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THE CLINICAL DIAGNOSIS OF PENICILLIN ALLERGY

By

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INTRODUCTION

Penicillin has been used in the treatment of infectious diseases in man for more than 25 years, during which its most important complications have been the *allergic reactions*. Among the population of the Western world 1.8-5.2 per cent are reported to have a history of penicillin allergy (58). In the event of infectious diseases such persons often pose problems in the clinical diagnosis of penicillin allergy.

Various diagnostic procedures, cutaneous tests, and serological studies have been recommended in the event of a suspicion of penicillin allergy, but have not always proved reliable. Moreover, cutaneous tests using penicillin derivatives may elicit anaphylactic = systemic reactions in persons with high sensitivity; even a fatal outcome of intracutaneous tests with penicillin has been reported (10).

Penicillin allergy is not a disease entity, but a number of motley symptoms and signs elicited by various immune reactions to different chemical determinants. This presumably excludes the possibility of making the clinical diagnosis of penicillin allergy by a single test.

A history of penicillin allergy usually prohibits future penicillin therapy. To observe this precaution and to refrain from unnecessary administration of penicillin are the possibilities

TABLE
Immediate-type Cutaneous Reaction to Penicillin in Patients

Author		Year	Method	
Kolodny & Denhoff	(35)	1946	intracut.	10^4 units/m ²
Hopkins & Lawrence	(32)	1947	intracut.	10^4 units/ml
Farmer	(22)	1953	intracut.	10^3 units/ml
Nilzén	(52)	1956	scratch	5×10^4 units/m ²
Johnson & Cazort	(34)	1959	scratch	10^4 units/ml
				2×10^5 units/m ²
Fernström	(24)	1962	intracut.	10^4 units/ml
van Arsdel et al.	(1)	1963	intracut.	10^4 units/m ²
Schwartz & Vaughan	(73)	1963	scratch + intracut.	10^3 – 10^4 units/ml
Budd et al.	(14)	1964	intracut.	10^3 – 10^4 units/m ²
Levine & Price	(39)	1964	intracut.	10^4 units/ml
Cazort	(17)	1965	scratch	10^4 units/m ²
Finke et al.	(25)	1965	intracut.	10^2 – 10^4 units/m ²
de Weck & Blum	(85)	1965	intracut.	10^3 units/m ²
Smith et al.	(76)	1966	intracut.	10^4 units/m ²
Redmond & Levine	(64)	1967	intracut.	5.9×10^3 units/m ²
Nilzén	(53)	1968	intracut.	10 – 10^4 units/m ²
Rosenblum	(68)	1968	scratch	10^4 units/m ²
Bierman & van Arsdel	(7)	1969	scratch + intracut.	10^3 units/m ²

Blank = investigation not performed.

we have in clinical practice of reducing the incidence of allergic reactions to penicillin.

Symptoms and signs arising during penicillin therapy, but without any immunological relationship to the treatment, may be erroneously interpreted as penicillin allergy. Furthermore, penicillin allergy may often subside in time, provided that the patient avoids further exposure to the antigen. Therefore, an

¹
with and without a History Suggesting Penicillin Allergy.

No. of pts. with a history suggesting penicillin allergy	Percentage with pos. cutaneous test	No. of pts. without a history suggesting penicillin allergy	Percentage with pos. cutaneous test	Comments
15	73	14 98	14 41	
27	37	100	0	
27	22			
14 (i)	100	> 7,000	< 0.1	(i) anaphyl. react. in all cases
115 (ii)	7	90	2.2	(ii) urticaria in all cases
27	19			
35	48	10	10	
49	6	40	0	
41	7	30	0	
29 (iii)	97	ab. 20,000	< 0.1	(iii) anaphyl. react. in all cases
120	15	156	1.3 (iv)	(iv) tolerated penicillin therapy
90	24			
97	1			
40	18			
32	53			
13 (v)	69			(v) severe cases, 3 with anaphyl. react.
160	6			

allergic reaction is far from always elicited by penicillin therapy in patients reporting a history of penicillin allergy. Parenteral treatment with penicillin o has been reported in 14 alleged penicillin allergies (82), with a penicillin-antihistamine preparation in 15 alleged penicillin allergies (27), and with benzathine penicillin in 12 alleged penicillin allergies (78) without causing an allergic reaction.

In other studies penicillin therapy has elicited allergic reactions in 2 per cent (60), 8 per cent (43), and 39 per cent (30) of people with a history of penicillin allergy. In one of these studies (43), however, 10 per cent of a total of 218 alleged penicillin allergies were not treated with penicillin because of strong evidence of manifest penicillin allergy, viz. a positive cutaneous reaction to penicillin compounds. In another of these studies (30) the strikingly high incidence of allergic reactions could be due to intensive and long-lasting penicillin therapy in 56 out of 71 patients with subacute bacterial endocarditis and a history suggesting penicillin allergy.

If allergic reaction occurs during penicillin therapy of patients with a history of penicillin allergy the symptoms and signs will usually be of the same nature as previously. However, patients who have had urticaria or exanthema may react to repeated therapy by alarming manifestations, e.g. anaphylactic reactions (15, 18, 23, 31, 80, 87). This risk is confirmed by the fact that in about 30 per cent of fatal allergic reactions to penicillin there has been a history of penicillin allergy, often of a clinically benign nature (2, 5, 9, 69).

Cutaneous tests with penicillin, read for immediate-type reaction at the end of 10–20 minutes, have been performed on alleged penicillin allergies, as well as on persons with no history of penicillin allergy (Table 1). In the early studies, a positive reaction was found in 14 per cent (35) and in 41 per cent (32) in those tested without a history of penicillin allergy. These results should presumably be ascribed to impure penicillin preparations.

Investigations since 1953 have shown a positive cutaneous reaction to penicillin in 1–100 per cent of presumed penicillin allergies and in 0.1–2.2 per cent of persons without a history of penicillin allergy except for a single study (73) which included only 10 patients.

The varying frequency of a positive cutaneous reaction to penicillin in presumed penicillin allergies is due, int. al., to the fact that the groups studied have included patients with

different clinical types of reaction. A high incidence (70–100 per cent) of positive cutaneous reactions to penicillin occurs in patients with anaphylactic reactions, a low incidence (< 10 per cent) in clinically mild reactions, such as exanthema.

The incidence of a positive cutaneous reaction of the immediate type in persons without a recognized history of penicillin allergy is low—in the two largest materials less than 0.1 per cent. In exceptional cases penicillin therapy is tolerated by such patients (25), but as a rule there will be manifest penicillin allergy, involving a considerable risk of systemic reaction in the event of penicillin therapy.

Cutaneous tests with penicillin in highly sensitized penicillin allergies have several times elicited serious allergic reactions, including anaphylactic shock. Indeed, this is confirmed by the literature (Table 2). Some patients exhibit a reaction on far less than 1 unit (6, 19), and a fatal result to an intracutaneous test with penicillin has been reported (10). Positive immediate-type cutaneous reactions with whealing a few minutes after applying a patch test with penicillin (16, 81) as well as severe allergic reactions to epicutaneous testing (8, 79) also imply that some penicillin allergies have an extremely high sensitivity to penicillin.

Cutaneous tests with penicilloyl-polylysine read for immediate type reaction at the end of 10–20 minutes were originally considered an alternative to the risky and often negative cutaneous testing with penicillin in the event of a suspicion of penicillin allergy. Especially in cases of clinically mild reactions, a higher incidence of positive cutaneous tests was found with penicilloyl-polylysine than with penicillin.

However, it has later been demonstrated by several authors that in penicillin allergy there may be a positive cutaneous reaction to penicillin and a negative cutaneous reaction to penicilloyl-polylysine (1, 61, 83), especially in patients with anaphylactic reactions. Therefore, penicilloyl compounds may supplement, but not replace penicillin in cutaneous tests on patients with alleged penicillin allergy.

A positive cutaneous reaction to penicilloyl-polylysine oc-

TABLE 2
Allergic Reaction in Penicillin Allergics on Cutaneous Testing with Penicillin.

