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PENICILLIN HYPERSENSITIVITY AND HAEMAGGLUTINATING ANTIBODIES IN WORKERS AT A PENICILLIN FACTORY

By

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The detection of hypersensitivity to penicillin has frequently been the object of research. This problem was usually approached by means of classic (1, 2, 6, 17, 18, 19, 20, 24, 29, 30) and modified (1, 2, 18, 20) skin testing, such as Prausnitz-Küstener reaction—direct (2, 13, 20) and reversed (2, 20), and also the haemagglutination test (3, 4, 5, 9, 12, 15, 19, 24, 25, 27, 29), the P.C.A. (23), the basophil degranulation response (18, 22), and the thrombocyte test (2, 9, 10, 16).

Other authors have in their investigations used compounds of similar chemical structure like 6APA (6-amino penicillanic acid) (1, 15, 22), and penicilloyl residue (8, 21, 24, 26, 27, 28, 29) instead of penicillin itself. Most of the studies on penicillin allergy was carried out on individuals previously treated with this antibiotic and on animals experimentally sensitized.

This paper describes a comparative study on the frequency of positive skin reactions to penicillin and the occurrence of penicillin haemagglutinating antibodies in the sera of individuals employed in the production of penicillin.

METHODS

1. *Material.* The population studied consisted of 331 workers employed in a penicillin factory. The series included 86 allergic cases, mainly with contact ec-

zema (79 persons), urticaria (6 persons) and bronchial asthma (1 person). Most of these individuals have never been treated with penicillin.

Under conditions existing in the production departments of the plant, the antibiotic could penetrate the organism through skin and/or the respiratory tract.

The degree of penicillin contamination of the air was unequal in the different sections of the plant. The departments in which the air contained more penicillin dust are hereafter referred to as "dusty".

2. *Haemagglutination Test* was performed using the method of *Ley et al.* (1958). Human group O, Rh(—) blood was mechanically defibrinated and centrifuged to obtain erythrocytes, which were then washed three times in physiological saline. 0.1 ml of the washed erythrocytes was added to 0.9 ml of saline containing 25,000 units of penicillin G and incubated in a water bath of 37° C for one hour, being frequently stirred.

The penicillin sensitized erythrocytes were washed three times in saline to remove the unadsorbed penicillin and resuspended in saline to a 2 per cent concentration.

The sera dilutions in saline ranged from 1:2 to 1:128, and 0.1 ml of each dilution was treated with 0.05 ml of the sensitized erythrocytes. The tubes were gently shaken to mix the contents, stored at room temperature for one hour and centrifuged for 2 minutes at 700–800 rpm. The results were read through a magnifying glass.

A control test was performed with each serum using erythrocytes that were not sensitized with penicillin. The known negative serum was always used as the kontrol, whereas the known positive serum was used only in some assays.

3. *Skin Tests* were made by means of an intracutaneous injection of 100 units of penicillin G in 0.1 ml of saline.

The results were read after 30 minutes (immediate reaction) and after 24 hours (delayed reaction).

RESULTS

1. *Immediate and Delayed Skin Reactions.*

The results of skin tests with penicillin in the group of individuals studied are summarized in Tables 1 and 2.

TABLE 1
Immediate Skin Reactions to Penicillin in the Workers of a Penicillin Factory.

	No. examined	Skin reactions			Total no. of positive skin reactions
		Negative	Weakly positive	Strongly positive	
Healthy workers	245	237	8	—	8
Allergic cases	86	78	6	2	8

TABLE 2
Delayed Skin Reactions to Penicillin in the Workers of a Penicillin Factory.

	No. ex- amined	Skin reactions			Total no. of positive skin reactions
		Negative	Weakly positive	Strongly positive	
Healthy workers	245	237	8	—	8
Allergic cases	86	79	5	2	7

As shown in the above tables, the positive skin reactions, both immediate and delayed were seldom seen in the population studied, and although they were relatively more frequent among workers with an allergic disease, even in this group an overwhelming majority of tests gave a negative reaction. It should be emphasized, however, that the positive immediate and delayed reactions may be found in clinically healthy individuals. In our series we observed 8 immediate and 8 delayed positive skin tests. The positive skin reactions which are not associated with any clinical symptoms may be quoted as a classic example of latent allergy.

Two cases of eczema reacted to intracutaneous penicillin with an exacerbation of the existing lesions. We consider this as a typical focal reaction characteristic of delayed allergy.

2. *Haemagglutination Test with Penicillin.*

Penicillin haemagglutinating antibodies demonstrable in this test, have been found in the sera of 14 individuals who constitute 4.23 per cent of the population studied. The relevant titres are shown in Table 3.

Table 4 contains reference regarding the occurrence of penicillin haemagglutinins in relation to clinical symptoms, and Tables 5 and 6 in relation to the results of the intradermal skin tests with penicillin.

The haemagglutinating antibody titres (of the penicillin factory employees examined for penicillin antibody) have generally been low, the highest being 1:32 (Table 3). They

TABLE 3

Penicillin Antibody Titres in the Haemagglutination Test with Penicillin.

No. examined	No antibody detected	Highest antibody titres						
		1:2	1:4	1:8	1:16	1:32	1:64	1:128
331	317	0	7	3	3	1	0	0

TABLE 4

The Occurrence of Penicillin Haemagglutinins in Relation to Allergic Manifestations.

