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AN EVALUATION OF THE INCIDENCE OF REACTIONS TO PENICILLIN*†

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Penicillin is the principal weapon in our fight against syphilis and gonorrhoea. Rumours of increases in the incidence and severity of reactions to penicillin are viewed with concern, for apprehension on the part of physicians charged with the responsibility of treating venereal disease patients could adversely affect the control programme. It was this concern which instigated a study of penicillin reactions which was conducted by the Public Health Service in 1954 with the cooperation of 24 treatment facilities representing fourteen states (Smith, Cutler, and Price, 1955).

During the intervening 5-year period some deaths attributable to penicillin have been reported. In fact, a review of the death certificates in one State (Thorner and Bond, 1958) revealed that penicillin was a contributory cause of death in nine persons in that State alone in 1958. In the past several years deaths have also occurred in venereal disease treatment clinics.

Are we merely more conscious of the risk involved in penicillin therapy or is the population becoming sensitized to penicillin? The vast amounts of penicillin marketed each year in the United States would indicate that few have escaped penicillin either as treatment for some ailment or through dairy products or other food.

With the 1954 study providing an excellent baseline for evaluating the present situation, a second reaction study, currently in progress, was initiated in March, 1959. The two studies are identical in design; the same study card (revised to include the total amount of penicillin and number of injections of the planned schedule) is being used; and, as before, no special follow-up was requested but patients were instructed to report to the clinic if complaints attributable to penicillin therapy were experienced. The only departure from the previous procedure was a request to clinics to detain patients for approximately 30 minutes after treatment to avoid the risk of anaphylactoid reactions occurring on the street.

The numbers of cases treated in the two surveys were approximately the same—20,687 in 1959, and 19,510 in 1954 (Table I, opposite). The reaction rate in the current series, however, is 67 per cent. higher than in 1954—9·96 as compared with 5·95 per 1,000 cases treated.

Treatment clinics were requested to classify reactions as urticaria, anaphylaxis, serum sickness, or other. In 1959, reactions classified as urticaria were observed in 5·90 per 1,000 treated as compared with 4·92 in 1954. Listed in Table I immediately under urticaria are other dermatological conditions which were classified as "other" on the reaction card; 22 reactions in 1959 were listed as generalized pruritus or angioneurotic oedema, but only two reactions had been so classified in 1954. It is quite possible that such reactions were considered as urticaria in 1954, but it could well be that the requested half-hour period of observation after the injection gave an opportunity to abort urticarial reactions by treating these early symptoms. In 1959, 51 per cent. of the reactions were reported as occurring on the first day of treatment; in 1954, only 16 per cent. had occurred on the first day.

This closer observation immediately after treatment undoubtedly reflects the number of anaphylactoid reactions observed—nineteen in 1959, only four in 1954. Seven of the nineteen, on the basis of the signs and symptoms reported, appeared to be moderate to severe in character. Roughly one in every 3,000 treated in 1959 and one in every 5,000 treated in 1954 suffered a definite anaphylactic reaction. The other twelve, described principally as cases of syncope, nausea, and chills, could have been overlooked without close observation.

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TABLE I

COMPARATIVE FREQUENCY OF REACTIONS TO PENICILLIN IN 1959 AND 1954

Type of Penicillin Reaction		1959 Study		1954 Study	
		Number	Rate/1,000	Number	Rate/1,000
Total Cases Treated		20,687		19,510	
Total Cases Reacting		206	9·96	116	5·95
Chief Reactions Noted	Urticaria	122	5·90	96	4·92
	Pruritus, generalized	17	·82	2	·10
	Angioneurotic oedema	5	·24	—	·00
	Dermatitis medicamentosa	4	·19	5	·26
	Erythema multiforme	1	·05	1	·05
	Dermatophytid	1	·05	1	·05
	Total	150	7·25	105	5·38
	Anaphylaxis	19	·92	4	·21
	Moderate to severe	7	·34	4	·21
	Mild	12	·58	—	—
	Serum Sickness	9	·44	5	·26
	Gastro-intestinal (nausea, vomiting, abdom. pain)	12	·58	1	·05
	Vertigo, syncope	15	·73	—	·00
	Chills, fever, headache	9	·44	—	·00
	Chest pain, dyspnoea	2	·10	2	·10
	Hysteria	1	·05	—	·00

Serum sickness was also observed more frequently in the present series—0·44 compared with 0·26 per 1,000 treated. Miscellaneous reactions, not associated with urticaria, anaphylaxis, or serum sickness—gastro-intestinal symptoms, vertigo, etc.—were also observed more frequently in the present series.

