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A CONTROLLED STUDY ON THE USE OF PARENTERAL AND ORAL ANTIHISTAMINES IN PREVENTING PENICILLIN REACTIONS

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MUCH has been written about penicillin allergy. Even by 1948, Brown¹ found well over 300 articles to review on this subject, and numerous publications have appeared since then. A perusal of the early case reports reveals that more than fifty different types of alleged penicillin reactions have been described, although all these are not allergic in type. As to the incidence of reactions, statistics may be found indicating reaction rates varying from less than 1 per cent² to 53 per cent,³ with all gradations between.

These comments are made not to compound the confusion but, rather, to emphasize how difficult it is to reach valid conclusions in this field. No doubt a major factor at the root of the difficulty is that there is no reliable, objective test for proving the diagnosis of all types of penicillin allergy. It is true that patch testing is a relatively reliable procedure in the occasional cases of penicillin contact dermatitis which are still encountered, and positive scratch or intracutaneous tests usually are obtained in the rare cases of anaphylactic type penicillin hypersensitivity. However, there has evolved a rather strong consensus, with which we are in agreement, that skin testing is not generally reliable in evaluating the vast majority of penicillin reactions. Thus, the diagnosis of penicillin allergy usually must be based on clinical judgment, and it is not surprising, therefore, that the statistics of various investigators are not entirely comparable.

In addition to various sources of error, there are a number of factors inherent in the data themselves which account in part for variations in the

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reported incidence of penicillin reactions. There is some reason to believe that the type of penicillin preparation used, its route of administration, dose, and duration of treatment have some influence on the incidence of reactions. The patient's age and sex, the amount of previous penicillin therapy, a history of previous allergy or of mycotic infections, and a history of local reactions at the site of earlier penicillin injections also have been correlated with the incidence of penicillin allergy by various observers. However, with some exceptions (most notably the statistical study of Lepper and his associates⁴), many of these correlations are based on general clinical impressions without adequate documentation. A secondary objective of this study is to test the correlation of these factors with the incidence of penicillin reactions in a relatively large group of subjects.

Interest in penicillin allergy has been heightened in the past few years by many reports of severe or fatal reactions of an anaphylactic type.⁵⁻⁷ There is reason to believe that these alarming reactions are increasing in frequency and will constitute an even more serious problem in the future. Thus, the problem of preventing penicillin reactions is assuming more and more importance. There is general agreement that this valuable drug should not be used indiscriminately. The topical use of penicillin on skin or mucous membranes should be discouraged, since it is attended by a high incidence of sensitization. Before prescribing penicillin, one always should ask the patient whether he had a reaction from any previous course of the drug, and a different antibiotic generally should be used (as is usually possible) when such a history is elicited. Preliminary skin testing may be of value when there is any possibility that the patient may be anaphylactically sensitized. Injections should be given in extremities, and a tourniquet and appropriate medications should be at hand for treatment of any possible severe reaction.

In spite of these precautions, there continue to be substantial numbers of unpredictable penicillin reactions. Further attempts at reducing the incidence of penicillin reactions have taken several forms, including the use of oral penicillin, penicillins O and BT, l-ephenamine penicillin (Compenamine), anti-histamines mixed with penicillin, and procaine amide used in a similar manner. Reports of success with all these measures should be reviewed critically. We feel that valid conclusions can be reached only if the following requirements are satisfied:

1. Each study must contain its own control group. Comparison with reaction rates quoted in the literature is inadequate in view of the tremendous variations in the latter.

2. Study and control groups should be similar in respect to the type of patients observed and general program of penicillin therapy. The latter information should be included in the report in order to facilitate comparison with other studies. For example, it is not valid to compare with adult reaction rates the incidence of reactions to supposedly hypoallergic penicillins in groups composed largely of children, since there is good reason to believe that children normally

experience much less penicillin allergy than adults. Nevertheless, such comparisons have frequently been made in the literature.

3. Control and study observations should be made concomitantly and possible reactions evaluated without knowledge as to the group to which individual patients belong. This is necessary because the diagnosis of penicillin allergy usually rests on clinical judgment, rather than on an objective test.

4. Patients should be followed for reactions for several weeks after completion of penicillin therapy, since reactions frequently are delayed in onset. Specific inquiry must be made about delayed reactions, as our experience indicates that patients may neglect to report delayed reactions voluntarily when they are mild in degree.

