

PENICILLIN REACTIONS IN CHILDREN

A STUDY OF THE VALUE OF THE SKIN TEST IN PENICILLIN SENSITIZATION

ABE MATHESON, M.D.,* AND LAWRENCE ELEGANT, M.D.,** CHICAGO, ILL.

WITH continued widespread use of penicillin, the problem of sensitization to it, with resulting symptoms, has become a distinct possibility. Since Waldbott's¹ report, in 1949, of death in an adult following an intramuscular injection of penicillin, there have been additional reports of such deaths by Mayer and associates,² Siegal and associates,³ Christenson and co-workers,⁴ Feinberg and his associates,⁵ and others. These authors also presented cases of anaphylactic-like reactions to penicillin, with recovery. We have been able to find only one recorded death in a child following penicillin injection,⁶ although we have knowledge of two such unrecorded deaths. It is interesting to note that, in the majority of instances recorded in the literature, of penicillin anaphylaxis in adults, the immediate skin reaction with penicillin has been positive. On the other hand, the skin test usually has been negative in the delayed or serum sickness type of reaction following penicillin administration.

Levin and Moss⁷ state that sensitization to penicillin in children is uncommon. These authors did not observe definite local or constitutional reactions in 226 allergic children who had received such injections on more than one occasion. Only one child in their series had a transient pruritic eruption. Collins-Williams and Vincent,⁸ from a study conducted in a hospital where thousands of children had received penicillin injections frequently, found only three children who were clinically sensitive to this antibiotic. Only one of these three children was skin tested with penicillin, and the result was negative. These same authors, however, in a study of children from their private practice, report that 6 per cent of allergic children gave histories of having had symptoms suggestive of penicillin sensitization as contrasted to 0 per cent of nonallergic children. They concluded, from their studies of cases in the hospital as well as from those in private practice, that the skin test had very limited value in determining clinical sensitivity to penicillin in children.

The primary purpose of our study was to evaluate the immediate reaction to the skin test with penicillin, in determining the presence of clinical sensitivity to it. To our knowledge, there is no reliable immunologic test at present to predetermine such sensitivity.

MATERIALS AND METHODS

Four hundred patients, including 397 children (between the ages of 1 year and 14 years) and three adult members of the hospital staff, were skin

From the Department of Pediatrics, Sarah Morris Hospital for Children of the Michael Reese Hospital and the Mandel Clinic, Michael Reese Hospital, Chicago, Illinois.

Read before the American Academy of Pediatrics (Allergy Section), Oct. 8, 1954.

Received for publication Dec. 2, 1954.

*Attending pediatrician, Michael Reese Hospital.

**Chief resident in pediatrics, Michael Reese Hospital.

children had acute infections and the penicillin given was only one of several antibiotics or drugs given at about the same time. There were nineteen positive skin tests to *Penicillium notatum* in the 341 children tested with this mold. There were 106 children, in our series studied, who had histories of manifestations of major allergy, including bronchial asthma and allergic rhinitis. The single positive skin test to penicillin occurred in one of the children in this group. We were not able to demonstrate any positive skin tests to procaine.

TABLE IA. SKIN TESTS FOR PENICILLIN SENSITIVITY IN CHILDREN

	TOTAL NO. OF CHILDREN TESTED	PREVIOUS PENICILLIN CONTACT	NO. WITH POSITIVE SCRATCH TESTS TO PENICILLIN	NO. WITH POSITIVE INTRACU- TANEOUS TESTS† TO PENICILLIN	TOTAL POSITIVE SKIN REAC- TIONS TO PENICILLIN	POSITIVE SKIN TESTS TO PROCAINE	POSITIVE SKIN TESTS TO PENICIL- LIUM NOTATUM
<i>Hospitalized Children*</i>							
Nonallergic group	235	215	0	0	0	0	9
Allergic group	6	4	0	0	0	0	2
Total	241	219	0	0	0	0	11
<i>Outpatient Children</i>							
Nonallergic group	50	48	0	0	0	0	Not done
Allergic group	100‡	86	0	1	1	0	8
Total	150	134	0	1	1	0	8
Grand total	391	353	0	1	1	0	19
Percentage of total		90 per cent			0.25 per cent		5.4 per cent

*Hospitalized for medical or surgical conditions.