	Total no. examined	Penicillin antibodies in the serum		Highest antibody titre
		Present	None	
Allergic cases	86	4	82	1:16
Healthy individuals	245	10	335	1:32

TABLE 5

The Occurrence of Penicillin Haemagglutinins in Relation to the Immediate Skin Reactions.

		Total no. examined	Penicillin antibodies in the serum		Highest antibody titre
			Present	None	
No. of individuals with immediate skin reactions	Positive	16	1	15	1:8
	Negative	315	13	312	1:32

TABLE 6

The Occurrence of Penicillin Haemagglutinins in Relation to the Delayed Skin Reactions.

		Total no. examined	Penicillin antibodies in the serum	
			Present	None
No. individuals with delayed skin reactions	Positive	15	0	15
	Negative	316	14	302

were not higher in the allergic cases as compared with the healthy individuals, and also the percentages of individuals producing penicillin haemagglutinating antibodies are similar in both groups (Table 4).

The data compiled in Tables 5 and 6 do not indicate the existence of any possible relationship between the occurrence of penicillin haemagglutinins and the frequency of immediate and delayed skin reactions to penicillin.

3. *Exposure to Penicillin Dust in Relation to the Frequency of Positive Skin Reactions and the Occurrence of Haemagglutinins.*

a. The Period of Employment: The data presented in Table 7 suggest that no correlation exists between the period of employment of all the individuals examined in the course of this study and the frequency of positive skin reactions as well as the occurrence of penicillin haemagglutinating antibodies.

TABLE 7

The Influence of the Period of Employment in the Penicillin Factor Upon Hypersensitivity to Penicillin and the Production of Penicillin Haemagglutinins.

Years	No. workers employed	% of workers with			
		Allergic disease	Positive skin reactions		Penicillin haemagglutinins
			Immediate	Delayed	
1947-51	48	46.16	2.08	2.08	0
1952-55	60	28.33	3.33	3.33	3.33
1956-59	103	34.95	10.67	6.79	4.38
1960-63	93	20.43	4.3	3.21	3.21

b. Penicillin Contamination of Air in the Production Departments: The influence of the penicillin contamination of air in the factory upon phenomena under discussion is shown in Table 8.

TABLE 8

The Relationship Between the Penicillin Contamination of Air and Hypersensitivity to Penicillin and the Occurrence of Penicillin Haemagglutinins.

Departments	No. of workers	% of workers with			
		Allergic disease	Skin reaction		Penicillin haemagglutinins
			Immediate	Delayed	
"Dusty"	231	35.45	17.35	5.62	3.08
Other	73	16.43	0	0	6.84

Whereas the frequency of positive skin reactions to penicillin depends upon the degree of air contamination with this antibiotic, there seems to exist no corresponding relationship between the occurrence of haemagglutinating penicillin antibodies in the contamination of air.

DISCUSSION

The results obtained in our study could not significantly be affected by previous treatment with penicillin as only 3 persons with positive skin reactions reported previous penicillin treatment and out of 14 persons whose sera contained anti-penicillin haemagglutinins only one person had received treatment with penicillin over a short period of time. It seems therefore, that the immunological phenomena described may have resulted from exposure to the allergen under the working conditions in the factory.

We have demonstrated that exposure to penicillin under the production conditions may in consequence lead to:

a. — *Allergic Diseases.*

In our material this has mainly been contact eczema (and as such resulting from the delayed allergy).

In a part of these cases there has been seen occasional coincidence of an immediate skin reaction or the presence of penicillin haemagglutinating antibody in the serum.

In the group of workers suffering from allergic diseases the significance of exposure to the allergen has been evident (Tables 7 and 8).

b. — *Positive Skin Reactions.*

The frequency of positive skin reactions has been greater in the group of allergic cases, however, positive immediate and delayed skin reactions were also observed in healthy individuals.

The positive skin reactions were found only among workers employed in the "dusty" departments, but their frequency did not increase in proportion to the period of employment.

There is some correlation between the frequency of positive skin reactions and exposure to the allergen, although this relationship is not as clear as in the case of allergic diseases.

c. — *Production of Haemagglutinins.*

The frequency of occurrence of the penicillin haemagglutinating antibodies in the serum has almost been the same in both healthy and allergic individuals, and the highest titre obtained in our study was that with the serum of a healthy person (1:32). In our series the occurrence of anti-penicillin haemagglutinins showed no traceable relationship with exposure to the allergen. There has neither been any increase in the percentage of persons with penicillin haemagglutinating antibodies depending upon the period of their employment, nor has it been higher in workers employed in the "dusty" departments. It may therefore be assumed that the production of anti-penicillin haemagglutinins does to a large extent depend upon constitutional factors.

SUMMARY

1. Positive skin reactions to penicillin are seen only in a small proportion of individuals with allergic diseases in 331 workers employed in the production of penicillin.
2. Positive skin reactions can also be found in healthy em-

ployees although their frequency is considerably smaller than in the allergic group.

3. Low titres of penicillin haemagglutinating antibody have been detected in the sera of nearly 5 per cent of all the individuals studied.

The frequency of their occurrence in the workers with contact eczema was not greater as compared with the group of healthy individuals.

4. No correlation exists between the occurrence of penicillin haemagglutinating antibodies and the results of skin testing.

5. The period of employment exerts no traceable influence on the production of penicillin haemagglutinins and the frequency of positive skin reactions.

6. The percentage of positive skin reactions evidently depends upon the degree of penicillin contamination of the air at the factory.

No such relationship could be found in the frequency of the haemagglutinating antibody.

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