5. Large numbers of patients must be observed to achieve statistically significant results. The level of confidence should be stated in the report.

6. Failure of previously penicillin-sensitive persons to react to a subsequent course of the drug does not prove a hypoallergic effect, since penicillin allergy often is spontaneously lost over a variable period of time.

7. Absence of anaphylactic type reactions in series of a few thousand cases does not prove a hypoallergic effect, because at present these severe reactions still occur relatively infrequently with all forms of penicillin.

Among the methods suggested for reducing the incidence of penicillin reactions, the use of antihistamines for this purpose offers several advantages: these drugs are readily available, there is much information regarding their toxicity, side effects, and pharmacologic properties, and they do not appear to affect the therapeutic efficacy of the penicillin.⁸ There also is no doubt that these drugs sometimes are effective in treatment of penicillin reactions, particularly those of an urticarial type. Thus, it is logical that the prophylactic administration of antihistamines might reduce the incidence of such reactions, and a number of reports⁹⁻¹⁹ have appeared in the literature asserting that this is the case. In fact, the publications appearing thus far have indicated a virtual elimination of all allergic reactions to penicillin by means of antihistamines. Furthermore, these amazing results have been achieved simply by using solutions of antihistamines as diluents for the penicillin solution before injection, a procedure which assures the patient's receiving the drug but with no added inconvenience. In addition, local reactions and discomfort at the site of injection are said to be reduced markedly by this procedure, and there seem to be less side effects from the antihistamine when it is given by injection.

The practical importance of this work is obvious. On a priori grounds, however, the previously reported results seem rather surprising. Although it is logical that antihistamines might suppress some allergic reactions during

the period of their pharmacologic effect, this period is generally thought of in terms of a number of hours following the administration of these drugs, and it is difficult to understand how they would inhibit delayed reactions which may not begin for many days. There is no convincing evidence that antihistamines inhibit antibody formation in general, and Dreisback²⁰ did not observe any inhibition in the development of experimental penicillin hypersensitivity in rabbits by the administration of antihistamines. Furthermore, although antihistamines might be expected to suppress urticarial reactions, several of the cutaneous manifestations of penicillin allergy are not known to be associated with histamine release, and yet the previously cited reports have indicated a virtual elimination of all types of penicillin reactions. In view of these considerations and the fact that most of the studies reporting favorably on the use of antihistamines do not satisfy the previously discussed requirements for definitive work in this field, it was thought worth while to report our controlled study on this subject.

PROCEDURE

This study was carried out during the twenty-two-month period ending in August, 1954, at the University of Michigan Student Health Service with the cooperation of the staff there. Every patient for whom penicillin was prescribed by any department of the Health Service was sent to the allergy clinic to receive the drug. Before this was given, he was requested to cooperate in the study by taking tablets designed to prevent penicillin reactions. He also was asked to fill out a form, giving pertinent information about his age, sex, number of previous courses of penicillin, routes of previous penicillin therapy, time interval since last penicillin, past penicillin reactions, other drug allergies, history of cutaneous fungus infections, personal history of the common allergic diseases, and family history of allergy. The procedure in hospitalized cases also was supervised by the allergy clinic. Patients retained a second form which was to be returned to the allergy clinic *no sooner* than three weeks after their last dose of penicillin. This form indicated the route, frequency of administration, and duration of penicillin therapy, the regularity with which the "preventive tablets" were taken, the nature and severity of any side effects noted from the "preventive tablets," and detailed information about any possible penicillin reactions. The latter included a description of the reaction, time of onset, duration, severity, and associated local reaction at the site of injection. In addition, patients were urged to return to the allergy clinic at the first sign of itching, rashes, or other possible manifestations of a penicillin reaction, and the information on the questionnaire concerning the reaction was amended as indicated by the evaluating physician.

The major portion of the study was designed so that patients received, in strict rotation, fortified aqueous crystalline procaine penicillin G (S-R penicillin) diluted either with physiologic saline solution or with a solution containing 10 mg. of chlorphenpyridamine (Chlor-Trimeton). Patients in each of these groups also were given, in rotation, either 8 mg. repeat-action Chlor-Trimeton tablets or similar placebo tablets to be taken three times daily

for the duration of penicillin therapy and for ten days thereafter. It was thought that prolonged oral administration of antihistamines might offer maximal opportunity for these drugs to show a beneficial effect, although it was realized from the outset that many of the patients would fail to take pills regularly for such a long period. Since there is some evidence that salicylates can inhibit the development of certain manifestations of serum sickness,^{21, 22} which delayed penicillin reactions sometimes resemble, in the early phases of this experiment there also was included a group of patients who received aspirin. When it became apparent that this drug was having no effect in the dosage used (2.65 Gm. per day), it was abandoned and the data were included with the placebo group. Our data do not exclude the possibility that much larger doses of salicylates might have some beneficial effect, but it was not possible for us to attempt further studies of this type under the conditions of our experiment.