†Includes presence of bronchial asthma, allergic rhinitis, and eczema (atopic).

‡Sixty cases from Pediatric Allergy Clinic, Michael Reese Hospital, and forty children from the private practice of Dr. Matheson.

TABLE IB. SKIN TESTS FOR PENICILLIN SENSITIVITY IN A SELECTED GROUP OF CHILDREN HOSPITALIZED BECAUSE OF ACUTE SYSTEMIC REACTIONS FOLLOWING PENICILLIN ADMINISTRATION

TOTAL NO. OF CHIL- DREN TESTED	PREVIOUS PENICILLIN CONTACT	NO. WITH POSITIVE SCRATCH TESTS TO PENICILLIN	NO. WITH POSITIVE IN- TRACUTANE- OUS TESTS* TO PENICIL- LIN	TOTAL POSITIVE SKIN REAC- TIONS TO PENICILLIN	POSITIVE SKIN TESTS TO PROCAINE	POSITIVE SKIN TESTS TO PENICIL- LIUM NOTATUM	POSITIVE ALLERGY HISTORY
6	6	3	2	5	0	0	4

*Intracutaneous tests done only where scratch tests were negative.

For details of cases, see Table II.

Analysis of Table II.—The table includes seven children. Six of the seven children presented were admitted to Sarah Morris Hospital as emergency cases because of severe constitutional reactions following intramuscular

TABLE II. ANALYSIS OF SYSTEMIC REACTIONS TO PENICILLIN AND SKIN REACTIONS TO PENICILLIN IN SAME

PATIENT	TYPE OF PENICILLIN AND MODE OF ADMINISTRATION	PREVIOUS PENICILLIN ADMINISTRATION AND HISTORY OF PREVIOUS REACTIONS	CLINICAL REACTIONS ON ADMISSION TO HOSPITAL	SKIN TESTS						PASSIVE TRANSFER PENICILLIN	ALLERGY HISTORY
				SCRATCH		INTRACUTANEOUS		PENICILLIN	PROCAINE		
				PENICILLIN	PROCAINE	PENICILLIN	PROCAINE				
1. M. A., 13-year-old girl	Crystalline procaine penicillin, 300,000 U., intramuscularly	Multiple; always intramuscularly. 1 week before had peculiar sensation in mouth following intramuscular injection of crystalline penicillin, also feeling of generalized itching and burning at same time	10 minutes following intragluteal injection of procaine penicillin began to experience pruritus, sweating, tightening in chest, and wheeze followed by generalized urticaria and edema of face	0	0	0	0	0	0	None done	Asthma, eczema, skin sensitivity to molds, house dust, etc.
2. T. G., 14-year-old girl	Crystalline procaine penicillin, 300,000 U., intramuscularly	Multiple intramuscular, also orally many times; no history of previous reactions obtained	About 10 days following intramuscular injection of procaine penicillin, patient developed marked laryngeal edema with stridor and generalized urticaria, lasted 1 week	+++	0	Not done	0	0	0	0	None known
3. S. R., 23-month-old boy	Crystalline procaine penicillin, 300,000 U., intramuscularly	Had one previous intramuscular injection of penicillin known to us; no history of previous penicillin reactions known	15 minutes following intramuscular injection of procaine penicillin, patient had generalized urticaria, swelling of face, laryngeal edema, and stridor, which lasted 3 days	0	0	++ (50 U.)	0	0	0	None done	Skin rash from orange juice, urticaria from aspirin
4. R. K., 15-month-old boy	Procaine penicillin with aluminum monostearate and peanut oil—recently	Penicillin injections intramuscularly (oral ?); no history of previous reactions obtained	3 days following intramuscular penicillin injection, patient developed severe generalized urticaria of entire body and face and hoarse cry	+++	0	-	0	0	0	++	None known

5. S. M. R., 9-year-old girl	Crystalline pro- caine penicillin, 300,000 U., in- tramuscularly	Two previous injec- tions of procaine penicillin intramus- cularly; also 8 to 10 oral doses of peni- cillin; no history of previous reactions obtained	About 10 days following intramuscular injection of procaine penicillin, child developed marked edema of face and ex- tremities; also had urticaria of face and body; lasted one week	0	0	0	+++	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0</
------------------------------------	---	---	---	---	---	---	-----	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	-----

