

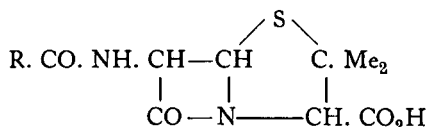
INVESTIGATIONS INTO PENICILLIN SENSITIVITY

By

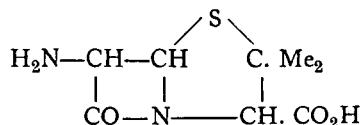
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Allergic reactions to penicillin are troublesome and sometimes dangerous; they restrict the use of penicillin. It is not known whether, or in what relative proportions, allergy is due to the penicillin nucleus or to the side-chain of the molecule. This is a point of some importance since some types of drug allergy are known to depend upon a side-chain. When this is so, cross sensitivity may exist with chemically similar substances having totally different biological effects; and on the contrary the substitution of a different side-chain in the original drug allergen may result in a drug with an analogous biological action but free from its specific allergenicity. The recent availability of the penicillin nucleus without any side-chain (*Batchelor et al.*, 1959) has made it possible for sensitive subjects to be tested with the penicillin nucleus alone and for the reaction thus obtained to be compared with the reactions to tests with existing penicillins.

Penicillin



6 - APA



It was decided in the first instance to test presumed penicillin-sensitive subjects with ordinary penicillin. A prick test was first made in order to exclude those who were so sensitive as to make intradermal testing dangerous. The prick test being negative, intradermal tests were then made successively with 1, 10, 100, 1000 units contained in 0.02 ml. of saline at twenty-minute intervals, until an immediate result was obtained. An increase in the size of the intradermal wheal of 1 mm. was recorded as doubtful ($\pm$); an increase of 2–3 mm. as positive (+); and an increase of 4–5 mm. as strongly positive (++). Benzylpenicillin was used because of its ready solubility.

Many published reports indicate the difficulty of obtaining positive tests; it was hoped to overcome this by careful selection of cases and by suitable test doses, but the first few results showed that this was no likely to be so. We therefore adopted the method of *Rajke & Vincze* (1959) whereby penicillin is conjugated with human gamma globulin. Gamma globulin solution was mixed with benzylpenicillin so as to give a proportion of 1 mg. globulin to 1000 units of penicillin. The mixture was incubated for at least a week at 4°C. before being used. Tests were then made with benzylpenicillin as before and also with the same dose of penicillin to which globulin had been added.

The penicillin nucleus, 6-amino-penicillanic acid (6-APA) was made available by the Beecham Research Laboratories. Doses of 0.6, 6 and 60 μ g. corresponding nearly to 1, 10 and 100 units of penicillin were used for testing, both alone and after the addition of globulin.

Control tests using globulin alone were carried out simultaneously in most cases.

RESULTS

A total of twenty patients completed the full range of tests together with two control subjects who had never received penicillin. All the patients gave histories of immediate-type penicillin allergy.

Case No.	Age	Sex	Penicillin (units)				Penicillin (units) + Globulin (1 μ gm)			
			1	10	100	1000	1	10	100	1000
1	34	F	+				++			
2	41	M	—	—	+		—	—	—	—
3	54	M	+				+			
4	47	M	—	—	—	—	—	—	—	+
5	30	F	—	—	—	$\pm$	—	—	—	$\pm$
6	47	F	—	$\pm$			—	+		
7	51	F	—	—	$\pm$		—	—	—	
8	65	M	—	—	++		—	++		
9	48	F	—	—	—	—	—	—	—	+
10	56	F	—	—	—	—	—	+		
11	27	F	—	$\pm$	$\pm$	—	$\pm$	+	—	$\pm$
12	68	F	—	—	—	—	—	—	—	—
13	55	F	—	—	—	—	—	—	—	—
14	43	F	$\pm$	—	$\pm$	++	$\pm$	—	$\pm$	+
15	20	F	—	—	—	—	—	—	—	—
16	40	F	—	+	—	—	—	$\pm$	—	—
17	53	F	$\pm$	+	—	+	$\pm$	$\pm$	++	
18	69	M	—	—	$\pm$	—	—	—	—	$\pm$
19	25	M	—	++			—	—	—	—
20	53	M	—	—	—	—	—	—	—	—
Normal	50	M	—	—	—	—	—	—	—	—
Normal	29	M	—	—	—	—	—	—	—	++

$\pm$ = Increase of wheal size by 1 mm.