Author	Year	Method of testing	Test material	Type of reaction elicited by cutaneous testing
van Studdiford	(79) 1947	p.t.	Penicillin	Glottic oedema
Leibowitz & Schwartz	(36) 1950	i.c.t.	Penicillin 10^3 units/ml	Anaphyl. react. + asthma
Blanton & Blanton	(8) 1953	p.t.	Penicillin O 10^3 units	Dyspnoea + rhinitis
Borger et al.	(10) 1953	i.c.t.	No further inform	Death
Icasiano	(33) 1953	i.c.t.	Penicillin G 2×10^3 units/ml	Flushing + angioneur. oedema
Mayer et al.	(48) 1953	i.c.t.	Penicillin G 10^3 units/ml	Anaphyl. react.
Madalin	(46) 1954	i.c.t.	Penicillin G 50 units	Anaphyl. react.
Berger & Eisen	(3) 1955	i.c.t.	Procaine penicillin 20 units	Anaphyl. react.
Peters et al.	(62) 1955	s.t.	Penicillin G 5×10^3 units/ml	Anaphyl. react.
Bierlein	(6) 1956	i.c.t.	Procaine penicillin 3×10^6 units	Anaphyl. react.
Coleman & Swineford	(19) 1956	s.t. + i.c.t.	Penicillin G 5×10^2 units	Anaphyl. react.
			Penicillin G 5×10^6 units	Anaphyl. react.
			Penicillin G 25 units	Anaphyl. react.
Linde	(44) 1956	i.c.t.	Procaine penicillin 3×10^5 units/ml	Anaphyl. react. + asthma
McCuiston	(49) 1957	c.t.	Procaine penicillin 3×10^5 units/ml	Anaphyl. react.
Smith	(77) 1957	s.t. + c.t.	Penicillin G 5×10^4 units/ml	Anaphyl. react.
Siegel	(74) 1959	i.c.t.	Penicillin G 10^4 units/ml	Asthma
Gaultier et al.	(28) 1962	s.t.		

s.t. = scratch test i.c.t. = intracutaneous test c.t. = conjunctival test p.t. = patch test

curs in 9-77 per cent of persons with and in 3-11 per cent of those without a history of penicillin allergy (Table 3). As a rule, patients in whom a positive cutaneous reaction to penicilloyl-polylysine is demonstrated by chance, tolerate penicillin therapy, during which only 5-12 per cent develop a clinical allergic reaction (12, 71, 75).

The dose of penicillin and the contamination of the penicillin with penicilloyl compounds presumably influence the frequency with which a clinical allergic reaction is elicited during penicillin therapy of persons showing a positive cutaneous reaction to the penicilloyl radical (58).

In cutaneous tests using penicilloyl compounds, complicating allergic reactions will be less common than in tests using penicillin. However, several reactions to penicilloyl-polylysine have been observed (12, 21, 54), including anaphylactic reactions (45, 66). As in cutaneous tests using penicillin it is not possible to state the complication rate, as the technique used in the cutaneous tests and the clinical assessment of possible allergic manifestations vary widely from one study to another.

However, cutaneous tests, with penicillin as well as with penicilloyl-polylysine in the event of a suspicion of penicillin allergy are probably not sufficient. Recent studies have shown that penicillin allergies may exhibit independent specificity to penicilloate (42, 56, 57, 64), often co-existing with specificity for penicillin or the penicilloyl radical. In a few cases, moreover, specificity for penicilloate and penicilloyl-amine has been reported (42). However, clinical results of cutaneous tests using all these antigens in penicillin allergies have not been used to an extent which permits a final evaluation.

Cutaneous tests using penicillin read for delayed-type reaction at 24-96 hours have been used, especially previously, on a suspicion of penicillin allergy of various clinical types, not only the eczematous one. Studies have been performed by the patch test technique or in the form of scratch and intracutaneous tests.

As early as 1944 reports appeared on penicillin-elicited eczema with a positive patch test (63) and on patients with

TABLE 4
Immediate-type Cutaneous Reaction to Penicilloyl-Polylysine

Author		Year	Method	No. of pts with a history suggesting penicillin allergy
Levine & Ovary	(38)	1961	Penicilloyl-gamma-globulin	6
Parker et al.	(54)	1962	i.c. PPL	59
Simpson	(75)	1962	i.c. PPL	330
de Weck	(84)	1962	i.c. PPL	77
van Arsdel et al.	(1)	1963	i.c. PPL 10^{-5} M	43
Rytel et al.	(71)	1963	i.c. PPL 5.3×10^{-5} M	43
Brown et al.	(12)	1964	i.c. PPL 6×10^{-5} M	1.003
Budd et al.	(14)	1964	i.c. PPL 1.25×10^{-4} M	49
Levine & Price	(39)	1964	i.c. PPL 1×10^{-6} M	41
Finke et al.	(25)	1965	i.c. PPL 6×10^{-5} M	120
Levine & Fellner	(40)	1965	i.c. PPL 1×10^{-6} M	24
de Weck & Blum	(85)*	1965	i.c. PPL 2.5×10^{-1} M	329
Smith et al.	(76)	1966	i.c. PPL 5×10^{-4} M	97
Nilzén et al.	(53)	1968	i.c. PPL 3.4×10^{-4} M	32
Bierman & van Arsdel	(7)	1969	i.c. PPL 5×10^{-6} M	160
Levine & Zolov	(43)	1969	i.c. PPL 1×10^{-6} M	185

Blank = investigation not performed.

PPL = penicilloyl-polylysine.

* = with supplementary data 1968.

positive delayed-type intracutaneous reaction of the tuberculin type to penicillin (86).

Positive delayed-type cutaneous reactions to penicillin occurs in 29–83 per cent of patients with penicillin-elicited eczema and in 30–100 per cent of penicillin allergies exhibiting urticaria, exanthema, and angioneurotic oedema which are usually considered to be immediate-type reactions (Table 4). In addition, a positive reaction occurs in 6–17 per cent of persons without any history of penicillin allergy (Table 4). There

Patients with and without a History Suggesting Penicillin Allergy.

Percentage with pos. cutaneous test	No. of pts. without a history suggesting penicillin allergy	Percentage with pos. cutaneous test	Comments
50			(i) On penicillin therapy allergic reaction in 39 per cent.
76	1,191	4 (i)	
36	2,837	6 (ii)	(ii) On penicillin therapy allergic reactions in 12 per cent against 0.7 per cent of patients with negative penicilloyl reaction.
77	1,284	4 (iii)	
30			
35	825	7 (iv)	(iii) On penicillin therapy allergic reactions in 40 per cent against 0 per cent of patients with negative penicilloyl reaction.
40	12,559	6 (v)	
55	40	5	
29	30	3	(iv) On penicillin therapy allergic reactions in 5.2 per cent against 0.9 per cent of patients with negative penicilloyl reaction.
37	156	7 (vi)	
33	130	5	
58	228	11	(v) On penicillin therapy allergic reactions in 7.1 per cent against 0.5 per cent of patients with negative penicilloyl reaction.
23			
69			
9			(vi) Tolerated penicillin therapy.
14			(vii) Children.

seems to be a question of a true delayed-type hypersensitivity with specificity for the penicilloyl radical (65).

OBJECT OF PRESENT STUDY

To present the results of a clinical investigation of 116 patients with a relevant history of penicillin allergy, in particular with a view to predicting manifest penicillin allergy on the basis of the history and of cutaneous tests with penicillin and penicilloyl-polylysine.

TABLE
Delayed-type Cutaneous Reactions to Penicillin in Patients

Author		Year	Method
Rostenberg & Welch	(70)	1945	i.c. penicillin 10^1 units/ml
Goldman et al.	(29)	1946	Patch test penicillin G 2×10^4 units/ml
Peck et al.	(55)	1948	i.c. penicillin G 2×10^4 units/ml
Swift	(80)	1954	?
Maffei & Napolitano	(47)	1955	Patch test penicillin G 10^4 units/ml
Mosko et al.	(51)	1955	i.c. penicillin G 10^4 units/ml
Nilzén	(52)	1956	i.c. penicillin G 10^3 units/ml Patch test penicillin G 10^4 units/ml
Fernström	(24)	1962	i.c. penicillin G 10^4 units/ml Patch test penicillin G 10^5 units/ml
Schwartz & Vaughan	(73)	1963	i.c. penicillin G 10^4 units/ml
Redmond & Levine	(65)	1968	i.c. penicillin G 5×10^4 units/ml

Blank = investigation not performed.

To confirm the diagnosis of penicillin allergy by provocation tests using penicillin in order to obtain reliable results.

To look for possible factors that may predispose to the occurrence of penicillin allergy and to elucidate the spontaneous course of penicillin allergy.

MATERIALS AND METHODS

Patients

A total of 118 patients with a history suggesting an allergic reaction to penicillin were investigated for penicillin allergy. The investigations were completed in 116 cases, as 2 patients failed to attend for the final tests. The sex and age distribution of the 116 patients are given in Fig. 1—average age 43 years.

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with and without a History Suggesting Penicillin Allergy.

No. of pts. with penicillin allergy	Type of previous reaction	Percentage with pos. tests	No. of pts. without a history suggesting penicillin allergy	Percentage with pos. tests
			144	6
12	Eczema	83	216	0
25	Urticaria	40	499	7
14	Urticaria + angioneur. oedema	100		
14	Dermatitis,	29	10	10
5	asthma + angioneur. oedema	60		
			119	12
15	Urticaria,	47		
14	dermatitis	43		
115	Urticaria	30		
35	Esp. urticaria + exanthema	34		
24	Urticaria + exanthema	33	159	17

The investigations were performed, as a rule on an outpatient basis, in a sub-specialized division for allergic diseases. Thereby, the material was, though not intentionally, selected—with a preponderance of serious and occupational cases.