All possible reactions were evaluated by a single investigator without knowledge as to which type of medications the patient had received. Criteria for the diagnosis of a penicillin reaction were: (1) clinical manifestations of a type known to be related to penicillin allergy; (2) a satisfactory time relationship between these manifestations and penicillin administration; and (3) the absence of other apparent cause for the observed reaction. Only those cases which seemed to represent definite penicillin reactions were included in the major portion of the statistical analysis. A separate record and analysis was made of the more questionable cases in which penicillin allergy could not be excluded but did not seem to be definite. The pre- and posttreatment questionnaires submitted by the patients were reviewed and amended as indicated by the investigators. They were then coded, punched on cards, and tabulated with the aid of IBM machines, a procedure which greatly facilitated handling the more than 100,000 items of data which accumulated during the course of the study.

As had been anticipated from the beginning, there were two problems which could not be entirely surmounted in carrying out this experiment. One was that although the patients were strongly urged to return *at the time* they experienced any possible symptoms or signs of penicillin reactions, they sometimes failed to do so, especially when their symptoms were mild. In such instances, they were contacted and personally interviewed by the evaluating investigator, such possible reactions usually being relegated to the "questionable reaction" group unless the patient's description was clearly and completely characteristic of a penicillin reaction. Although this procedure was not ideal, it would be very hard, indeed, to achieve conditions under which very large numbers of patients could be followed more closely for some period of time following completion of penicillin therapy.

The other major problem was failure to take the "preventive tablets" as prescribed. Forty-five per cent of the patients in the entire study failed to take the tablets with reasonable regularity, in spite of strong encouragement

to do so. This would limit considerably the practicality of this form of therapy, although it is possible that under other conditions (such as if the patients had paid for the tablets) cooperation might have been better. Side effects of the antihistamines were not a major factor, since the record of pill taking was the same in the placebo pill group. Among those who had reactions to penicillin, pill taking was considered adequate if it had been reasonably regular for the prescribed period or up until the start of the reaction. Under these conditions, 11 per cent of penicillin reactors were considered to have taken their pills inadequately.

RESULTS

Table I shows the general characteristics of the group studied. The preponderance of male patients reflects the higher male student enrollment. As would be expected in a university student group, only two persons were under 17 years of age and thirty-seven were over 40 years of age. It is interesting that only 20 per cent of the students had never received penicillin before, whereas almost 40 per cent had received three or more previous courses. Very appreciable numbers had received the drug previously in dosage forms other than by injection.

TABLE I. GENERAL CHARACTERISTICS OF THE GROUP STUDIED (2,299 COURSES OF PENICILLIN)

<i>Sex:</i>	
Males	61.7 per cent
Females	38.3 per cent
<i>Age:</i>	
Median	21 years
Under 17 years	2
Over 40 years	34
<i>Previous Penicillin Therapy:</i>	
None	20 per cent
One course	24 per cent
Two courses	18 per cent
Three or more courses	38 per cent
<i>Route of Previous Therapy:</i>	
Injection	1,631
Oral tablets	426
Troches	413
Ointment	99
Other	44

Table II shows that of the 2,299 patients who entered the study, an adequate follow-up was achieved in all but 100, this better than 95 per cent follow-up being accomplished with the aid of hundreds of reminder postcards and telephone calls. Because of the danger of severe anaphylactic-like reactions to penicillin, we did not encourage the employment in this study of patients known to have reacted previously. The small group falling in this category is considered separately in the statistical analysis of our data. Likewise, except where otherwise specified, the major portion of our statistical analysis is confined to the 1,922 courses of penicillin given only by injection.