TABLE III. ANALYSIS OF SYSTEMIC REACTIONS TO PENICILLIN IN THREE ADULTS

PATIENT	TYPE OF PENICILLIN AND MODE OF ADMINISTRATION	PREVIOUS PENICILLIN ADMINISTRATION AND HISTORY OF PREVIOUS REACTIONS	SKIN TESTS							PASSIVE TRANSFER PENICILLIN	ALLERGY HISTORY	
			SCRATCH		INTRACUTANEOUS			PENICILLIN	PROCAINE			PAIN
			PENICILLIN	PROCAINE	PENICILLIN	PROCAINE						
1. S. H., 26-year-old female nurse's aid	Crystalline procaine penicillin, 300,000 U., intramuscularly	Multiple injections of crystalline penicillin and procaine penicillin in peanut oil, with aluminum monostearate; history of generalized pruritus and urticaria 10 days following the last injection of procaine penicillin	+++	0	-	-	-	0	0	++	None known	
2. R. K., 47-year-old male physician	Crystalline procaine penicillin, 300,000 U., intramuscularly	Multiple injections of procaine penicillin; also oral penicillin on several occasions; 3 days after intramuscular injection of procaine penicillin in deltoid area, patient developed pruritus, burning, and edema of hands and feet, accompanied by chills and fever to 101° F.; lasted 3 days	+++	0	-	-	-	0	0	0	Perennial allergic rhinitis, skin sensitivity to alternaria, etc.	
3. C. H., 33-year-old male physician	Procaine penicillin in sesame oil 300,000 U., intramuscularly	Multiple courses of oral and inhaled penicillin; 5 days after injection of procaine penicillin, patient developed pruritus, generalized burning and urticaria which was progressive and involved especially the extremities; lasted 12 days	++	0	-	0	0	0	0	++	None known	

injections of penicillin by private physicians at the patients' homes. All patients except one (Case 7) had either immediate (Cases 1, 3, and 6), accelerated (Case 4), or delayed (Cases 2 and 5) systemic reactions following such penicillin contact. It is questionable whether Case 2 can fit into the delayed or serum sickness type of reaction *at the time of our testing* or, rather, into the anaphylactic type, since this child evidenced an immediate, constitutional reaction from the scratch test with aqueous penicillin G. It rather suggests a transition stage from the last delayed to the present immediate type of reaction.

Four of the patients who had clinical as well as skin sensitivity to penicillin were distinctly allergic children and three of the four gave histories of having bronchial asthma or allergic rhinitis. It is noteworthy that in all cases, except Case 7, the skin test to *Penicillium notatum* was negative. The occurrence of a positive skin test to aqueous penicillin G in Case 7, who gave a history of no penicillin contact in any form, is difficult to explain. This child has bronchial asthma, is skin-sensitive to house dust, alternaria, *Penicillium*, and many foods. She is being hyposensitized in the Pediatric Allergy Clinic to house dust and alternaria.

These patients who presented systemic reactions responded readily to treatment with Adrenalin and cortisone, with or without antihistamines. In a few instances, the urticaria persisted for ten to twelve days.

The three cases in Table III represent adults on our children's hospital staff. They are not included in the statistical analysis of the child groups, but are presented for the interesting data revealed in our study of their skin reactivity to penicillin. These adults were well aware of their clinical sensitivity to penicillin because of past reactions from contact with this antibiotic.