19 patients were suspected of allergic reactions due to occupational contact with penicillin.

21 patients were suspected of allergic reactions due to current or recently completed penicillin treatment.

In 24 patients there was an indication for penicillin therapy and a history suggesting penicillin allergy.

In 54 patients there was a history suggesting penicillin allergy and a wish to confirm or disprove the diagnosis.

Apart from suspected penicillin allergies the following patients without a history of penicillin allergy were studied:

NUMBER OF PATIENTS INVESTIGATED

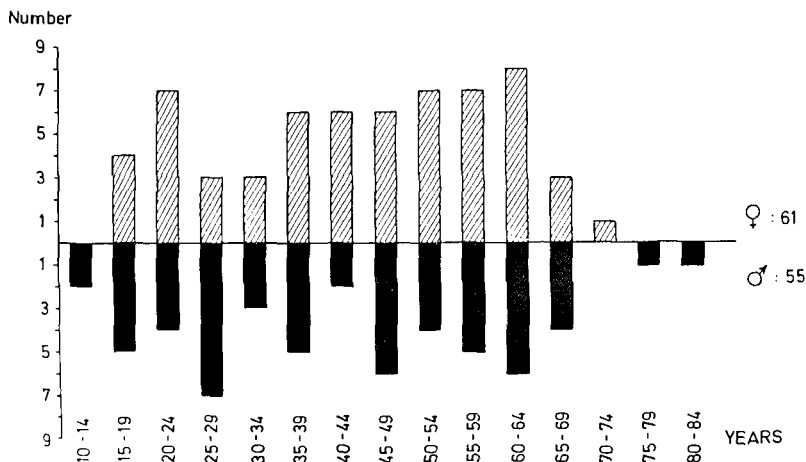


Fig. 1.

Control group A: 120 patients from medical or dermato-venereological out-patients clinics, 52 females and 68 males, average age 40 years.

Control group B: 120 medical and surgical in-patients, 64 females and 56 males, average age 44 years.

Within control group A 14 patients were included particularly because of recently completed penicillin therapy. Control group B did not include patients with severe and generalized diseases in the terminal phase, as such diseases did not occur among the penicillin allergies or in control group A. Apart from these limitations, all patients of control groups A and B were selected at random.

Clinical Studies

In all 116 patients suspected of penicillin allergy a thorough history was taken with a view to:

- (1) Occurrence of allergic diseases in the family. Apart from penicillin allergy, the hereditary allergic diseases: asthma, vasomotor rhinitis, Besnier's prurigo, hay fever and the non hereditary diseases urticaria and angioneurotic oedema had been recorded in the patients' grandparents, parents, parents' siblings, their own siblings and children as reported by Schwartz (72).
 - (2) Personal history of allergic diseases.
 - (3) Number of previous penicillin treatments, local as well as systemic, and occupational contact with penicillin, if any.
 - (4) Allergic symptoms and signs on previous exposure to penicillin.
- After the history had been taken each patient had a clinical examination comprising:

- (5) Intracutaneous tests with benzylpenicillin. The initial dose was 10^{-8} units ($= 6$ pg), followed by 10^{-4} , 10^{-3} , 10^{-2} and up to 10^4 units at 10–20-minute intervals. The tests were applied on the volar aspect of the forearm and read for immediate-type reaction at 10–20 minutes, for delayed-type reaction at 24–96 hours. The patients were closely observed, for any complicating allergic reaction, for at least one hour after the last injection of each day. If a complication occurred, the cutaneous testing was stopped immediately. In the event of a positive cutaneous reaction to penicillin in the weakest dilution, a control test was done with normal saline. If doubtful positive cutaneous reactions appeared, a higher concentration of penicillin was applied. The daily preparation of fresh penicillin solution and dilutions with autoclaved isotonic saline as well as the criteria of positive cutaneous reactions have been described in a previous paper (59).
- (6) Scratch test with benzylpenicillin, phenoxymethyl penicillin and procaine penicillin 10^6 units/ml, but a lower concentration for a few highly sensitized patients. A control test was performed in all cases with isotonic saline. The tests were read for immediate-type reaction at 10–20 min and for delayed-type reaction at 24–96 hours. The criteria of positive reactions to scratch tests were the same as to intracutaneous tests as reported previously (59).
- (7) Patch tests with benzylpenicillin, phenoxymethyl penicillin, and procaine penicillin, 10^6 units/ml, control with isotonic saline. The patch was removed at the end of 24 hours and the reactions were read at 24–96 hours. The criterion of a positive patch test was distinct erythema and infiltration at the site of application, provided that the reaction to isotonic saline was negative.
- (8) Intracutaneous tests with penicilloyl-polylysine, injecting, as in the intracutaneous tests with penicillin, 0.05 ml penicilloyl-polylysine dilution intracutaneously. The initial concentration was 10^{-12} M, thereafter successively 10^{-11} M, 10^{-10} M up to 10^{-6} M at 10–20 min intervals. The patients were closely observed after the injections. The criteria of a positive immediate-type reaction were the same as in the intracutaneous tests with penicillin.
- (9) Provocation tests with benzylpenicillin. Intracutaneous injections were continued in increasing doses as mentioned under item (5) until possible allergic manifestations. If 10^4 units intracutaneously was tolerated, benzylpenicillin was injected successively in a dosage of 10^2 , 10^3 , 10^4 , 10^5 , and in most cases 10^6 units intramuscularly at intervals of a few hours to a few days. In intramuscular provocation 1–3 injections of penicillin were administered daily, and in the event of questionable allergic reactions also isotonic saline as a placebo.

After the completion of the clinical investigations serum samples for immunological study were obtained from all 53 patients with demonstrated penicillin allergy, from 12 who tolerated penicillin in a therapeutic dose in spite of a history suggesting penicillin allergy, and from all 120 patients of control group

A. Some of the results of the serological testing have been published previously (56), and others are in press.

Reagents

- (1) Commercial crystalline benzylpenicillin as the sodium salt: Penicillin Leo®, stored at room temperature as dry powder in rubber-capped vials of 10^5 and 10^6 units (Leo Pharmaceutical Products Trading Ltd., Copenhagen).
- (2) Commercial phenoxymethyl penicillin as the calcium salt, Calcipen®, stored at room temperature as dry powder in rubber-capped vials of 6×10^5 units (Leo Pharmaceutical Products Trading Ltd., Copenhagen).
- (3) Commercial procaine benzylpenicillin, Penicillin-Procain Novo® in the form of a suspension containing 3×10^5 units/ml in rubber-capped vials of 2 ml, stored at room temperature (Novo Industri A/S, Copenhagen).
- (4) Penicilloyl-polylysine: Cilligen® containing 1×10^{-5} M penicilloyl compound (Sigma Company, St. Louis, Missouri, U.S.A.), stored at 4°C .

RESULTS

A family history of allergic diseases in patients with a personal history suggesting penicillin allergy was found as shown in Table 5. The data are given only for 92 patients, referred for investigation exclusively because of penicillin allergy. 24 patients are not included in the table, as they were primarily or simultaneously referred for investigation for an other allergy. In 46 cases of confirmed penicillin allergy there was a family history of bronchial asthma in 28 per cent, of urticaria in 11 per cent, and of hay fever in 11 per cent.

The occurrence of other allergic diseases in patients with a history suggesting penicillin allergy is shown in Table 6. In this table too, the data are given only for 92 patients, referred exclusively for investigation of penicillin allergy. The table shows a high incidence of asthma, vasomotor rhinitis, hay fever, and angioneurotic oedema among 46 patients with confirmed penicillin allergy.

Allergy to other drugs occurred in 34 out of 116 patients with a history suggesting penicillin allergy (Table 7). The drugs blamed were most often streptomycin, sulphonamide, tetracycline, and salicylate. The highest frequency of allergy to other drugs was recorded in persons who were occupationally exposed to drugs.

TABLE 5

Family History of Allergic Diseases in 92 Patients with a History Suggesting Penicillin Allergy.

Allergic disease	46 patients with penicillin allergy confirmed by provocation test			46 patients with a history suggesting penicillin allergy, but who tolerated benzylpenicillin in a therapeutic dose		
	Total familial cases of the disease	No. of pts. with at least 1 familial case of the disease	Percentage of patients with at least 1 familial case of the disease	Total familial cases of the disease	No. of pts. with at least 1 familial case of the disease	Percentage of patients with at least 1 familial case of the disease
Bronchial asthma	16	13	28	11	7	15
Vasomotor rhinitis	1	1	2	0	0	0
Hay fever	7	5	11	5	4	9
Urticaria	7	5	11	8	8	17
Penicillin allergy	4	3	7	5	5	11

TABLE 6

Incidence of Other Allergic Diseases in Patients with a History Suggesting Penicillin Allergy.