Table III shows the comparability of the four treatment groups. Group I, as indicated, is a control group given penicillin diluted with saline and oral

TABLE II

<i>Total Courses of Penicillin:</i>	2,299
Unable to follow	100
Followed for 3 weeks or more	2,199
Persons having reactions to previous courses of penicillin	47
	2,152
<i>Route of Penicillin Administration:</i>	
Injection only	1,922
Tablets only	106
Troches only	81
Ointment	1
Injection and tablets	28
Injection and troches	13
Not recorded	1

placebo tablets. Group II received saline penicillin and oral Chlor-Trimeton, Group III received Chlor-Trimeton penicillin and an oral placebo, and Group IV received Chlor-Trimeton penicillin and Chlor-Trimeton orally. A comparison of these data shows no very major differences among any of the groups in respect to the factors listed: age, sex, previous penicillin therapy, history of other drug allergies, history of cutaneous fungus infection, history of allergic diseases, or duration or dosage of penicillin treatment. Incidentally, one may be surprised at the very high percentage of patients in all groups giving a history of hay fever or asthma. This aspect of our data will be the subject of a further report.

TABLE III. COMPARABILITY OF TREATMENT GROUPS

	GROUP I SALINE PENICILLIN ORAL PLACEBO	GROUP II SALINE PENICILLIN ORAL CHLOR- TRIMETON	GROUP III CHLOR- TRIMETON PENICILLIN ORAL PLACEBO	GROUP IV CHLOR- TRIMETON PENICILLIN ORAL CHLOR- TRIMETON
Total courses of penicillin	501	443	478	491
Median age (years)	21	21	20	20
Sex:				
Male	66%	60%	59%	61%
Female	34%	40%	41%	39%
Previous penicillin therapy:				
None	25%	20%	19%	20%
Three or more courses	32%	40%	38%	42%
History of other drug allergies	7.0%	8.1%	7.3%	9.7%
History of cutaneous fungus infection	67%	59%	63%	60%
History of allergy:				
Allergic rhinitis	24%	21%	20%	25%
Asthma	8%	6%	8%	9%
Urticaria	16%	16%	17%	13%
Average days of treatment	2.8	2.7	2.8	2.8
Average number of injections per day	1.06	1.08	1.04	1.08

Fig. 1 shows the gross results of the study. There were sixty-four reactions to injected penicillin, an incidence of 3.3 per cent, distributed among the four groups as indicated. It is apparent that there is nothing approaching virtual elimination of penicillin reactions among the antihistamine groups. The statistical analysis of this and the following data was done by the Chi-

