts of sensitization.

Dr. Rose.—Dr. Schiller has a slide which he would like to show.

Dr. Schiller.—First, I would like to state a few facts about the patient before showing the slide. He is S. F., a 58-year-old man who has had bronchial asthma for about seventeen years. In the past eighteen months his asthma had increased in severity and, because we were unable to control it adequately, he was given several short courses of oral cortisone with beneficial effects. Because we will have something to say about this later, we would have you remember that when he was tested intracutaneously

and by inhalation to house dust extract he showed significant reactions, and, incidentally, he has been receiving weekly injections of house dust extract.

During December, 1951, at which time he had not been on cortisone for about three months, he developed a respiratory infection and a purulent sinusitis and because of this was given 400,000 units of procaine penicillin intramuscularly. He had had penicillin in the past on a number of occasions with no untoward reactions. Within a matter of a minute or less, he appeared flushed, was dyspneic, and had marked asthma. Urticarial wheals were seen over the chest and abdomen. He was the picture of a typical constitutional reaction. Within ten minutes following the administration of several small doses of Adrenalin, the reaction subsided.

TABLE I. TESTS WITH PENICILLIN

(S. F., 57, W., M.) (BRONCHIAL ASTHMA)		OCTOBER 1952	NOVEMBER	JANUARY	FEBRUARY 1953
Skin test	"G"	Immediate	0	+++	+++
		Delayed	+++	+	0
	"O"	Immediate	0	+++	++
		Delayed	+++	±	0
Passive transfer	"G"		0		0
	"O"		0		0

In October, 1952, about eleven months later, S. F. was skin-tested with several penicillins and these results are shown in Table I. These tests were done intracutaneously using 0.05 ml. of the 10,000 unit per cubic centimeter strength. You can see that the immediate intracutaneous tests were negative to both penicillins G and O but the delayed reactions, observed forty-eight hours later, were markedly positive. These reactions were raised, indurated, quite red and itchy. The reactions to both penicillin G and O were equal in size and measured about 25 mm. in diameter. S. F. was retested in November and showed the same picture—negative immediate reactions and positive delayed reactions. At this time blood was drawn for passive transfer studies but passive transfer antibody was not detected. Results of retests in January were somewhat surprising in that the patient had immediate reactions to both penicillin G and O and the delayed reactions were markedly decreased. When last tested in February, 1953, the immediate reaction was again found to both G and O, somewhat less to O, but at this time he showed no delayed reactions. Passive transfer studies at this time were again negative. One other point should be made. In the interval that we were studying S. F.'s skin response to the various penicillins, we had another patient who had had a "serum-sickness" like reaction about nine days following the administration of intramuscular penicillin. This was a patient of Dr. F. C. Lowell's and we will refer to him as W. M. About two weeks after W. M. had received his injection of penicillin, when his urticarial reaction was subsiding, he had, when tested intracutaneously with penicillin, an immediate reaction with a 20 mm. wheal and erythema. A delayed reaction was not observed. At that time blood was drawn from W. M. for passive transfer

studies and S. F., the patient who has just been described to you, acted as a recipient. This was November, 1952, when you will recall S. F. had no passive transfer antibody in his serum and showed only delayed positive reactions. When the site in S. F. (which held W. M.'s serum) was challenged with penicillin, there developed an immediate wheal and erythema which was pseudopodic and about 20 or 25 mm. in diameter, a definite passive transfer reaction. This indicated that S. F.'s skin was capable of reacting in the same manner as W. M.'s if he had only developed the appropriate type of antibody. We know that S. F. was able to react this way because he did so to house dust. We were interested in following this passive transfer reaction for the next forty-eight hours to see whether or not he would have a delayed reaction. At the site where the passive transfer reaction occurred, a delayed reaction developed which was far less intense than a control site which was injected with only penicillin. In discussing this response at a recent meeting,⁸ Dr. Lowell brought up several interesting possibilities. First, one might say that the antibody in W. M.'s serum might have neutralized the penicillin, thereby bringing about a less intense reaction. Second, since the reaction involves the production of a wheal and the accumulation of a lot of fluid in the area, penicillin may have simply been diluted. Finally, the skin having reacted quite intensely with a wheal and erythema may become nonspecifically desensitized and was therefore unable to react with the violence that it did previously. This recalls the observation that in patients who exhibit the immediate reaction to tuberculin or purified protein derivative, the reaction at forty-eight to seventy-two hours is usually absent or, if present, is of small degree. I think this is a very interesting sequence of events and there may be other possibilities to explain it.