DISCUSSION

Though reports in the literature on anaphylactic reactions following penicillin administration to children are scarce, such reactions do occur and, in our experience, are not uncommon. Such reactions may be so sudden in onset and so severe in character that the physician who witnesses them, in all probability, will reduce appreciably his indications for penicillin administration. It is well to remember that even the delayed or serum sickness type of reaction can be very severe in character, particularly in children, in whom there is a marked tendency for the occurrence of laryngeal or subglottic edema as a part of such a reaction. Accidental intravenous entrance of penicillin should be considered as a possible cause for such immediate reactions in some instances and may have occurred in Case 1 (Table II) when the child experienced a bitter taste in the mouth following the penicillin injection. Experiments with rabbits by Kagan and associates⁹ demonstrated that two of three rabbits who received 1 ml. aqueous procaine penicillin intravenously, died rapidly.* Autopsies on two rabbits who died two minutes after intravenous

*Autopsy reports not available, personal communication with author.

injection of 1 ml. procaine penicillin in sesame oil demonstrated fat embolism in the lungs and kidneys, pulmonary edema, and hyperemia of the liver. On the other hand, similar clinical symptoms do appear when penicillin is administered by other routes. Thus, Leibowitz and Schwartz¹⁰ report anaphylactic reactions from penicillin aerosol therapy and Everett¹¹ reports similar untoward symptoms of immediate character following instillation of penicillin into the nasal sinuses.

The types of reactions that may result from penicillin administration are too numerous to be discussed in this article, as almost any organ or organ system can be involved in such a reaction. In a general way, however, the pattern of such reactions closely simulates that following administration of heterologous serum. Thus, the symptoms may be immediate, accelerated, or delayed, the latter being a serum sickness type of reaction. Many other types of penicillin reactions may occur which, in the main, are not allergic reactions and include the Schwartzman phenomenon. The mechanism involved in the Herxheimer-like reactions, as well as the so-called ninth day erythema reactions following penicillin administration, is complicated. Possibly, some such reactions may be explained on the basis of sensitization to the antibiotic involved. In other instances, such an explanation is inadequate and the mechanism involved remains obscure.

There are certain immunologic, as well as clinical, differences between serum sickness type reactions resulting from administration of penicillin and those following heterologous serum administration. Thus, most attempts to demonstrate antibodies in the serum of patients having such reactions from penicillin have been unsuccessful, whereas such tests are frequently positive in cases of reactions following heterologous serum injections.¹² The clinical differences referred to are still more striking. When a child has had a serum sickness type of reaction from penicillin, a reinjection of this antibiotic frequently results in (1) no clinical reaction whatsoever or (2) a similar or another type of serum sickness-like reaction with the same incubation period. However, when heterologous serum is reinjected in a child, the resulting reaction is frequently of the accelerated or immediate type.

Such differences are hard to explain. Does penicillin act as a complete antigen or as a hapten? Do the ecologic or biotrophic mechanisms suggested by Rostenberg and Webster¹³ play a part? The answer to these questions is not clear at present.

The low incidence of penicillin anaphylaxis in children, as judged by statistical reports, is not a true measure of its frequency. It is fair to assume that one may expect a greater incidence of sensitization with continued wide use of penicillin and penicillin combinations with other drugs.

Experience has taught that history of previous symptoms resulting from penicillin contact, especially by injection, is a highly significant warning sign as to possible presence of penicillin allergy. This is especially true when such clinical reactions, even if mild, are of the immediate or accelerated variety. Had attention been given to the histories obtained on the patients in Table II,

the constitutional reactions in these children might have been avoided. On the other hand, on many occasions the histories obtained from parents are unreliable. Similarly, the symptoms following penicillin contact may be vague and not very impressive to the parent or physician. One of the authors (A. M.) has been particularly impressed with the seriousness of penicillin reactions. As a result, he has established as a routine office procedure the skin testing and periodic retesting of children, particularly children with respiratory allergy, who had previously had penicillin contact. Such a method for detecting penicillin sensitization, although uniformly negative in children who have delayed or serum sickness type of reactions, will be truly rewarding in the occasional case where potential penicillin anaphylaxis exists. In such serious immediate reactions, the skin test with penicillin is usually positive. Waldbott's¹ suggestion, of injecting subcutaneously a few drops of the penicillin to be given and waiting about a minute for possible resulting symptoms before injecting the remaining dose, is not practical in children. Furthermore, the time interval suggested for waiting is too short, as in all instances that we experienced the reactions occurred ten to twenty minutes following such injections of penicillin.

SUMMARY AND CONCLUSION

Our study of penicillin reactions in children and the use of the skin test in evaluating clinical sensitivity to this antibiotic has demonstrated the following:

1. Three hundred and ninety of a group of 391 children who had received penicillin injections on many occasions did not demonstrate skin sensitivity to same. Approximately 4 per cent of this group of children gave histories of vague symptoms only suggestive of serum sickness type of reaction following penicillin injections.