GENERAL PENICILLIN REACTIONS

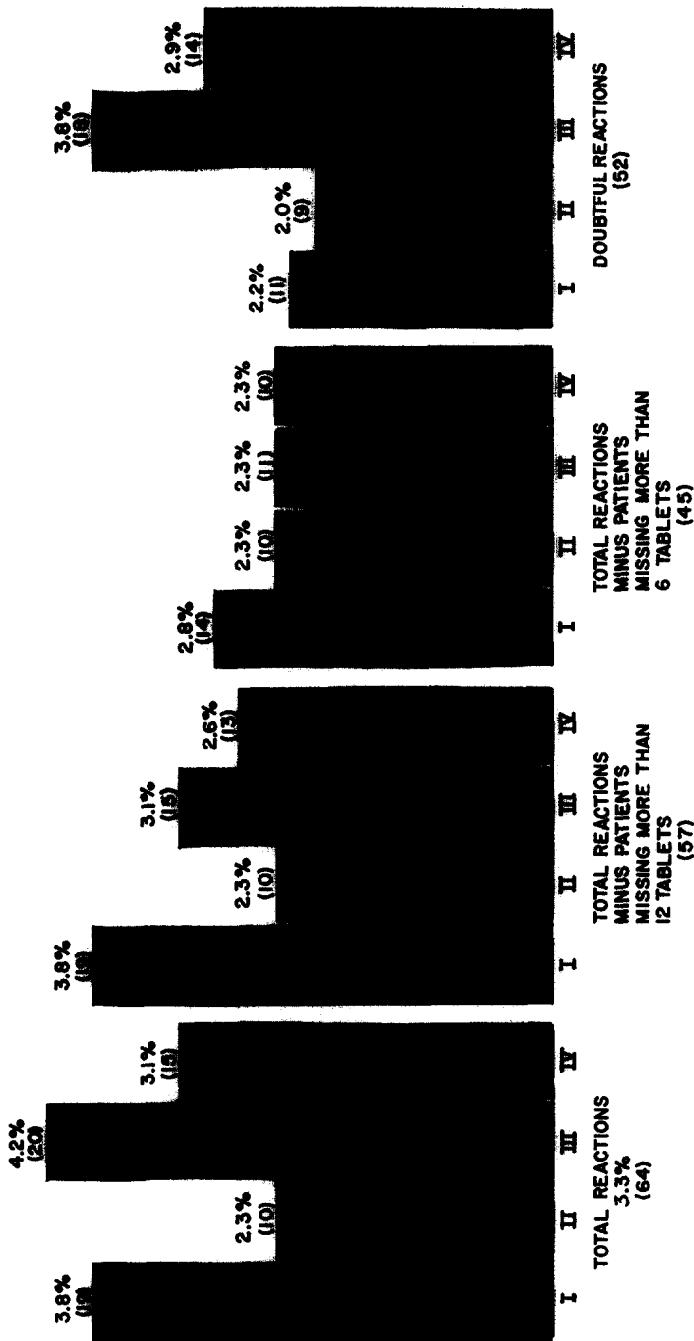


Fig. 1.—Group I was the control group given penicillin diluted with saline and an oral placebo; Group II received saline penicillin and oral Chlor-Trimeton; Group III received Chlor-Trimeton penicillin and an oral placebo; Group IV received Chlor-Trimeton penicillin and oral Chlor-Trimeton.

square test (with Yates' correction), using a 5 per cent level of significance. The somewhat lower reaction rate among those receiving oral antihistamines in Groups II and IV is not statistically significant with this number of cases. The next two figures are presented to show the reaction rates after deleting those cases where the reacting patients did not take their pills regularly, but it is apparent that even less difference is observable between various groups after making this correction. Most of the subsequent statistical analysis is based on only the fifty-seven cases where the patients are known to have taken their pills with at least moderate regularity. As mentioned previously, a separate record was kept of questionable or doubtful cases where penicillin allergy was uncertain but could not be excluded. The last figure on Fig. 1 shows that inclusion of these cases in the main body of data would not have altered the results.

TYPES OF PENICILLIN REACTIONS

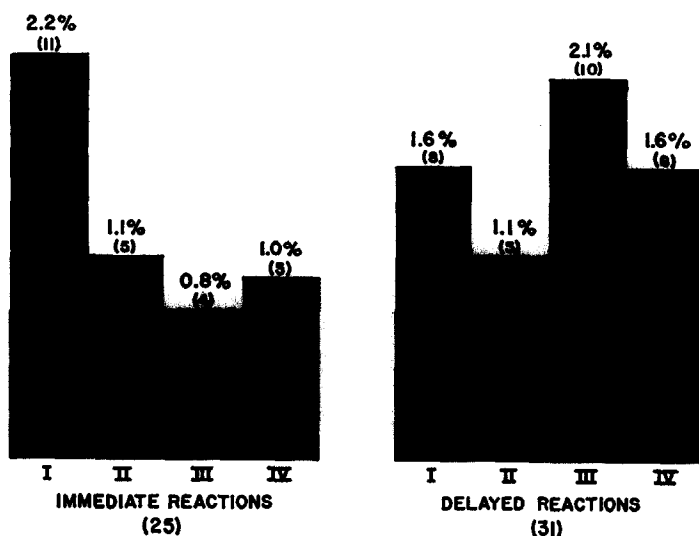


Fig. 2.

Fig. 2 indicates a subdivision of penicillin reactions into "immediate" ones coming on within forty-eight hours of starting penicillin therapy and delayed reactions beginning at any time thereafter. There is a statistically significant reduction in the incidence of immediate reactions among the three antihistamine-treated groups as compared with the control group. There is no significant difference in the incidence of delayed reactions. These results are in agreement with the theoretical expectations regarding the results of antihistamine administration.