Perhaps Dr. Sherman would like to comment on the immunologic setup present in the case we have just mentioned.

Dr. Sherman.—I think this is an exceedingly interesting case. I do not know how often this type of thing occurs, but this is one thing that does have some analogy in relation to sensitization to heterologous serum because at least occasionally the earliest stage of sensitization to heterologous serum is associated with a delayed reaction and the immediate reaction occurs subsequently. However, I think that we have no way of knowing that this situation will be observed often and I do not believe you want to go away with the impression that a delayed reaction to penicillin is the forerunner of the immediate reaction because I am sure that a great many patients have been tested repeatedly over a period of months or years and have always shown delayed reactions and never shown immediate reactions. However, I think we can at least speculate that this is a patient who is in danger of having the anaphylactic type of reaction and we can only say that we do not know how often this may occur.

Dr. Boger.—I want to agree wholeheartedly with Dr. Sherman's observations. There are no infallible rules covering the phenomena of hypersensitivity to penicillin. Our inability to predict what will happen is

attested to by the following experience. A patient was given 1.2 million units of procaine penicillin suspended in aluminum monostearate and oil gel and two weeks later he had as near to an exfoliative dermatitis as I care to see. We despaired of the man's life but he recovered and was discharged from the hospital. Unbeknown to those of us who went through this harrowing experience, the man came back to the antisiphilitic clinic and he was given another 1.2 million units of procaine penicillin suspended in oil and aluminum monostearate gel. I was all ready to take up residence in the nearest penal institution offering luxury accommodations, but to our amazement and my relief the man did not even turn a hair. This experience convinced me that you cannot predict anything with regard to penicillin reactions.

TABLE II. SKIN SENSITIVITY TO PENICILLIN

RESPONSE TO SKIN TEST	GROUP A NO KNOWN PENICILLIN THERAPY		GROUP B PREVIOUS TREATMENT WITH PENICILLIN		GROUP C KNOWN REACTION TO PENICILLIN		TOTALS	
	NO. OF PATIENTS	%	NO. OF PATIENTS	%	NO. OF PATIENTS	%	NO. OF PATIENTS	%
+G, +BT	6 of 137	4.5	8 of 113	7.1	14 of 26	53.5	28 of 276	10.0
+G, +O	2 of 93	2.2	11 of 110	10.0	12 of 21	55.0	25 of 224	11.2

Dr. Rose.—That gives you some idea of the complexity of this enormous subject. In order that we may complicate it a little more, before we actually come to the period of treatment, I am going to ask Dr. Boger to speak again and this time discuss the reactions to the various types of penicillin, such as "G," "O," and "BT."

Dr. Boger.—It has been stated earlier that an individual's past penicillin experience is significant. You will observe (Table II) that in Group A, with no known penicillin experience, there was 2.2 per cent reactivity; in Group B, with known penicillin experience—oral, intramuscular, repository or otherwise—a 10 per cent reactivity. In Group C, those patients who had shown allergic responses, 55 per cent reacted to intracutaneous skin test. With regard to the supposedly hypoallergenic penicillin O, these observations should not be interpreted to mean that all patients sensitive to G also react to O, for some patients sensitive to G have been reported to tolerate O and in such cases penicillin O has extreme value. The skin tests were read at a half-hour and again at twenty-four and at forty-eight hours. No test was regarded as positive unless erythema and induration measured at least 4 mm. in two diameters.