Allergic disease	46 patients with penicillin allergy confirmed by provocation tests	46 patients with a history suggesting penicillin allergy, but who tolerated penicillin in a therapeutic dose	Incidence of the disease in the general population (Schwartz (72))
Bronchial asthma	8 (17 %)	0 (0 %)	1.0 %
Vasomotor rhinitis	8 (17 %)	3 (7 %)	1.4 %
Besnier's prurigo	0 (0 %)	0 (0 %)	0.1 %
Hay fever	3 (7 %)	0 (0 %)	0.3 %
Urticaria	11 (24 %)	9 (20 %)	7.2 %
Angioneur. oedema	7 (15 %)	5 (11 %)	1.5 %

Previous treatment with penicillin in 116 patients with a history suggesting penicillin allergy and in 240 persons of control groups A and B, without a history of penicillin allergy, is shown in Table 8. Patients with confirmed penicillin allergy

TABLE 7

Other Drug Allergy in 34 out of 116 Patients with a History Suggesting Penicillin Allergy.

19 pts. with occupational exposure to drugs and a history suggesting penicillin allergy					
Drug	Urtic., angioneur. oedema, exanthema	Asthma	Vasomotor rhinitis	Anaphyl. react.	Eczema
Streptomycin	2	2	2	3	3
Sulphonamide	2				
Tetracycline				3	
Iodine					
Salicylate	1				
Neomycin			1		
Barbiturate					
Others	3	2	2		1
Drug allergy in a total of:			12		
40 pts. with confirmed penicillin allergy, but no occupational exposure to drugs					
Drug	Urtic., angioneur. oedema, exanthema	Asthma	Vasomotor rhinitis	Anaphyl. react.	Eczema
Streptomycin					
Sulphonamide	2				1
Tetracycline	1				
Iodine					2
Salicylate	2			1	
Neomycin					
Barbiturate	1				
Others	1	1			
Drug allergy in a total of:			7		
57 pts. with a history suggesting penicillin allergy, who now tolerated penicillin, not occupationally exposed to drugs					
Drug	Urtic., angioneur. oedema, exanthema	Asthma	Vasomotor rhinitis	Anaphyl. react.	Eczema
Streptomycin				1	
Sulphonamide	3				
Tetracycline	1				
Iodine					2
Salicylate	2				
Neomycin	1				1
Barbiturate	1				
Others	5	1			2
Drug allergy in a total of:			15		

Blank: no case recorded.

without occupational contact with penicillin showed the heaviest previous exposure to penicillin by the oral or parenteral route. However, the differences between the various groups of patients in respect to the number of previous penicillin treatments were slight.

The history of penicillin allergy in 116 patients is illustrated by Tables 9 and 10. 67 patients had had only one clinical sign of penicillin allergy (Table 9). Out of this group 43 (64 per cent) were found to tolerate penicillin in a therapeutic dose. 49 patients had had several clinical signs at the same time, and among them only 20 (41 per cent) tolerated penicillin in a therapeutic dose. It will be seen that a large number had serious clinical reactions.

Thirty-three patients had several times had allergic reactions upon repeated exposure to penicillin. Five had daily reactions upon occupational contact with penicillin. Previous reactions and the symptoms and signs in the clinical investigation of the remaining 28 patients are recorded in Table 10.

On intracutaneous testing with benzylpenicillin of all 116 patients with a history suggesting penicillin allergy a *positive immediate-type reaction* was found in 19 (Table 11).

The most sensitive patient, EMW, developed a positive intracutaneous reaction to 10^{-5} units benzylpenicillin. A total of 7 patients reacted to 1 unit or less. Two patients (KÅH and MPA) did not show an indisputable positive cutaneous reaction until 10^4 units benzylpenicillin intracutaneously, a slightly local-irritant dose.

Seven patients with a positive immediate-type intracutaneous reaction to penicillin developed definite allergic signs and symptoms at the cutaneous testing, 3 developed mild anaphylactic reactions, and 1 had an attack of asthma (Table 11).

In continued provocation tests, intracutaneous or intramuscular, with benzylpenicillin on 9 patients who had given a positive immediate-type intracutaneous reaction to penicillin, all patients developed allergic reactions. Two (EKS and EJ 1) developed mild anaphylactic reaction, the others urticaria or exanthema (Table 11).

TABLE 8

No. of Previous Penicillin Treatments of Alleged Penicillin Allergies and Patients without History Suggesting Penicillin Allergy.

No. of previous systemic penicillin treatments	27 pts. with proven penicillin allergy, without other atopic allergy or occupational contact with penicillin	13 pts. with proven penicillin allergy and other atopic allergy, but without occupational contact with penicillin	19 pts. with occupational contact with penicillin and a history suggesting penicillin allergy	57 pts. who tolerated penicillin despite a history suggesting penicillin allergy. No occupational contact with penicillin	240 pts. without a history suggesting penicillin allergy
0	7 (26 %)	1 (8 %)	4 (21 %)	23 (40 %)	30 (12 %)
1-2	10 (37 %)	1 (8 %)	8 (42 %)	16 (28 %)	105 (44 %)
3-5	5 (19 %)	5 (38 %)	4 (21 %)	15 (26 %)	67 (28 %)
6-10	2 (7 %)	4 (31 %)	2 (11 %)	1 (2 %)	26 (11 %)
> 10	3 (11 %)	2 (15 %)	1 (5 %)	2 (4 %)	12 (5 %)
Previous local penicillin treatment	7 (26 %)	5 (38 %)	4 (22 %)	8 (14 %)	Unknown

Three patients (EJ 2, EGC, and HEN) with a definite history of penicillin allergy, with positive intracutaneous reaction to penicillin, and a positive finding of reagin in the serum (56) were not provoked to allergic reactions for various reasons.

On intracutaneous testing with benzylpenicillin 10³ units in 120 patients with no history of penicillin allergy (control group A), there were no positive immediate-type cutaneous reactions or complicating allergic generalized reactions.

Positive delayed-type cutaneous reactions to penicillin were demonstrated in 25 out of 116 patients with a history of penicillin allergy (Table 12). In all patients the intracutaneous tests with benzylpenicillin were read for delayed reactions; positive reaction was demonstrated in 20 patients. Patch tests with benzylpenicillin were done on 82 patients. A positive re-

TABLE 9
History Suggesting Penicillin Allergy (Major Symptoms - Minor Symptoms) in
116 Patients Investigated.

Major symptoms in previous allergic reaction to penicillin (main diagn.)	Minor symptoms in previous allergic reaction to penicillin (sub-diagn.)							
	None	Urti- caria	Angio- neur. oedema	Exanthema + erythema	Asthma	Vasomot. rhinitis	Gastro- intest. symp.	Fever
Anaphyl. reaction	20 (11)	5 (4)	4 (3)	5 (4)	3 (3)	2 (1)	5 (3)	2 (1)
Urticaria	10 (23)	4 (17)	4 (5)		1		3 (3)	3 (1)
Angioneur. oedema	5 (6)	4 (6)		1		1	1	1
Exanthema + erythema	6 (11)	5 (7)	1 (1)			1 (1)	1 (2)	
Asthma	8 (5)	4 (4)	1 (1)	1	1	1 (1)	1	1
Eczema	3 (2)	2 (2)	1					
Others	1 (5)	(3)	1 (1)				1 (1)	1 (1)
Total	53 (63)	24 (43)	6 (4)	12 (10)	4 (3)	3 (1)	7 (5)	8 (6)

Blank = No patient recorded with this sign.

6 = Patients with confirmed penicillin allergy.

(6) = Patients who tolerated penicillin in a therapeutic dose.

TABLE 10
Type of Clinical Reactions in 28 Patients with a History of Allergic Reaction to Penicillin on Several Occasions.

Case	History of allergic reactions to penicillin		Last reaction	Sensitivity to units penicillin	Reaction on provocation with penicillin
	Previous reactions				
EMW		Urticaria	S. anaphyl.	10^{-5}	M. anaphyl.
OMN		Itching	M. anaphyl.	5×10^{-4}	M. anaphyl.
EKS		Urticaria	S. anaphyl.	10^{-2}	M. anaphyl.
MHJ	S. anaphyl.*	S. anaphyl.*	S. anaphyl.*	10^{-1}	S. anaphyl.
ELC	Eczema*	M. anaphyl.*	S. anaphyl.*	1	M. anaphyl.
HHM		Asthma	Asthma	10	Asthma
EJ 2		M. anaphyl.	S. anaphyl.	10	(pos. cut. react.)
AEL		S. anaphyl.	M. anaphyl.	10	M. anaphyl.
MAS		Ser. sickn.	S. anaphyl.	10^2	Urticaria
OEP		Urticaria	Urticaria	10^2	Urticaria
EGC		Loc. react.	S. anaphyl.	10^2	(pos. cut. react.)
DJ		Urticaria	M. anaphyl.	3×10^2	Erythema
AK		Urticaria	S. anaphyl.	10^3	M. anaphyl.
ANT		Ang. oedema	Eryt. multif.	10^3	Eryt. multif.
AGJ	Exanthema	Exanthema	Urticaria	10^4	Urticaria
TP		M. anaphyl.	M. anaphyl.	10^4	S. anaphyl.
JPP		M. anaphyl.	Ang. oedema	10^4	M. anaphyl.
JMW		S. anaphyl.	M. anaphyl.	10^4	Vas. rhin.
ASJ	Exanthema	Exanthema	Exanthema	3×10^5	Erythema
OMJ	Ser. sickn.	Ang. oedema*	Ang. oedema*	10^5	Ang. oedema
OTP		Urticaria	M. anaphyl.	Tolerates	penicillin
BVS		Loc. react.	Ang. oedema	Tolerates	penicillin
AAH		Exanthema	Asthma*	Tolerates	penicillin
AKM		Loc. react.	Urticaria	Tolerates	penicillin
HMW		Exanthema	Urticaria	Tolerates	penicillin
DJH		Exanthema	M. anaphyl.	Tolerates	penicillin
OKP	M. anaphyl.	Eczema	M. anaphyl.	Tolerates	penicillin
AHH	Rhinitis	Vas. rhin.*	Eczema	Tolerates	penicillin
		Exanthema	Exanthema	Tolerates	penicillin

* = Reactions elicited by occupational contact with penicillin.
 S. = severe.