The duration of the reactions which occurred was no longer in the control group than in the antihistamine groups, as indicated in Fig. 3. These data

TYPES OF PENICILLIN REACTIONS

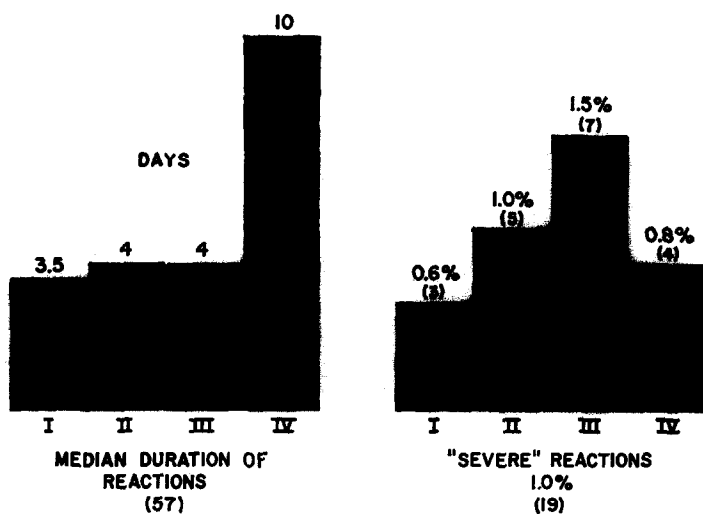


Fig. 3.

URTICARIAL REACTIONS

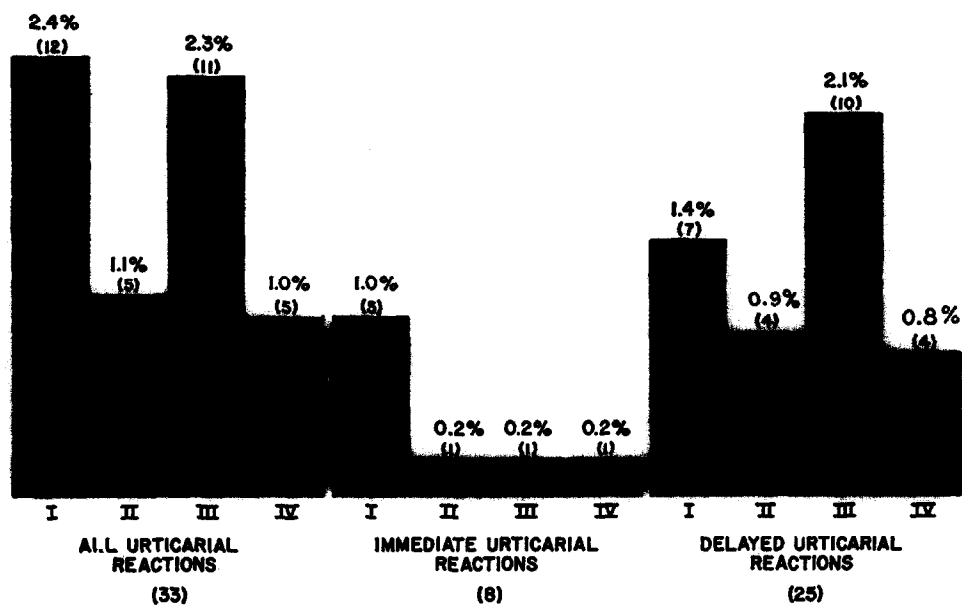


Fig. 4.

are influenced by other treatment which was initiated once a penicillin reaction had definitely been diagnosed. The other figure in Fig. 3 is an important one. It must be admitted that many of the penicillin reactions encountered in this study were rather trivial, and antihistamine prophylaxis would be of value if it simply eliminated or modified the more severe reactions. This definitely was not the case. Even in Group IV, there were patients who required hormone therapy or hospitalization in the Health Service infirmary for relatively severe penicillin reactions. Seventeen of these nineteen reactions were of the delayed type. No anaphylactic type reactions were encountered in either the control or antihistamine-treated groups in this particular study.

PATIENTS HAVING HAD REACTIONS TO PREVIOUS COURSES OF PENICILLIN

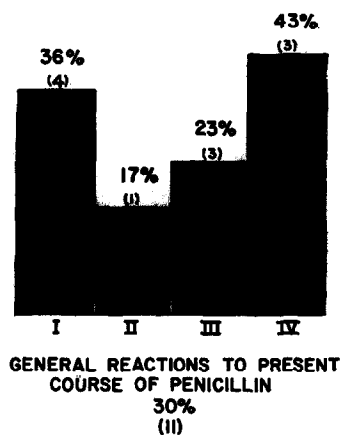


Fig. 5.

