

Penicillin Reactions: Analysis of a WHO Questionnaire*

by R. R. WILLCOX, M.D., *Consultant, Venereal Disease and Treponematoses Section, World Health Organization, Geneva, Switzerland*

In order to obtain some information concerning the incidence of penicillin reactions, a questionnaire was sent in December 1956 to members of the WHO Advisory Panel on Venereal Diseases and Treponematoses. Thirty replies were received relating to venereal diseases clinics in the following countries and referring in the main to large centres in urban areas: Argentina, Austria, Ecuador, Egypt, Finland, France, Greece, India, Indonesia, Iran, Iraq, Ireland, Israel, Mexico, Panama, Santa Lucia, Singapore, Trinidad, Venezuela, the United Kingdom and the USA.

Figures from 25 centres indicated that at least 2 342 000 persons had been treated with penicillin in the clinics concerned during the years 1952-56. The numbers of penicillin injections given per patient varied from one to 25.

Incidence of penicillin reactions. Reaction rates of 2% or less of patients were recorded for the five-year period (in a few instances for shorter periods of time) in: Santa Lucia (0); Singapore (0.02%); Indonesia (0.09%); Israel (0.5%); India (0.5%); Panama (0.8%); Austria (0.9%); Finland (0.9% in one series and 0 in another); USA (1.5%); Egypt (2.0%); Greece (2.0%); and Mexico (2.0%).

Reaction rates above 2% were noted in Iran (0.5% serious plus 2.0% mild) and in France (3.7% and 5.0%). For the countries not mentioned, no answer was received to this part of the questionnaire. Variations were doubtless due to differences in definition of reactions. In some cases it is probable that only serious reactions were recorded, in others that only milder ones were included.

The report from Madras, India, for the years 1953-56 states that 83 reactions occurred in 21 747 patients treated (0.38%). The number of injections was stated to be 102 550. The reaction rate for injections was thus 0.8 per 1000.

Twenty-eight replies to the question whether there was any difference in the incidence of reactions in children or adults were received, of which 19 were negative and nine were affirmative. The wording of the question

* This inquiry was preliminary to a wider study of the question undertaken by or on behalf of WHO: O. Idsøe and P.-N. Wang report on penicillin-sensitivity reactions in Taiwan on page 323 of this issue; R. R. Willcox and G. R. Fryers have published an account of similar reactions in a British venereal disease clinic (*Brit. J. vener. Dis.*, 33, 209); and a full review of the literature on untoward penicillin reactions, by T. Guthe, O. Idsøe and R. R. Willcox, will appear in a forthcoming number of the *Bulletin of the World Health Organization*.

did not encourage further elucidation, but some participants noted that the patients with reactions were all adults (Turku, Finland; Trinidad; Austria) or that the incidence of reactions was less in children (Iran; New York, USA; and United Kingdom), and others (e.g., Argentina; and Bordeaux and Paris, France) that there had been little opportunity to treat many children.

Participants were asked to state which type of reaction ("eczematous"; "serum-sickness-like symptoms" or "anaphylactic reactions") was relatively the most frequent. Some difficulty was experienced in placing temperature rise and urticaria, which may account for the striking lack of agreement expressed. Of 26 replies, 10½^a chose "eczematous manifestations" as the most common, 11 chose "serum-sickness-like symptoms" and 4½^a chose "anaphylactic symptoms". One participant (Santa Lucia) referred to "local abscess formation from inability to absorb the drug".

TABLE 1. TREND IN INCIDENCE OF PENICILLIN REACTIONS

Country	Reaction rates (% of patients)					Trend
	1952	1953	1954	1955	1956	
Argentina	2.2	nil	1.5	nil	nil	decrease
Ecuador	0.5	0.5	1.0	1.0	1.0	stationary
Egypt	2.0	2.0	3.0	1.0	nil	decrease
Finland (Turku)	nil	1.6	nil	0.6	2.3	increase
Finland (Helsinki)	nil	nil	nil	nil	nil	stationary
France	4.0	5.0	5.0	6.5	8.0	increasing
Greece	2.5	2.0	2.0	1.5	2.4	stationary
India	NA	0.01	0.03	1.2	1.2	increase
Iraq ^a	0.002	0.001	0.002	0.003	nil	decrease
Ireland	NA	NA	1.65	3.55	2.44	stationary
Indonesia	NA	nil	nil	0.059	0.19	increasing
Mexico	1.0	1.0	1.5	2.0	3.0	increasing
Panama	1.0	1.0	0.8	0.7	0.6	decrease
Santa Lucia	NA	NA	0.9	0.18	0.27	increasing
Singapore	0.03	nil	0.012	0.027	0.024	stationary
Venezuela	3.0	4.0	4.0	6.0	7.0	increase
USA (New York)	NA	NA	NA	0.37	0.19	decrease ^b

NA — Not available.