BT penicillin is an unavailable biosynthetic penicillin similar to O, and the experience with it parallels that with O (Table II). With no previous penicillin therapy, there was a 4.5 per cent reactivity. This is an original response for which we have no explanation other than the existence of a common antigen shared by penicillin and a variety of naturally occurring fungi. The exposure of the patient to this common antigen may be in the

form of unrecognized fungus infection or ingestion of fungi and their products. In Group B, out of 113 with known penicillin experience, there was 7.1 per cent reactivity; in the small group with previous known reactivity, the incidence was 53.5 per cent. Those observations are submitted only to show that one's past penicillin does have some bearing on the skin sensitivity.⁷ A patient with subacute bacterial endocarditis during the second week of therapy with water-soluble penicillin G developed high fever and reactivation of the bacteremia. We were desirous of substituting penicillin O in order that penicillin therapy could be continued, but by skin test the patient reacted just as violently to O as to G.

In a discussion of hypoallergenic penicillins, it is appropriate to mention l-ephedamine penicillin G ("Compenamine"). The same claim for lesser potential of sensitization has been made for this preparation as for penicillin O, but regrettably our own experience is not extensive enough to comment on this point. In connection with a discussion of hypoallergenic penicillin it seems proper to mention that although we may feed chemical precursors to microorganisms producing penicillin in an attempt to produce a penicillin that is not normally produced and so overcome the sensitization problem, Nature cannot be made to forget completely her natural manufacturing methods. Hence, according to all the information that has come to my attention, penicillins BT and O contain a small amount of penicillin G as a contaminant.

While efforts have gone forward to produce new penicillins with less sensitizing potential, other efforts have been made to alter the penicillin molecule with the idea of accentuating certain valuable properties. Procaine penicillin by combining a local anesthetic and penicillin G has given us a repository or long-acting preparation. To date there is no convincing evidence that the procaine portion of the molecule has occasioned any additional sensitization, but we should be alert to this possibility. Penethamate ("Neo-Penil") has been shown to diffuse more readily into lymph glands, the respiratory tract, and the central nervous system, than penicillin G itself. These established advantages of this new penicillin are probably negated by the serious side-effects which have been recently reported. Benzethacil ("Bicillin" or "Permapen") represents a chemical modification of penicillin which results in an insoluble penicillin that gives prolonged plasma concentrations after intramuscular injection and this type of penicillin will probably find a considerable use in the treatment of syphilis.

All of the new penicillins represent a chemical union of two drugs and as such the potentials of sensitization are increased. In this connection attention is called to the current practice of administering combinations of penicillin and sulfonamides, penicillin and salicylates, penicillin and probenecid, and penicillin and streptomycin. It should be borne in mind that all of such combinations of penicillin with other drugs increase the likelihood of the patient being sensitized to one or all of the components of these combinations. In view of the grave potentials of sensitization in terms of serious side-effects, our use of penicillin should be as discriminating as possible.

Dr. Rose.—Now, apparently, there may be another way of testing for penicillin sensitivity and I am going to let Dr. Schiller tell you something about that.

Dr. Schiller.—Inhalation tests using penicillin as an aerosol were carried out comparing the reactivity of the bronchial tree or lung to the inhalation of penicillin G and O. The patient studied is the one described earlier as S. F., whose skin tests with penicillin G and O, you will recall, were of the delayed type which, subsequently, became immediate. I would call your attention