The incidence of urticarial reactions is specifically analyzed in Fig. 4, since it is in regard to this type of reaction that antihistamines would be expected to be most effective. There is a statistically significant higher incidence of urticaria in Groups I and III, not receiving prophylactic oral antihistamines, than in Groups II and IV which did receive these drugs orally. The other two figures in Fig. 4 show that this difference is accounted for to a considerable extent by a decreased incidence of immediate urticarial reactions. The difference in delayed urticarial reaction rates is not significant. These results all are in agreement with the previously discussed *a priori* expectations.

Fig. 5 shows the results in patients who gave what seemed to be a bona fide history of a previous allergic reaction to penicillin. The number of patients involved here is too small to enable one to draw any conclusions about differences in reaction rates among the different groups, which were of quite unequal size. The two points of importance are: (1) substantial num-

bers of these patients had reactions in spite of receiving oral or parenteral antihistamines and (2) 64 per cent of patients in the control group did not have reactions, again emphasizing the point that penicillin allergy may be lost spontaneously.

There were inadequate numbers of patients receiving penicillin by routes other than or in addition to injection to justify a statistical analysis of these groups. It is of interest, however, that what data are available do show a trend toward a relatively low reaction rate among those receiving oral penicillin and a high rate among those using troches, as shown in Fig. 6. This is in agreement with the literature. The one reaction from oral penicillin was rather trivial.

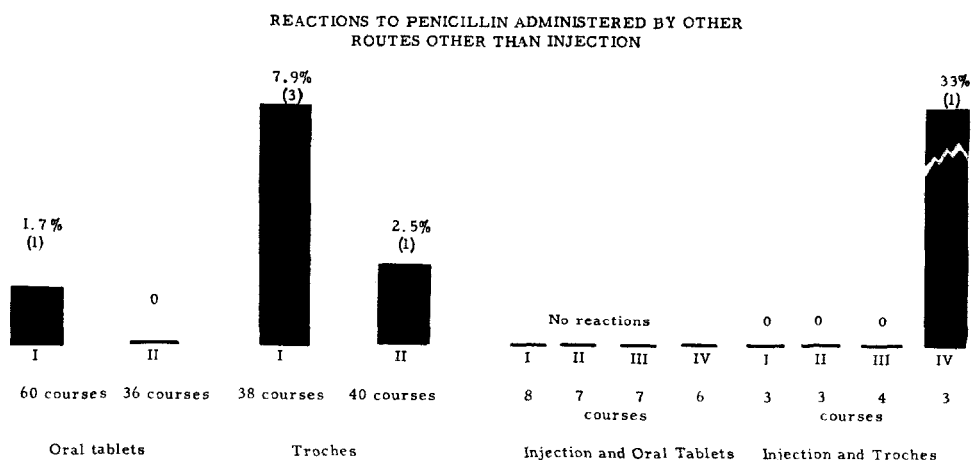


Fig. 6.

The types of reactions observed among those receiving penicillin by injection during this study are summarized in Table IV. Since quite a few patients exhibited more than one manifestation of penicillin allergy, the number of reactions listed here exceeds the number of patients who experienced them.

A secondary objective of this study has been to analyze the data for factors predisposing to penicillin reactions. Table V shows the incidence of various factors among those who had reactions and those who did not. There is no statistically significant sex difference. In regard to age, there was a trend toward more frequent reactions in the older age group, although this was not statistically significant. No appreciable differences were noted in the incidence of other drug allergies or cutaneous fungus infections between the two groups, although the accuracy of obtaining information about the latter by questionnaire might well be challenged. There was a slight trend toward a higher incidence of allergic rhinitis, asthma, and hives among the reactors than among the nonreactors, but this difference was not significant, and the trend regarding family history of allergy was in the opposite direction. These

TABLE IV. TYPES OF REACTIONS OBSERVED AMONG PATIENTS RECEIVING PENICILLIN BY INJECTION

TYPE OF REACTION	"IMMEDIATE" REACTIONS	DELAYED REACTIONS	TOTAL REACTIONS
Urticaria and/or angio- edema	8	26	34
Papulovesicular eruptions	7	2	9
Erythematous eruptions	5	3	8
Serum sickness syndrome	1	8	9
Other rashes	5	3	8
Others	1	1	2
Totals	27	43	70

observations are in agreement with those of many others that the lack of an atopic background is no assurance whatever that a patient will not have an allergic reaction to penicillin.