TABLE 11

Positive Immediate-type Intracutaneous Reaction to Benzylpenicillin in 19 Patients with a History Suggesting Penicillin Allergy.

Case	Positive cutaneous react. to units penicillin	Allergic sympt. elicited by intracut. tests	Allergic sympt. on continued i.c. provocation, units	Allergic sympt. on i.m. provocation, units	Latent period between inj. of penicillin and subsequent allergic react. in present test	Months last allergic reaction to penicillin and present study
EMW	10^{-5}	Mild anaphyl. react			2'	4
ELP	10^{-4}	Mild anaphyl. react			5'	1
EKS	10^{-3}		Mild anaphyl. react. 10^{-2}		2 h	1
EJ 1	10^{-2}		Mild anaphyl. react. 10^2		2½ h	60
EMT	1	Exanthema			1 h	12
KU	10				40'	1
EJ 2	10	Mild anaphyl. react				½
JVN	10^2	(Prev. anaphyl. react.)				⅔
MAS	10^2	Erythema		Urticaria 10^2	72 h	⅔
OEP	10				48 h	1
OCC	1		Urticaria 10^2		2 h	4
EGC	10^2	(Prev. anaphyl. react.)		Urticaria 10^2	6 h	1
DJ	10^{-1}				20'	36
EJN	10^3	Urticaria	Erythema 3×10^2		3 h	¼
HEN	10^3	(Prev. exanthema)				36
KÄH	10^4	Asthma			5'	⅓
JS	10^3			Urticaria 2×10^4	48 h	4
MPA	10^4			Exanthema 10^6	3 h	72
KLH	10^2			Urticaria 10^6	30'	1

TABLE
*Positive Delayed-type Intracutaneous Reaction
 Patch Test with Benzylpenicillin in 15 Patients*

Case	Units of penicillin needed for positive intracut. reaction	Patch test with benzylpenicillin	Allergic symptoms on intracut. testing	Allergic on i.c. units
EMW*	—	+	Mild anaphyl. react.	10^{-5}
JVN*	—	+	Erythema	10^2
OCC*	1	+		
EVP	10^2	+	Eczema	
EMB	10^2	+		Eczema
AMJ	10	+		Angioneur.
IV	10^4	—		
AGJ	10^4	+	Urticaria	
FRB	—	+		Asthma
EC	10^3	—		Angioneur.
ASJ	10^4	+		
ALJ	10^3	—		
HMP	10^3	+		
EF	10^3	+		
OBO	10^2	+		
OMJ	10^4	—		
GAB	10^3	—		Tolerates penicillin
CHC	10^3	+		Tolerates penicillin
CFØ	10^3	—		Tolerates penicillin
TAT	10^3	—		Tolerates penicillin
IDT	10^4	—		Tolerates penicillin
HVA	10^4	—		Tolerates penicillin
ECL	10^4	—		Tolerates penicillin
MT	—	+		Tolerates penicillin
LKL	—	+		Tolerates penicillin

* = simultaneously positive immediate-type cutaneous test with benzylpenicillin.

action was elicited in 15, 10 of whom also had a positive delayed-type intracutaneous reaction to penicillin (Table 12).

Among the 25 patients with positive delayed-type cutaneous reaction to penicillin 4 (EMW, JVN, EVP and AGJ) de-

12

*to Benzylpenicillin in 20 Patients and Positive
with a History Suggesting Penicillin Allergy.*

symptoms provocation,	Allergic symptoms on i.m. provocation, units	Latent period between inj. of penicillin and subsequent allergic react. in present study	Months between last penicillin react. and present study
		2'	4
		72 h	$\frac{2}{3}$
	Urticaria	6 h	4
		5 h	0
oedema	10^3	4 h	0
		3 h	1
	Severe anaphyl. react	1'	48
		10 h	36
		5'	0
oedema	10^4	24 h	0
		2 h	1
	Erythema		
	Urticaria	10^6	72
	Exanthema	10^6	1
	Urticaria	10^6	1
	Exanthema	10^6	5
	Angioneur. oedema	10^6	6
10^5 units			2
10^6 units			48
10^6 units			0
10^6 units			$\frac{1}{4}$
10^5 units			12
10^5 units			24
10^6 units			$\frac{1}{4}$
10^6 units			$\frac{3}{4}$
10^6 units			120

+ = positive reaction. — = negative reaction.

veloped respectively anaphylactic reaction, erythema, eczema and urticaria, in relation to the intracutaneous testing.

On continued intracutaneous or subsequent intramuscular provocation by penicillin another 12 patients developed defi-

nite allergic symptoms and signs. One patient (IV) exhibited a very severe anaphylactic reaction which required injections of adrenaline, to a total amount of 3.5 mg. Most of the other reactions were of the clinically benign type.

Seven patients with positive delayed-type intracutaneous reaction to penicillin and two with positive patch tests tolerated penicillin in a therapeutic dose: 10^5 – 10^6 units i.m. without demonstrable allergic symptoms or signs (Table 12).

One of the 82 examined patients with a history suggesting penicillin allergy had a positive patch test, and one a positive scratch test with *procaine penicillin*, while the reactions to benzylpenicillin were negative. Both patients had had allergic reactions which could be ascribed to exposure to procaine, but they tolerated benzylpenicillin in a therapeutic dose.

Scratch test with phenoxymethyl penicillin in 82 patients and patch tests in 59 patients with a history suggesting penicillin allergy did not afford evidence of an independent specificity for the phenoxymethyl group. The reactions observed were identical with, or weaker than, the corresponding ones to benzylpenicillin.

On patch testing with benzylpenicillin, phenoxymethyl penicillin, and procaine penicillin, in 120 patients without a history of penicillin allergy (control group B) there was *no case of a positive reaction to benzylpenicillin* or phenoxymethyl penicillin. One patient with a history of allergic reactions to local anaesthesia gave a positive patch test to procaine penicillin.

Negative cutaneous reactions to benzylpenicillin were found in 75 out of 116 patients with a history suggesting penicillin allergy. However, 9 of these patients developed allergic reactions in relation to intracutaneous testing with penicillin (Table 13), including severe anaphylactic reactions to 10^{-1} and 10^4 units in cases MHJ and TP. In EJ 3 only itching occurred.

Another 11 patients with negative cutaneous reactions to penicillin developed allergic symptoms and signs upon subsequent intramuscular provocation with benzylpenicillin. JPP developed a mild anaphylactic reaction on benzylpenicillin 10^4 units, the other 10 milder reactions (Table 13).

Benzylpenicillin in a therapeutic dose: 10^5 or 10^6 units i.m. was tolerated without any complaints by 55 patients with a history suggesting penicillin allergy and negative cutaneous reactions to penicillin.

Intracutaneous testing with penicilloyl-polylysine read for immediate-type reaction was positive in 10 out of 41 patients with a history suggesting penicillin allergy. Out of the 41 tested patients 19 had manifest penicillin allergy at the time of the examination. Of them 8 exhibited a positive cutaneous reaction to penicilloyl-polylysine (Table 14). 12 patients tolerated penicillin in a therapeutic dose. Among them, one (MT) also gave a positive reaction to penicilloyl-polylysine (Table 14). In one patient (MJ) with a positive and in one (GSB) with a negative cutaneous reaction to penicilloyl-polylysine the clinical examination for penicillin allergy was not completed, as the patients failed to attend the final tests. Eight patients had intracutaneous tests with penicilloyl-polylysine at a follow-up study several years later. The reactions were negative in all (Table 16).

Allergic reaction occurred as a complication to intracutaneous tests with penicilloyl-polylysine in 3 out of 41 patients (Table 14). The patient who had the highest sensitivity to penicillin (EMW) developed urticaria and weakness, MJ developed angioneurotic oedema, and GSB exhibited a reaction, probably anaphylactic. All the allergic reactions to penicilloyl-polylysine were fairly mild.