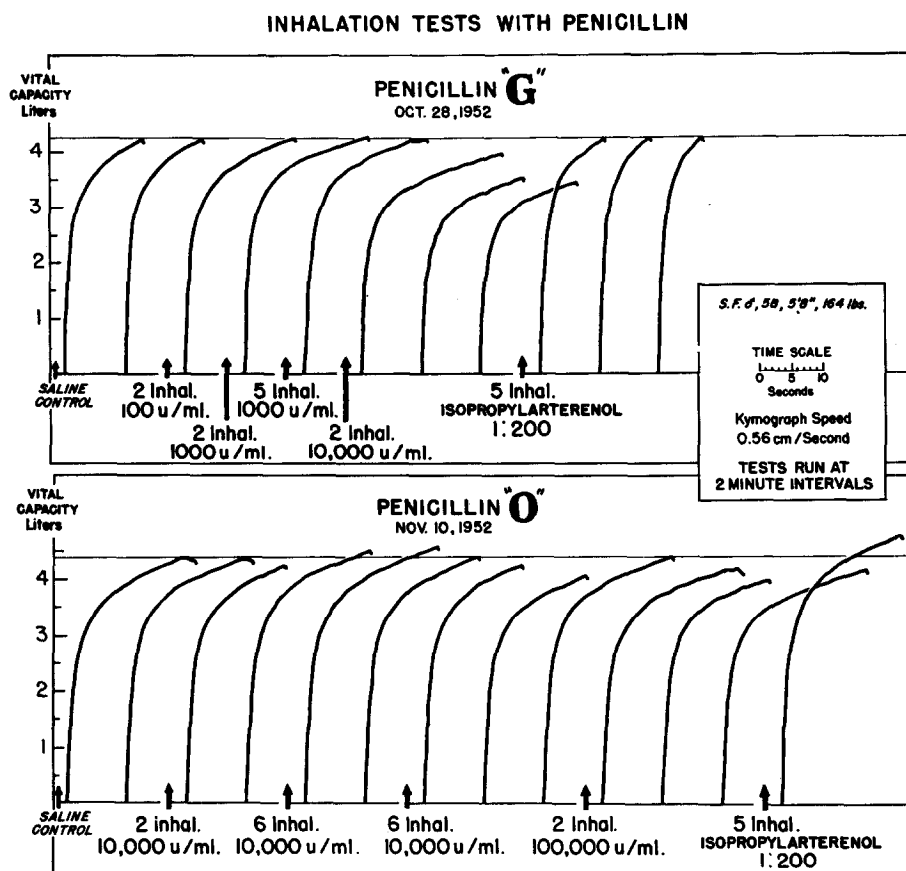


Fig. 8.

now to the upper portion of Fig. 8 which shows the expiratory tracings of S. F.'s vital capacities recorded on a moving drum. This experiment on October 28 utilized penicillin G as the test aerosol. The patient's control vital capacities were in the vicinity of 4 liters and showed no change after the inhalation of a saline control. Vital capacities were performed at about one and one-half to two-minute intervals. Following two inhalations of the 100-unit strength aerosol and again following a total of seven inhalations of the 1,000 unit solution, the vital capacities remained essentially at the

normal control value, though examination of the tracings indicates that the patient was having some difficulty in getting air out of his lungs. The careful measurement of the volume expired in the first second indicates this. He was then given two inhalations of the 10,000 unit strength of penicillin aerosol and, as you can see, within a minute or two thereafter there was a sharp fall in vital capacity as well as a marked decrease in the rate of expiration. It is interesting that during this period he experienced little or no asthmatic symptoms. Since we felt that we had a very significant response, we did not wait any longer and gave him five inhalations of isopropylarterenol 1:200 and, as you can see, his vital capacity returned to normal. The patient was again tested on November 11 in the same way but was exposed to an aerosol of penicillin O. This is seen in the lower portion of Fig. 8. After inhalation of the saline control he had a total of fourteen inhalations of the 10,000 unit strength with only a very equivocal response, which very shortly returned to normal control value. After two inhalations of the 100,000 unit strength there again was a suggestion of a pulmonary response but, in contrast to penicillin G, this was not significant. Note the tenfold increase in concentration of the penicillin O aerosol. With five inhalations of isopropylarterenol his vital capacity exceeded the control value. We think, then, that this man might have tolerated penicillin O, but that is purely speculative. There is one other interesting point that I would like to make: at the time these inhalation tests were done, the patient exhibited only the delayed positive type of skin reaction. This is the first patient in our experience, and we have been testing patients by the inhalation method since 1946, who has had an immediate pulmonary response in the absence of the immediate type skin test.

Dr. Boger.—This is a very definitive technique for showing sensitivity, namely, inhalation of the allergen, but for my part I choose to have nothing to do with such a means of determining reactivity. In this connection I have two most disturbing recollections. One person who loves the experimental method and will not listen or learn from the experience of others used an inhaler that was sent to him during that short period of time when penicillin dust in the nostrils was enjoying some degree of acceptance. This "investigator" narrowly escaped a tracheotomy, for he developed severe angioneurotic edema with involvement of the larynx. A child who received penicillin nose drops was not so fortunate; he had to have a tracheotomy.