Table VI shows that there were no significant differences between the reactors and nonreactors in respect to duration of penicillin treatment or dosage. It should be emphasized, however, that almost all patients in this study received relatively small amounts of penicillin, and therefore, in certain

TABLE V. ANALYSIS OF FACTORS PREDISPOSING TO REACTIONS FOLLOWING PENICILLIN INJECTIONS

	REACTORS	NONREACTORS
Total courses of penicillin	64	1797
Sex:		
Male	55%	62%
Female	45%	38%
Age:		
Median	20 years	20 years
Average	21.9 years	21.3 years
Over 30 years	10.9%	5.4%
Under 19 years	20.3%	19.3%
History of other drug allergies	7.8%	7.7%
History of cutaneous fungus infection	56%	63%
History of allergy:		
Allergic rhinitis	29.5%	22.2%
Asthma	9.5%	7.7%
Urticaria	17.5%	15.1%
History of familial allergy:		
Allergic rhinitis	33.3%	25.8%
Asthma	12.7%	18.7%
Urticaria	11.1%	14.6%

respects, these data may not be applicable to other groups⁴ receiving much larger quantities of the drug (for example, patients with subacute bacterial endocarditis). Although the average length of time since the last course of penicillin was very similar in the reactor and nonreactor groups as a whole, further analysis of the data shows that those persons who experienced delayed penicillin reactions significantly more often had not received penicillin within one year than either "immediate" reactors or nonreactors. It was rather surprising to find that, in this series of cases, the penicillin reactors had not received any more courses of penicillin therapy in the past than nonreactors. Previous use of penicillin ointment was noted more than twice as often in the reactor as in the nonreactor groups, although the number of cases involved

TABLE VI

	REACTORS		NONREACTORS
Average duration of therapy	2.88 days		2.77 days
Injections per day:			
One	92.2%		92.9%
Two or more	7.8%		7.2%
Time since last penicillin therapy:			
Average	14.0 months		14.3 months
	"Immediate"	Delayed	
Less than 1 year	67%	33%	56%
Over 1 year	33%	67%	44%
Number of previous courses of penicillin:			
None	29%		21%
One or two	45%		40%
Three or more	25%		39%
Route of previous penicillin:			
Injection	84%		93%
Tablet	20%		23%
Troche	22%		21%
Ointment	13%		6%
Other	4%		3%
Local reactions:			
None	50%		73%
Moderate or severe	22%		6%

was too small to make this difference statistically significant. Last, a significantly greater percentage of the penicillin reactors complained of moderate or severe local reactions at the injection sites than did those without general reactions.

TABLE VII. COMPARATIVE SEVERITY AND DURATION OF "IMMEDIATE" AND DELAYED REACTIONS

		"SEVERE"		LESS SEVERE
"Immediate" reactions	(25)	12%		88%
Delayed reactions	(36)	53%		47%
		<i>1 or 2 Days'</i>	<i>3 to 7 Days'</i>	<i>Over 7 Days'</i>
		<i>Duration</i>	<i>Duration</i>	<i>Duration</i>
"Immediate" reactions	(25)	40%	40%	20%
Delayed reactions	(35)	17%	46%	37%

Table VII shows that delayed reactions are likely to be more severe than "immediate" reactions by a statistically significant difference. An important exception to this generalization is the rare anaphylactic type reaction which is likely to come on within seconds or minutes after the injection of penicillin. Fortunately, no such reactions were encountered in this series of cases. The delayed reactions also tended to be more prolonged, although the observed differences here were not significant and were influenced by other therapy.

CONCLUSIONS

1. Experimental conditions have been defined for evaluating procedures influencing the incidence of penicillin reactions.

2. A controlled study failed to show that an oral and/or parenterally administered antihistamine produced any significant effect on the incidence of

delayed or severe penicillin reactions, although there was a reduction of early reactions, particularly those of an urticarial type. These findings are in accordance with the known pharmacologic properties of the antihistamines.

3. Penicillin reactors had a significantly higher incidence of moderate or severe local reactions than nonreactors. Delayed reactions were severe more often than early ones and occurred relatively less often in patients who had received penicillin within one year. Numerous other attempted correlations failed to be statistically significant.

The authors wish gratefully to acknowledge the splendid cooperation of the University Health Service staff in carrying out this study. We are particularly indebted to Mrs. Helen B. Walker and Mrs. Pauline M. White for much technical and clerical assistance. The authors also wish to acknowledge the skillful assistance of Mr. John J. Freysinger, M.P.H., for much valuable aid in tabulating our data.

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