A sample of 14,065 of the 20,687 records received to date have been tabulated by the factors which were shown to influence the rate of reactions in our 1954 study (Table II). The reaction rate in the sample is 9·8 per 1,000 as compared with 9·96 in the total group. Principal categories only are shown, so that

TABLE II

COMPARATIVE FREQUENCY OF REACTIONS TO PENICILLIN IN 1959 AND 1954, BY VARIOUS FACTORS KNOWN TO INFLUENCE THE RATE

Classification			1959 Study			1954 Study		
			Total Cases	Cases Reacting		Total Cases	Cases Reacting	
				Number	Rate/1,000		Number	Rate/1,000
Grand Total			14,065	138	9·8	19,510	116	5·9
Reason for Treatment	Epidemiologic Treatment		3,637	22	6·0	3,757	10	2·7
	Gonorrhoea		8,726	46	5·3	12,026	29	2·4
	Syphilis		1,624	67	41·3	3,442	77	22·4
Type of Penicillin	Procaine penicillin G in oil		5,707	67	11·7	12,179	97	8·0
	Benzathine penicillin G		3,347	42	12·5	7,109	17	2·4
Dosage Schedule	Single-session		11,983	75	6·3	17,710	51	2·9
	2 to 7-day		1,162	23	19·8	694	14	20·2
	8 days or more		920	40	43·5	1,106	51	46·1
Previous Treatment	Previous penicillin:							
	Reacted		104	11	105·8	121	12	99·2
	Did not react		12,008	109	9·1	14,214	56	3·9
	No previous penicillin		1,511	10	6·6	3,750	34	9·1
Race and Sex	White	Male	1,096	14	12·8	965	7	7·3
		Female	1,088	17	15·6	670	7	10·4
	Negro	Male	6,770	48	7·1	9,548	32	3·4
		Female	5,057	59	11·7	7,738	51	6·6
Age (yrs)	10–19		3,031	12	4·0	3,908	12	3·1
	20–29		6,741	53	7·9	9,512	37	3·9
	30–39		2,586	29	11·2	3,674	34	9·3
	40–49		857	22	25·7	1,252	21	16·8
	50 and Over		597	22	36·9	1,012	11	10·9

the totals in the groups do not necessarily agree with the grand total.

As in 1954, the highest reaction rate is found in patients treated for syphilis, the lowest in those treated for gonorrhoea. Unfortunately, the 1954 study failed to include in the questionnaire the amount of penicillin administered. It was reasoned that patients sensitive to the drug would react to small doses as readily as to large doses. This was fallacious reasoning, for in our current study the reaction rate increased from 4·5 per 1,000 treated with 1,200,000 to 2,400,000 units to 46·2 per 1,000 treated with 4,800,000 units or more. The difference in treatment schedules readily explains the apparent differences in the diagnostic groups. Changes in treatment schedules in the United States during the last 5 years could also account for the increased incidence of reactions. The standard penicillin dose for gonorrhoea in 1954 was 600,000 units. In the 1959 sample, 1,600 patients were given less than 1,200,000 units and 9,000 were treated with 1,200,000 to 2,400,000 units.

In 1954 it appeared that patients tolerated benzathine penicillin G better than procaine penicillin in oil (PAM). In the current series, the rates are practically the same, 11·7 for PAM and 12·5 for benzathine penicillin. Here again dosage schedules have changed in some clinics with doses of 4,800,000 to 9,600,000 units replacing the standard 2,400,000 benzathine dose employed in 1954. When the comparison is limited to those treated with 1,200,000 to 2,400,000 units, the reaction rates are 4·5 for benzathine penicillin, 5·1 for PAM, and 4·0 for these two types combined. 4,000 patients were given combined therapy in the above dosage; this was a schedule designed to produce both an initial high and a prolonged blood level for patients with gonorrhoea.

It is interesting that, when schedules are tabulated by duration, the reaction rates for the two studies differ significantly only in the single-session group. This is further evidence that more reactions were recorded because the patients were detained longer after receiving the injection.

It is the practice in most clinics to treat with other drugs patients who have previously shown sensitivity to penicillin. Therefore, few cases in either study fall into this classification. In both series approximately 10 per cent. of such patients experienced reactions—105·8 per 1,000 in 1959 and 99·2 per 1,000 in 1954, Of the 104 treated in 1959, 45 were given concomitant antihistamine therapy. The incidence of reactions in the group was less than half of that observed in the group without concomitant treatment—66·7 compared with 135·6 per 1,000.