On *intracutaneous testing with penicilloyl-polylysine* 0.05 ml 10^{-5} M in 120 patients without any history of penicillin allergy (control group A) 3 persons gave a positive reaction. Two of them had been treated with penicillin without any complaints, less than 3 months prior to the investigation, and all tolerated benzylpenicillin 10^6 units intramuscularly without complaints.

The allergic reactions elicited by intracutaneous testing and in provocation experiments with penicillin were in most cases of the same clinical type as previous penicillin reactions. However, 6 patients who had a history of anaphylactic reactions

TABLE 13
Provocation Tests with Benzylpenicillin in 75 Patients with a History Suggesting Penicillin Allergy, But Showing Negative Intracutaneous and Patch Tests with Benzylpenicillin.

Case	Allergic sympt. on intracut. testing with penicillin, units	Allergic sympt. on intramuscular provocation with penicillin, units	Latent period between inj. of penicillin and subsequent allergic react. in present study	Months between last penicillin react. and present study
OMN	Mild anaphyl. react. 5×10^{-1}		2'	1
MHJ*	Severe anaphyl. react. 10^{-1}		10'	4
ELC*	Mild anaphyl. react. 1		3'	1
HHM*	Asthma 10		10'	1
AEL	Mild anaphyl. react. 10		5'	48
KKT	Mild anaphyl. react. 10^2	Urticaria 10^3	2'	24
ATJ		Exanthema 10^1	3 h	24
MH			5'	48
AK	Mild anaphyl. react. 10^3	Erythema multiforme 10^3	3	2
ANT		Asthma 10^3	2 h	$1\frac{1}{2}$
MOP			2 h	1
TP*	Severe anaphyl. react. 10^1		2'	12
JPP*		Mild anaphyl. react. 10^1	10'	$1\frac{1}{2}$
JMW		Allergic rhinitis 10^1	3 h	2
HP		Exanthema 10^1	14 h	1
JEM		Eczema 10^1	24 h	48
MR		Urticaria 10^3	12 h	18
KED		Asthma 10^5	3 h	3
JJN		Allergic rhinitis 10^6	24 h	0
BSJ		Tolerates penicillin without complaints 10^6		$1\frac{1}{2}$
EJ 3	Itching 10^4		4 h	$1\frac{1}{2}$

54 patients: no relevant allergic symptoms on provocation

**

* = described in detail in a previous publication (59).

** 0-1 month: 19 patients; 2-6 months: 10 patients; 7-24 months: 14 patients; ≥ 24 months: 11 patients.

TABLE 14
Immediate-type Intracutaneous Reaction to Penicilloyl-Polylysine in 19 Patients with Manifest Penicillin Allergy, 2 Patients Who Failed to Attend for the Final Tests, and 1 Patient Who Tolerated Penicillin in a Therapeutic Dose.

Case	Sensitivity to penicillin, units	Clinical signs on provocation with penicillin	Intracut. test benzyl-penicillin 20 min	Intracut. test penicilloyl-polylysine 20 min	Allergic react. to cut. testing with penicilloyl-polylysine	Intracut. test 24-96 hours or patch test with benzyl-penicillin
EMW	10^{-5}	Anaphyl. react.	+	$+10^{-13}$ M	Urticaria + weakness	+
EKS	10^{-2}	Anaphyl. react.	+	—	—	—
MHJ*	10^{-1}	Anaphyl. react.	+	$+10^{-11}$ M	—	—
EMT	1	Exanthema	+	$+10^{-7}$ M	—	—
KC	10	Anaphyl. react.	+	$+10^{-12}$ M	—	—
AEL	10	Anaphyl. react.	—	—	—	—
DJ	3×10^2	Erythema	—	$+10^{-10}$ M	—	—
MOP	10^3	Asthma	—	—	—	—
FRB	10^4	Asthma	—	—	—	+
TP	10^4	Anaphyl. react.	—	—	—	—
JMW	10^4	Vasomot. rhinitis	—	—	—	—
HP	10^4	Exanthema	—	$+10^{-6}$ M	—	—
JEM	10^4	Eczema	—	$+10^{-9}$ M	—	—
JS	2×10^4	Urticaria	+	—	—	—
KED	10^5	Asthma	—	$+10^{-7}$ M	—	—
ALJ	10^6	Urticaria	—	—	—	+
OBO	10^6	Exanthema	—	—	—	+
JJN	10^6	Vasomot. rhinitis	—	—	—	—
OMJ	10^6	Angioneur. oedema	—	—	—	+
MJ	10^{-2}	Anaphyl. react.	—	$+10^{-9}$ M	Angioneur. oedema Anaphyl. react.?	—
GSB	?	?	—	—	—	—
MT	?	None	—	$+10^{-9}$ M	—	—

* = investigated after hypersensitization with penicillin. Initially a negative immediate-type intracutaneous reaction to penicillin.
 Blank = investigation not performed.
 + = positive reaction. — = negative reaction.

TABLE 15

Allergic Reactions on Intracutaneous Testing and Provocation Tests with Penicillin in 6 Patients with Penicillin Allergy Indicating Hyposensitization By the Tests.

Case	Dose of penicillin	Route of administration	Reaction to provocation with penicillin
EJ 1	10^{-1} units	i.c.	Erythema + weakness
	10^2 units	i.c.	Anaphyl. reaction
AK	1 units	i.c.	Weakness + itching
	10^3 units	i.c.	Mild anaphyl. react.
	3×10^5 units	p.o. $\times 3$	Angioneur. oedema
HP	10^4 units	i.m.	Exanthema
	2×10^6 units	i.m.	No complaints
EC	1 units	i.c.	Weakness + itching
	10^4 units	i.c.	Angioneur. oedema
	10^3 units	i.m.	Nausea
	10^6 units	i.m.	No complaints
KLH	1 units	i.c.	Itching
	10 units	i.c.	Erythema + itching
	10^6 units	i.m.	Urticaria + erythema
OMJ	10^{-2} units	i.c.	Nausea + itching
	10^3 units	i.m.	Nausea + flushing
	10^6 units	i.m.	Angioneur. oedema + nausea
MPA	10^{-3} units	i.c.	Weakness + nasal itching
	10^{-3} units	i.c.	Nausea
	10^{-1} units	i.c.	Weakness + nausea
	10^2 units	i.c.	Rhinitis + conjunct. + diarrhoea
	10^5 units	i.m.	Rhinitis + exanthema

i.c. = intracutaneously i.m. = intramuscularly p.o. = by the oral route

developed only mild reactions at the testing, three (EMT, MH, and MPA) developing exanthema, 1 (DJ) erythema, 1 (JMW) vasomotor rhinitis, and 1 patient (MAS) urticaria. Two patients (ELP and JPP), with a history of angioneurotic oedema upon contact with penicillin, developed anaphylactic reactions at the testing, and two (MR and JJN), who had

TABLE 16
Re-Examination of 9 Patients with Previously Confirmed Penicillin Allergy.

Case	Sensitivity to benzylpenicillin, units	Clinical reaction on exposure to penicillin	Immediate-type intracut. reaction to penicillin	Immediate-type intracut. reaction to penicilloyl- polylysine	Delayed-type cutaneous reaction to penicillin
EKS	10^{-2} 2 yrs. later 10^{-4}	Mild anaphyl. react.	+	—	—
EJ 1	10^2 4 yrs. later 10^4	Mild anaphyl. react. Mild anaphyl. react.	+	—	—
EGC	10^2 5 yrs. later 10^4	Not provoked Gastroint. ÷ joint symptoms	+	—	+
ATJ	10^3 6 yrs. later 10^3	Urticaria Mild anaphyl. react.	—	—	—
KÅH	10^4 4 yrs. later 10^4	Asthma Asthma	+	—	—
AGJ	10^4 5 yrs. later 10^4	Urticaria Erythema	—	—	+
MPA	10^5 4 yrs. later 10^3	Exanthema Severe anaphylaxis	+	—	—
HMP	10^6 5 yrs. later ?	Exanthema Not provoked	—	—	+
EF	10^6 4 yrs. later ~	Urticaria Tolerated penicillin	—	—	+

Blank = Investigation not performed.

+ = positive reaction.

— = negative reaction.

previously had asthma, developed urticaria and rhinitis respectively at the provocation test with penicillin.

The *latent period* between intracutaneous or intramuscular injection of penicillin and the occurrence of allergic reaction in 49 patients with manifest penicillin allergy is shown in Tables 11, 12, and 13. The symptoms occurred at the end of periods ranging from 1 minute to 72 hours—the anaphylactic reactions usually at the end of minutes, exanthema and urticaria hours after the injection.