Laryngeal edema is something I have tremendous respect for, and I want no penicillin in my nasopharynx.

Dr. Schiller.—In answering Dr. Boger, this is not the time or place to go into the discussion of the merits of the inhalation test. I would only refer him to the articles on the subject that have come out of our laboratory in the past five or six years.^{9, 10} The method is simple and innocuous. If I were allowed to do but one test, and one test only, on a patient with bronchial asthma for specific diagnostic purposes, the choice would be the inhalation test. What we did with this patient just described bears no resemblance to the inhalation

of penicillin powder (quantitatively, the difference is vast), and we would agree with Dr. Boger that the inhalation of such powdered penicillin is potentially dangerous in anyone who is sensitive to the drug.

Dr. Rose.—I think we ought to have several very short words about the treatment of these penicillin reactions; I am going to ask each member of the panel to brief you on that subject.

Dr. Siegal.—I do not think I have anything very new or important to say on the subject. Some of the patients, of course, who have severe reactions simply will not respond to ordinary antihistamines. I have found that phenergan is probably the single most effective antihistamine for the urticarial type of reaction. When this fails I think all of us, sooner or later, rely upon ACTH or cortisone. I would like to mention one thing. Occasionally we see patients who have very prolonged reactions of urticaria following penicillin. I personally have seen three lasting from five to six months, and Epstein in *California Medicine*¹¹ has recorded one of fifteen months' duration following penicillin. In such cases, if these measures fail, desensitization with penicillin is well worth trying and has been successful in my hands.

Dr. Sherman.—I do not think there is anything to add to what Dr. Siegal has said. In the immediate anaphylactic type of reaction, of course, the treatment is that of any anaphylactic reaction with Adrenalin the main reliance. In the severe urticarial type of reaction, in my experience, the antihistaminic drugs have not been very satisfactory. When cortisone or ACTH became available we very quickly came to use these. I think that essentially all the other cutaneous reactions that we have mentioned, including exfoliative dermatitis, respond better to ACTH and cortisone than to any other drugs available.

Dr. Schiller.—The antihistaminic drugs may be helpful in relieving both the pruritus and severity of the urticaria seen in the course of the serum-sickness-like syndrome in penicillin allergy. However, these agents have little or no effect on the joint pains, lymphadenopathy, or renal disturbances. In severe cases, we have found cortisone to be very effective in controlling both the skin and joint manifestations. I think the treatment of the immediate reaction has been well covered.

Dr. Boger.—Epinephrine is of real value in the ordinary case, but ACTH or cortisone may be mandatory for severe cases. A 5 per cent solution of glucose containing 10 mg. of ACTH is dripped in intravenously over an eight-hour period. This dose may be repeated twice or three times during the twenty-four hour period. In some instances it may be necessary to duplicate this treatment on the second day. ACTH used intravenously has five to seven times the potency of intramuscularly administered drug and we feel that ACTH acts faster and is more physiologic than cortisone. ACTH and cortisone are the best answer for the problem of severe reactions that have followed penicillin administration.

Dr. Rose.—I will not attempt to summarize this excellent exposition on penicillin sensitivity in any detail. Perhaps it is sufficient to emphasize the importance of these reactions primarily from the incidence of reactions of a fatal nature. There are undoubtedly many more reactions than have been reported in the literature, and I personally am aware of three, fortunately not my own cases. The variety of nonfatal responses is of extreme interest to anyone with a training in allergy, and it may be that further careful study of the skin reactions may elucidate basic allergic mechanisms.

I would add a word regarding treatment. We have used the intravenous administration of hydrocortone with success in one case of near-fatal shock. This compound, 100 mg. in 500 ml. of 5 per cent dextrose, acts quickly and is probably the most rapid acting of all hormone preparations. Since penicillin is still one of the most useful antibiotics at our disposal, let us continue to use it carefully and wisely.

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