2. When another group of six children who had experienced severe constitutional reactions following administration of penicillin was similarly tested, the following results were obtained. Four of the five children who had immediate or accelerated reactions and one child who had severe, delayed, constitutional symptoms had immediate positive skin tests to penicillin. In two of three such cases, when passive transfer skin tests were performed, the tests were positive and indicated the presence in the blood of reagins to penicillin.

3. Although most of the constitutional reactions to penicillin administered occurred in those who had manifestations of atopic allergy, similar reactions occurred in nonallergic children.

4. With one exception, we were unable to find any correlation between dermal sensitivity to penicillin and that to *Penicillium notatum*.

5. An extremely high degree of clinical sensitivity to penicillin may exist in some children who have had penicillin injections previously. In one child we observed constitutional symptoms following a scratch test with penicillin of average concentration (1 drop of 5,000 units of penicillin per milliliter).

6. A negative skin test with penicillin does not rule out a potential anaphylactic-like reaction resulting from a subsequent injection of penicillin (see Case 1, Table II).

7. Anaphylactic-like reactions from penicillin administration may occur in children who have previously had no reaction from administration of this antibiotic (see Cases 2 and 3, Table II).

8. There was no dermal sensitization to procaine in the entire series of cases tested.

It is our opinion that an immediate positive skin test with penicillin in children who have had penicillin contact indicates the presence of potential clinical sensitization. When such a child, in addition, presents a history of symptoms resulting from previous penicillin administration, further injection of penicillin will likely result in a constitutional reaction. In such cases, if penicillin is the sole effective antibiotic, its oral use should be tried.

REFERENCES

1. Waldbott, George L.: Death From Penicillin, *J. A. M. A.* **139**: 526-527, 1949.
2. Mayer, Peter S., Mosko, M. M., and Schutz, P. J.: Penicillin Anaphylaxis, *J. A. M. A.* **151**: 351-353, 1953.
3. Siegal, S., Steinhardt, R. W., and Gerber, K.: Fatal and Near Fatal Penicillin Anaphylaxis, *J. ALLERGY* **24**: 1-10, 1953.
4. Christenson, W. N., Hedrich, G. W., and Schugman, R. F.: Fatal Anaphylactic Reaction Following Penicillin Injection, *U. S. Armed Forces M. J.* **4**: 249-252, 1953.
5. Feinberg, S., Feinberg, A., and Moon, C.: Penicillin Anaphylaxis, Non-Fatal and Fatal Reactions, *J. A. M. A.* **152**: 114-119, 1953.
6. Harpman, J. A.: Death From Penicillin, *Brit. M. J. Correspondence*, 392, Aug. 16, 1952.
7. Levin, S., and Moss, S. S.: Repository Penicillin Injection in Allergic Children, *Ann. Allergy* **9**: 471-476, 1951.
8. Collins-Williams, C., and Vincent, J.: Sensitivity Reactions to Penicillin in Children, *Ann. Allergy* **11**: 454-469, 1953.
9. Kagan, B. M., Nieremberg, M., Goldberg, D., and Milzer, A.: Studies of Penicillin in Pediatrics, *Pediatrics* **5**: 664-671, 1950.
10. Leibowitz, A., and Schwartz, E.: An unusual Reaction to Penicillin, *Ann. Allergy* **8**: 668, 1950.
11. Everett, R.: Anaphylactic Reaction From Local Use of Penicillin, *J. A. M. A.* **146**: 13-14, 1951.
12. Sherman, W. B.: Allergic Reactions to Penicillin; Panel Discussion, *J. ALLERGY* **24**: 396, 1953.
13. Rostenberg, A., Jr., and Webster, J.: Mechanisms of Cutaneous Drug Reactions, Especially to Antibiotics, *J. A. M. A.* **154**: 3-224-228, 1954.
14. Siegal, S., Steinhardt, R. W., and Gerber, K.: Fatal and Near Fatal Penicillin Anaphylaxis, *J. ALLERGY* **24**: 1-10, 1953.