One patient (EKS) did not develop a mild anaphylactic reaction until 2 hours after intracutaneous injection of benzylpenicillin 10^{-2} units (Table 11). Another patient (JPP) developed a mild anaphylactic reaction 10 minutes after intramuscular injection of 10^4 units and upon repeated provocation a severe anaphylactic reaction 6 hours after the injection of 5×10^3 units (Table 13).

A total of 5 patients (DJ, KIH, ALJ, OMJ, and MH) exhibited erythema, urticaria, angioneurotic oedema, or exanthema only 5–30 minutes after injections of penicillin.

The *reliability* of the clinical investigations was verified by placebo injections in 20 cases. In addition, the provocation with penicillin was sometimes repeated; thus, 13 out of 53 patients with confirmed penicillin allergy were provoked to allergic symptoms several times. Most patients developed definite clinical reactions, of the same nature as in previous allergic reactions to penicillin; in such cases, further testing was considered unnecessary.

In the intracutaneous testing and provocation experiments several patients showed signs that the method might lead to a “*rush hyposensitization*” to penicillin. The allergic symptoms and signs in 7 patients (Table 15) occurred after injections of penicillin; lower and intermediate doses had caused no signs of allergic reactions.

A *follow-up investigation* 2–6 years after the initial one, was performed on 9 out of 53 patients with definite penicillin allergy (Table 16). The sensitivity to penicillin was found to have increased in one patient (EKS), to be unchanged in

three, and reduced in two (EJ 1 and EGC). One patient (EF) now tolerated penicillin in a therapeutic dose, and one did not have another provocation test.

DISCUSSION

The role of heredity in penicillin allergy has been touched upon in several previous publications. The problem is primarily whether a genetic relationship exists between penicillin allergy and the hereditary atopic diseases asthma, vasomotor rhinitis, Besnier's prurigo, and hay fever, or whether penicillin allergy occurs independently of these diseases, like *e.g.* eczema and serum sickness.

A sufficient investigation to elucidate these factors, according to the lines given by *Schwartz* (72) with a thorough family study, has never been performed for penicillin allergy. The data in Table 5 were given by the penicillin allergics themselves, and as members of their families were not interviewed individually, some cases of disease, especially mild ones such as vasomotor rhinitis and urticaria, have probably escaped detection. This assumption is strengthened by comparison with results obtained by *Schwartz* (72) in the families of patients with asthma and of control persons.

Nevertheless, 46 patients with definite penicillin allergy showed, in spite of a presumably insufficient recording, an increased incidence of asthma and hay fever in the family: 28 per cent and 11 per cent (Table 5) as compared with 10 per cent and 2½ per cent in non-allergic control persons (72). The difference is significant for the occurrence of asthma ($P < 0.01$, χ^2 test). The results indicate a probable, but not definite genetic relationship between atopic diseases and cases of penicillin allergy as described in the present paper.

The common occurrence of other atopic diseases, in particular asthma, in penicillin allergics (25, 37, 83, 87) and of penicillin allergy in patients with atopic diseases (4, 20, 26, 50) may be due to a genetic relationship between penicillin

allergy and the atopic diseases. However, other factors may also cause a common occurrence of atopic disease and penicillin allergy in the same patient: (1) Selection, wholly or partially, of penicillin allergics among atopic patients in a specialized division for allergic diseases, (2) increased exposure to penicillin in patients having other allergic diseases, in particular bronchial asthma with a tendency to infection, and thereby an increased possibility of sensitization.

None of the factors mentioned under (1) and (2) can explain the significantly increased incidence of asthma, vasomotor rhinitis, hay fever, and angioneurotic oedema in 46 patients with confirmed penicillin allergy (Table 6) as compared with the incidence of these diseases in the normal population (72) ($P < 0.001$, χ^2 test). Thus, twenty-four patients who were referred simultaneously or primarily, for investigation for other allergy are not included in Table 6. Furthermore, ten patients with confirmed penicillin allergy and simultaneous atopic disease, but without occupational exposure to penicillin, did not have a history of a significantly larger number of previous penicillin treatments than other categories of patients (Table 8).

Simultaneous allergy to penicillin and to other drugs has previously been mentioned in numerous case reports, more rarely in major series (76). Out of the present 116 patients 34 (29 per cent) gave a history of penicillin allergy and allergy to other drugs at the same time. The most common manifestations were urticaria, angioneurotic oedema, and exanthema, and the most common antigens were streptomycin and sulphonamide. The highest frequency of other drug allergy was recorded in patients who were occupationally exposed to drugs.

The frequency of allergy to other drugs is strikingly high in penicillin allergics as compared with a frequency of around 10 per cent in patients having other allergic diseases (13). Part of the explanation is that cases of eczema were included in the present study and besides there was an ample representation of patients with occupational exposure to drugs.

In spite of a relevant history of previous penicillin allergy in all 116 patients, 64 (55 per cent) tolerated penicillin in a therapeutic dose at the time of the investigation. The remaining 52 (45 per cent) again responded with an allergic reaction on intracutaneous testing or provocation experiment with penicillin. Only one previous paper (30) has reported an almost equally high frequency (39 per cent) of manifest penicillin allergy among patients with a history suggesting penicillin allergy. In the present material the result must be ascribed to the many serious cases of penicillin allergy.

The most relevant information concerning a history of penicillin allergy was that of an anaphylactic reaction, simultaneous occurrence of several clinical signs of allergy, and repeated allergic reactions after contact with penicillin (Tables 9 and 10). But even among such patients 29–41 per cent tolerated penicillin in a therapeutic dose without a demonstrable allergic reaction.

The demonstration of a positive immediate-type intracutaneous reaction to benzylpenicillin in 19 out of 116 patients with a history suggesting penicillin allergy (16 per cent), in 19 out of 53 patients with confirmed penicillin allergy (36 per cent), and in none of 120 patients without a history of penicillin allergy (control group A) is in conformity with a large number of the reports listed in Table 1. In supplementary provocation tests, the present study showed that a positive immediate-type intracutaneous reaction to benzylpenicillin was tantamount to clinical penicillin allergy (Table 11).

Previous observations of allergic reaction to fractions of a unit of penicillin (6, 19) were confirmed (Table 11). Such highly sensitive patients are probably not as very rare as generally assumed. The extremely varying sensitivity to penicillin among the patients indicates that it is not possible to fix a given penicillin concentration for intracutaneous testing of alleged penicillin allergics. Doses which in some patients will be insufficient for eliciting a positive cutaneous reaction may elicit anaphylactic reactions in others.

Complicating allergic reactions occurred on intracutaneous

testing with benzylpenicillin in 17 out of 116 patients with a history suggesting penicillin allergy (15 per cent) and in 17 out of 53 patients with confirmed penicillin allergy (32 per cent) (Tables 11, 12, and 13). These reactions occurred in spite of very cautious testing, starting with 10^{-5} units intracutaneously. These results may perhaps seem surprising, but on perusal of the literature (Table 2) a number of similar cases may be found, mainly in the form of case reports.

The demonstration of a positive delayed-type cutaneous reaction to penicillin in 25 out of 116 patients with a history suggesting penicillin allergy (22 per cent), and in 16 out of 53 patients with confirmed penicillin allergy (30 per cent) is in keeping with several of the reports listed in Table 4. A positive delayed-type cutaneous reaction to penicillin did not occur exclusively in patients with penicillin eczema, but also in patients with anaphylactic reactions (EMW and IV, Table 12), urticaria, exanthema, angioneurotic oedema, and asthma. A positive delayed-type cutaneous reaction to penicillin was not tantamount to clinical penicillin allergy; this was confirmed in 9 out of 25 patients (Table 12) who tolerated benzylpenicillin in a therapeutic dose without demonstrable allergic reactions.

Except in penicillin eczema, we do not yet know the role of delayed-type hypersensitivity in eliciting allergic reactions to penicillin. According to recent immunological theories delayed-type hypersensitivity is conditioned by thymus-derived t-lymphocytes. The cooperation of a small number of these cells is also needed for the formation of circulating antibody from bursa-equivalent b-lymphocytes (67). The hypothesis that delayed-type hypersensitivity on a cellular level is needed for the development of immediate-type hypersensitivity is compatible with the demonstration of positive blast transformation and positive delayed-type cutaneous reactions to pollen in a high percentage of patients with hay fever (11) and to penicillin in penicillin allergies.

The demonstration of a positive immediate-type intracutaneous reaction to penicilloyl-polylysine in 10 out of 42 pa-

tients with a history suggesting penicillin allergy (24 per cent), in 8 of 19 with proven penicillin allergy (42 per cent) (Table 13), and in 3 out of 120 patients without a history of penicillin allergy (2.5 per cent) (control group A) is in keeping with several of the previous studies listed in Table 3. The frequency of a positive cutaneous reaction to penicilloyl-polylysine in patients with a history suggesting penicillin allergy is significantly higher than among the control patients ($P < 0.001$, χ^2 test).