In 1954 it appeared that patients who had previously tolerated penicillin were less apt to react than patients who as far as was known had never been treated with penicillin. In the present series the reverse of this appears to be the case. The difference observed in 1954 between 3·9 and 9·1 was statistically significant at the 5 per cent. level. In the 1959 series the difference between 9·1 and 6·6 is not significant.

The 1959 study confirms the race-sex differences observed in 1954. Namely, the incidence of reactions is higher among females in both races and higher among white, in both sexes—or highest in white females and lowest in Negro males.

It appears in both series that the incidence of reactions increases with age. The age factor, however, is complicated by the amount of treatment administered. The young patients, in general, represent cases of gonorrhoea and low dosage schedules, while the older patients represent cases of syphilis and high dosage schedules. When limited to epidemiological treatment or treatment for gonorrhoea, the age differences are much less striking. The rates are 3·6, 5·6, and 6·4 per 1,000 for the three 10-year age groups between 10 and 40, the only three with sufficiently large numbers for comparison.

No deaths occurred during the period covered by the study in 1954, and to date, no deaths have been reported in the present series. Because of the large numbers of patients at risk in venereal disease treatment centres, emphasis has been placed on preparedness. Clinicians have been urged to have therapeutic materials and supplies ready for immediate use so that fatal reactions may be averted.

Summary and Conclusions

In 1954 the Public Health Service conducted a study of penicillin reactions in venereal disease treatment centres in the United States. With this 1954 study serving as a baseline, a similar study is currently in progress to determine whether there has been an increase in the incidence and severity of reactions to penicillin.

Data accumulated to date from more than 20,000 venereal disease patients suggest that the incidence of reactions is greater now than in 1954. It is believed, however, that this increase is more apparent than real, for at least two factors operating in the present study would tend to increase the number of reactions observed. First, as a safeguard, treatment centres cooperating in the present study were requested to detain patients in the clinic for 30 minutes after treatment. Possibly as a result of this

one change, 51 per cent. of the reactions reported were seen to occur on the first day of treatment. In 1954, only 16 per cent. occurred on the first day. As further evidence of the effect of this 30-minute observation period, the increase over 1954 was noted only in patients treated on single-session schedules.

The second factor is the increase since 1954 in the standard 600,000-unit dosage for gonorrhoea. The majority of the patients in the present series were treated with 1,200,000 or 1,800,000 units of penicillin, and some clinics were using schedules as high as 2,400,000 units for uncomplicated gonorrhoea.

Taking these two factors into consideration, the higher incidence of reactions reported in 1959 is in no way alarming and no essential changes in the present treatment practices seem to be indicated.

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Evaluation de la fréquence des réactions à la pénicilline

Résumé

En 1954 le Service de Santé Publique avait procédé à une enquête sur des réactions à la pénicilline dans les centres de traitement des maladies vénériennes aux Etats Unis. Avec l'enquête de 1954 comme ligne de repere, on en procède maintenant à une autre, pour déterminer si la fréquence et la sévérité des réactions à la pénicilline aient augmenté.

Des données recueillies jusqu'à présent de plus de 20.000 malades atteints de maladies vénériennes suggèrent que la fréquence des réactions est plus grande maintenant qu'en 1954. On croit, cependant, que cette augmentation est plus apparente que réelle, car il y a au moins deux facteurs opérant dans l'enquête présente et tendant à augmenter le nombre des réactions observées. Tout d'abord, comme précaution, on avait demandé aux centres de traitement participant à cette enquête de retenir les malades à la clinique pendant 30 minutes après le traitement. Probablement comme conséquence de cette mesure, 51% des réactions signalées furent observées le jour du traitement. En 1954, seulement 16% des réactions survinrent au premier jour. Une autre preuve de l'effet de cette période d'observation de 30 minutes est offerte par le fait que l'augmentation par rapport à 1954 fut notée seulement chez des malades traités par la méthode d'une seule visite.

Le deuxième facteur est représenté par l'augmentation depuis 1954 de la dose habituelle de 600.000 unités contre la blennorragie. La majorité des malades dans la série présente furent traités par 1.200.000 ou 1.800.000 unités de pénicilline, et certaines cliniques allaient même jusqu'à 2.400.000 unités pour une simple blennorragie.

En prenant en considération ces deux facteurs, la fréquence augmentée des réactions rapportée en 1959 n'est pas terrible et des modifications essentielles des méthodes présentes de traitement ne sont pas indiquées.