+ = Increase of wheal size by 2-3 mm. /

No systemic reaction or other untoward reaction to the tests was observed, and no prick tests were positive.

Although the addition of globulin gave more positive results, these were also seen from the tests with globulin alone. Twelve of fourteen subjects tested gave an increase in wheal size from 1 mg. of globulin alone; this we interpret as a non-allergic osmotic effect. We feel obliged to explain similarly the penicillin-globulin and the APA-globulin conjugates at their highest concentration for the same reason. Disregarding doubtful ($\pm$) reactions to which we hesitate to attach significance, there remain five cases (1, 8, 11, 14, 17) in which a positive

intracutaneous tests

Globulin (μ gm)				6-APA (μ gm)			6-APA (μ gm) + Globulin (μ gm)		
1	10	100	1000	0.6	6	60	0.6 10	6 100	60 1000
++							±		
				—	—	+			
				—			+		
—	—	—	—	—	—	±	—	—	+
				—	—		—	—	++
				—	—	+	—	±	++
				—	—	±	—	—	++
—	—	—		—	—		—	—	—
+			+	—	—	—	—	—	+
±	—	—	+	+	+	—	—	—	+
±	+	±	++	±	+	±	±	+	+
—	—	—	++	—	—	—	—	—	—
±	—	±	++	—	—	±	—	—	+
++				±	—	±	±	+	++
—	—	—	—	—	—	—	—	—	++
—	±	—	+	—	—	±	—	—	±
++	±	±	++	±	±	—	±	±	±
—	—	±	++	—	—	++	—	—	±
—	—	—	+	—	—	—	—	—	+
—	—	—	+	—	—	—	—	—	—
—	—	—	+	±	—	—	—	—	++
—	—	—	++	—	—	—	+		

++ = Increase of wheal size by 4-5 mm.

response was obtained to smaller doses of globulin alone. It is possible that these are a manifestation of the nonspecific vascular reactivity which others (*Kalz & Pritchard, 1952*) have noted to follow penicillin therapy. In view of this abnormal reactivity the positive tests to penicillin or APA given by these five patients are of questionable significance.

Because of this we felt also that the enhancement of penicillin tests by globulin which *Rajka & Vincze* obtained should be interpreted with caution.

Excluding these five doubtful cases, six (Cases 2, 3, 6, 10, 16, 19) out of fifteen subjects gave positive reactions to peni-

cillin and of these four were also positive to APA. Nine out of fifteen were negative to penicillin and of these one reacted to APA.

From this series of tests we have concluded:

1. That intradermal immediate reactions to penicillin and penicillin-globulin conjugates must be interpreted with great care and are indeed of doubtful value as an indication of specific penicillin allergy.
2. That with these considerable reservations it appears that subjects who have become hypersensitive to penicillin have often become hypersensitive to the nucleus of the penicillin molecule. When this is so, cross-allergy to various other penicillins must be anticipated.

SUMMARY

Intradermal tests have been made with penicillin and 6-amino-penicillanic acid alone and with gamma globulin in an attempt to assess cross-sensitivity.

Twenty patients who had shown penicillin allergy were tested.

Of the total, nine gave negative reactions to penicillin, five gave false positives and six were positive; of these, four also reacted to 6-APA, suggesting cross-sensitivity.

We are indebted to Dr. W. d'A. Maycock of the Lister Institute, Elstree, for supplies of gamma globulin, and to Beecham Research Laboratories Ltd. for supplies of 6-APA.

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