A positive cutaneous reaction to penicilloyl-polylysine was not tantamount to clinically manifest penicillin allergy. Thus, 4 patients with a positive intracutaneous reaction to penicilloyl-polylysine, tolerated benzylpenicillin 10^6 units intramuscularly without a demonstrable allergic reaction. One of these patients had a history of penicillin allergy, 3 were not alleged penicillin allergies.

Complicating allergic reactions occurred on intracutaneous testing with penicilloyl-polylysine in 3 patients (Table 13). EMW who had reacted to 10^{-5} units penicillin developed urticaria and weakness, MJ who had reacted to 10^{-2} units penicillin developed angioneurotic oedema. GSB in whom there had been a suspicion of an anaphylactic reaction on previous exposure to penicillin, developed palpitations, weakness, sweating, and abdominal pressure in relation to intracutaneous testing with penicilloyl-polylysine. The cutaneous reaction was negative. The symptoms soon subsided after application of a tourniquet on the arm. In spite of repeated requests, this patient did not attend again, as she was afraid to have further tests.

Two patients (EMT and ALJ) showed positive intracutaneous reaction to penicilloyl-polylysine 10^{-7} M, the others to lower concentrations. Thus, 10^{-6} M penicilloyl-polylysine is a sufficient concentration to elicit maximum wheal-and-flare reactions in penicillin allergies (41).

Three patients (HP, ALJ, and MJ) with proven penicillin allergy showed positive intracutaneous reaction to penicilloyl-polylysine and a negative reaction to penicillin. One patient

(EKS) showed a positive intracutaneous reaction of the immediate type to penicillin, but a negative reaction to penicilloyl-polylysine. These findings confirm what was stated above that in diagnosing penicillin allergy cutaneous tests should be performed with penicilloyl-polylysine as well as with penicillin.

The prediction of penicillin allergy by cutaneous tests using penicillin derivatives has been a matter of heated dispute, and by some authors it is considered extremely hazardous and unreliable. In a recent study (43) comprising 218 patients with a history suggesting penicillin allergy, negative cutaneous tests with penicilloyl-polylysine and "minor determinant mixture" seem to exclude immediate (including anaphylactic) reactions and as a rule also accelerated urticarial reactions in subsequent penicillin therapy.

The present results are not compatible with this view. Out of 19 patients with proven penicillin allergy and entirely negative cutaneous reactions to penicillin (Table 13) seven (AEL, MOP, TP, JMW, JEM, KED, and JJN) also showed negative intracutaneous reaction to penicilloyl-polylysine (Table 14) and sixteen showed no demonstrable skin-sensitizing antibodies in the serum reacting to benzylpenicillin, penicilloyl-polylysine, or benzylpenicilloate (56). Three patients (IV, MIJ, and MOP) had clinically proven penicillin allergy and penicillin-specific skin-sensitizing antibodies in the serum, but nevertheless negative immediate-type intracutaneous reaction to penicillin. One patient (EJ 1), when re-examined 4 years later, no longer showed a positive immediate-type intracutaneous reaction to penicillin, although he still had manifest penicillin allergy of an anaphylactic type (Table 16).

Many cases of penicillin allergy can no doubt be predicted by cutaneous tests using penicillin derivatives. However, it is apparent from the results submitted here that in their present form cutaneous tests with penicillin are so unreliable and hazardous that they are not suitable for routine clinical use in diagnosing penicillin allergy.

Provocation tests have previously been widely used in other forms of reagin-mediated allergy and have also played a role

in penicillin allergy. If the cutaneous reactions to penicillin (Table 13) and penicilloyl-polylysine (Table 14) were negative in patients with a history suggesting penicillin allergy, provocation tests using penicillin were of decisive diagnostic importance. There might even be severe penicillin allergy with an alarming reaction. If a positive delayed-type cutaneous reaction to penicillin was found (Table 12) or a positive immediate-type cutaneous reaction to penicilloyl-polylysine (Table 14), provocation tests were needed only if the diagnosis of penicillin allergy had to be made with certainty. Positive immediate-type intracutaneous reaction to penicillin was tantamount to clinically manifest penicillin allergy, and provocation tests were apparently superfluous in such patients (Table 11). Provocation tests using benzylpenicillin in the event of a suspicion of penicillin allergy proved extremely hazardous.

However, doubts arose regarding the reliability of provocation tests, as performed in the present study. There were indications that intracutaneous and intramuscular injections of penicillin in increasing concentration might entail a "rush hyposensitization" to penicillin. Several patients (Table 15) exhibited slight or doubtful allergic reaction to one concentration of penicillin, no complaints after a concentration 10 or occasionally 10^2 times higher, but definite allergic reaction to a still higher concentration. Two patients (HP and EC, Table 15) developed suspicious allergic reactions at lower concentrations of penicillin, but finally tolerated penicillin in a therapeutic dose. One patient (BSJ, Table 13) tolerated all the injections of penicillin. These three patients, therefore, were originally considered non-allergic to penicillin. Subsequent serological study, (56), however, revealed in HP and EC penicilloyl-specific and in BSJ penicillin-specific skin-sensitizing antibodies. On this background, the diagnosis was revised and changed to manifest penicillin allergy in all three patients.

The technique used involved, in addition to the possibility of hyposensitization, also a risk of sensitizing the patients to penicillin. However, this factor cannot be assessed on the basis of the results in the present material.

The spontaneous course of the penicillin allergy varied. As already mentioned, the history in patients who had had several previous reactions (Table 10) sometimes suggested an increasing and in others an unchanged or decreasing sensitivity. These assumptions were confirmed by comparing the primary clinical investigations and follow-up examination of 9 patients at the end of 2-6 years (Table 16). It is remarkable that one patient (EJ 1) was negative when tested at the end of 4 years, while previously he had given a positive immediate-type cutaneous reaction to penicillin. In both investigations, this patient developed anaphylactic reactions to provocation with penicillin. The patient who showed the mildest reaction and least sensitivity to penicillin (EK) tolerated penicillin in a therapeutic dose when re-examined.

The results show that cutaneous tests as used here could not predict manifest penicillin allergy with sufficient certainty. They also show that intracutaneous tests with penicillin, even when performed with the utmost caution, might elicit serious systemic allergic reactions. Accordingly, a history of penicillin allergy should be respected, and cutaneous tests should be omitted in routine clinical use.

SUMMARY

A clinical study of 116 patients with a relevant history of penicillin allergy is submitted. This series included 31 patients with suspected anaphylactic reactions and 19 with occupational exposure to penicillin. The diagnosis penicillin allergy was confirmed in 53 patients, while 63 tolerated penicillin in a therapeutic dose.

Patients with proven penicillin allergy had a significantly increased incidence of asthma in their families and personal histories of asthma, vasomotor rhinitis, hay fever, and angio-neurotic oedema. It is probable, though not proved, that a genetic relationship exists between penicillin allergy and the atopic diseases.

The most relevant information indicating penicillin allergy

was a history of previous anaphylactic reactions, of several clinical symptoms and signs at the same time, or of repeated allergic reactions upon contact with penicillin.

Intracutaneous tests using benzylpenicillin, and read for an immediate-type reaction, were done on all 116 patients with a history suggesting penicillin allergy. The tests were positive in 19 patients, all of whom had manifest penicillin allergy. One patient reacted to 10^{-5} units penicillin and one to 10^{-4} units. Intracutaneous tests with benzylpenicillin read for immediate-type reaction were done on 120 patients without a history of penicillin allergy and were negative in all.

Cutaneous tests with benzylpenicillin read for delayed-type reaction were positive in 25 out of 116 patients with a history suggesting penicillin allergy. In subsequent provocation tests 16 proved to have manifest penicillin allergy, while 9 tolerated penicillin in therapeutic doses without complaints.

Intracutaneous tests with penicilloyl-polylysine, read for immediate-type reaction, were positive in 10 out of 41 patients with a history suggesting penicillin allergy. One of these 10 patients tolerated penicillin in a therapeutic dose, whereas 8 proved to have manifest penicillin allergy. Three out of 120 control patients without a history of penicillin allergy also showed positive cutaneous reaction to penicilloyl-polylysine; all 3 tolerated penicillin in a therapeutic dose without complaints.

Provocation tests with penicillin were done on 75 patients with a history suggesting penicillin allergy and entirely negative cutaneous reactions to penicillin. On this provocation, 20 developed definite allergic symptoms, including 7 with anaphylactic reactions.

Complicating allergic reaction occurred on intracutaneous testing with benzylpenicillin in 18 out of 116 patients with a history suggesting penicillin allergy despite great caution in the testing. On intracutaneous testing with penicilloyl-polylysine 3 out of 41 patients developed complicating allergic reaction.

The results indicate that cutaneous tests as used in the pre-

sent study cannot predict penicillin allergy with sufficient certainty for use in clinical practice.

It was found probable that intracutaneous tests and provocation tests with penicillin as performed, might entail a "rush hyposensitization" of the patients to penicillin.

At the end of 2-6 years 9 of the penicillin allergics were re-tested, and 7 still exhibited manifest penicillin allergy.

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