^a The figures for Iraq refer to reaction rates based on percentage of injections and not of patients.

^b See text, page 460.

^a The halves are accounted for by an equal frequency being given to two groups in one instance.

TABLE 2. DEATHS FROM PENICILLIN REACTIONS *

Country of clinic	Cases treated in 5 years	Number of deaths	Deaths per 1000 patients
Argentina	281	nil	—
Austria	1 476	nil	—
Ecuador	1 200	nil	—
Finland	1 981	nil	—
France	25 986	nil	—
Greece	1 000 ^a	nil	—
India	24 000 ^b	2	0.83
Indonesia	40 245	nil	—
Iran	25 000	3	0.12
Israel	25 300	1 ^c	0.039
Mexico	196 152	1	0.005
Panama	16 800	nil	—
Santa Lucia	21 300	nil	—
Singapore	100 000 ^a	1 ^d	0.01
Trinidad	35 830	nil	—
United Kingdom	15 000 ^a	nil	—
USA	95 000 ^a	1	0.01
	626 551	9	0.014

* Where there has been more than one valid return from a country, cumulative figures are given.

^a Approximate figure

^b A minimum figure

^c In a known asthmatic

^d Plus two cases of Herxheimer reaction in congenital syphilitics

The question, "Have reactions occurred following the first penicillin injection?" could have been taken to include Herxheimer reactions. The participant from Singapore said "Yes" and quoted two such examples. It is possible that others who replied in the affirmative also had Herxheimer reactions in mind. Seventeen participants replied "Yes" and ten replied "No".

Twenty persons stated that reactions were more frequent after repeated injections, seven stated the contrary, and three did not reply. Whether the mild and serious reactions are more frequent with one particular preparation was a difficult question to answer. A number of participants indicated that reactions were most common after a particular preparation because this was the preparation in routine use. Eight participants replied in the negative and of 13 replying in the affirmative, seven named PAM (although

this was sometimes the only preparation used), three named procaine penicillin, two aqueous crystalline penicillin and one benzathine penicillin. The only conclusion which can be drawn from this is that reactions *may* occur from all of the penicillin preparations mentioned.

Trend in incidence of reactions. Only 16 countries were able to give the reaction rates over a number of years. These are presented in Table 1.

The apparent decrease in the New York figures is stated to be due to the more careful questioning of patients regarding sensitivity during 1956, and to the increasing use of other antibiotics in the place of penicillin when sensitivity was suspected. In 1956, 3.2% of the 3263 patients treated for syphilis were given oxytetracycline orally instead of penicillin.

Thus of the series of 17 presented from 16 countries an increase in the numbers of penicillin reactions was noted in eight, a stationary situation in five and a decrease in four. To the straight question "Do you think the frequency of untoward penicillin reactions has increased during the last five years?", there were 27 replies. Of these 13 were a definite "Yes", two a doubtful "Yes", and 12 a "No".

Deaths following penicillin injections. In Table 2 the reported numbers of deaths are related to the total numbers of patients treated in clinics concerned.

From the way the questionnaire was worded the fatalities could have arisen from any type of penicillin reaction, not merely anaphylaxis. One participant returned two deaths from the Jarisch-Herxheimer reaction in congenital syphilis. It is likely, but not certain, that deaths from this cause were omitted by others. On the other hand, it is conceivable that some of the recorded deaths could be due to the Herxheimer reaction. It is probable, however, that the great majority of deaths were due to anaphylaxis.

The probable death-rate from penicillin sensitivity was thus 1 per 69 600 cases treated, or 0.014 per 1000.

Skin tests. Ten participants stated that they used skin tests, while 19 said not. Of the 10 using the skin tests one did not give an opinion on their value and one had not used them recently. Of the eight remaining, five found them of no value, and three found them of some value, naming the intracutaneous test and scratch test, intracutaneous test, and patch test, respectively.