THE EVOLUTION OF SYPHILIS AFTER SMALL DOSES OF PENICILLIN: A CRITICAL SURVEY

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The early work of Mahoney and others (1943) demonstrated that penicillin in doses of 60,000 to 100,000 units would produce rapid but temporary healing of primary syphilitic lesions. Even local applications of penicillin will destroy surface spirochaetes and may hinder the recognition of syphilitic disease (Cronin, 1946). What, so far, has not been adequately determined is whether 100,000 units of penicillin administered during the incubation period of syphilis delays the appearance of the primary chancre and a positive blood test; and, if they are so delayed, what reasonable period of surveillance is necessary to exclude their later occurrence. This problem is not restricted to venereal infection alone, but applies to any medical or surgical condition in which penicillin is used in similar amounts. How great is the risk of masking a syphilitic infection which may appear months or years hence? Can we ignore this risk completely, or is it necessary to subject our patients to interminable blood tests extending over an indefinite period of time?

The literature abounds with many personal opinions, but with little positive evidence. Canizares (1944) advises that patients who have received 100,000 units of penicillin for gonorrhoea should have blood tests done at intervals for 1 year "and preferably longer." Lydon and Cowe (1945) think a period of surveillance for 2 years is necessary. Allan (1946) urges blood tests during a period of 12 months. The administrative instructions in the British Army require a 6 months' surveillance. Magnusen and Eagle (1945), basing their views on rabbit experiments, consider a minimum follow-up of 4 months to be essential. From this welter of contradictory statements, having little clinical data to support them and purely arbitrary in character, it is impossible to reach

any definite conclusion. One must examine the cases recorded to see what justification, if any, there is for these views.

In a previous communication (Cronin, 1945), 10 cases of gonococcal infection were reported which had been treated with 100,000 to 150,000 units of penicillin and in which syphilis subsequently developed without any intervening exposure. In all these cases a primary syphilitic lesion appeared within 3 months of treatment, associated with varied blood test results. Since then, 19 further cases have been seen and the relevant details are given in Table I, which shows that 17 of these 19 cases developed a primary chancre and 1 a secondary syphilide within 3 months of penicillin therapy. One case of secondary syphilis occurred after this period.

Discussion

Many apparent examples of the delay caused by penicillin in the appearance of syphilitic lesions have been reported. In several of them penile lesions were already present before penicillin administration, but they were either not seen, were undiagnosed, or were dark-ground negative. As was to be expected from the work of Mahoney and others already referred to, these lesions rapidly disappeared after penicillin therapy, but they either reappeared after an interval, or else were succeeded by positive blood tests and secondary syphilides. These cases, while interesting and informative in showing that small doses of penicillin may alter the natural evolution of syphilitic disease, are not strictly germane to the immediate problem under discussion. The salient features are presented in Table II.

Some of the cases that remain have been excluded from further review. In case 2 of Ricchiuti's (1944) report, the diagnosis of

TABLE I

INCUBATION PERIOD AND STAGE OF SYPHILIS DEVELOPING AFTER THE TREATMENT OF GONORRHOEA WITH PENICILLIN (PERSONAL CASES)

Case No.	Time in days from		Units of penicillin given	Probable incubation period in days	Kahn result	Clinical notes
	exposure to penicillin treatment	penicillin treatment to clinical lesion				
1	18	34	100,000	52	—	Primary chancre
2	13	36	100,000	49	—	Primary chancre
3	10	61	100,000	71	+++	Acute phimotic balanitis for preceding 2 weeks
4	15	35	100,000	50	+++	Primary chancre
5	3	36	100,000	39	+++	Primary chancre
6	5	36	150,000	41	—	Primary chancre
7	5	26	200,000	31	—	Primary chancre
8	10	142	100,000	152	++++	Maculo-papular syphilide (rash 3 weeks)
9	3	69	100,000	72	++++	Macular syphilide (scabies with non-healing penile ulcers 52 days after treatment)
10	5	61	100,000	66	+++	Primary chancre
11	9	16	100,000	25	—	Primary chancre
12	6	43	100,000	49	+	Primary chancre (ulcers of penis for 3 weeks)
13	6	39	100,000	45	—	Primary chancre
14	12	36	100,000	48	—	Primary chancre
15	5	41	100,000	46	—	Primary chancre
16	36	37	150,000	73	Doubtful	Primary chancre (non-healing chancroidal ulcers 1 week after treatment)
17	13	41	100,000	54	—	Primary chancre
18	27	55	60,000	82	+++	Primary chancre
19	5	10	100,000	15	+++	Primary chancre

TABLE II

RECRUDESCENCE OF SYPHILIS AFTER INITIAL INVOLUTION FOLLOWING PENICILLIN THERAPY FOR GONORRHOEA

Time in days from			Units of penicillin given	Clinical notes	Authors
last exposure to penicillin treatment	penicillin treatment to clinical lesion	penicillin treatment to positive blood tests			
41	28	28	100,000	Ulcers of penis first appeared 22 days after exposure. Blood tests and D.G.'s negative.	Hailey (1944)
32	23		50,000		Canizares (1944)
	57	57	100,000	Macular syphilide preceded by recurrence of penile ulcer for unknown period.	Shafer and Zakon (1944)
		16	100,000		Ricchiuti (1944)
30	26	59	80,000		Boyd, Wagner, and Hewson (1944)
18	31	41	50,000		Carpenter (1944)
	35	35	80,000	Macular syphilide, recurrence of scrotal papule 14 days earlier.	Walker and Barton (1945)
		10-14	125,000	Penile ulcer, D.G. negative after penicillin. Did not heal.	Van Slyke and Steinberg (1944)
		10-14	125,000	Penile ulcer, D.G. negative after penicillin. Did not heal.	Van Slyke and Steinberg (1944)
31		23-43	100,000		Baier and Pincus (1944)
		10	125,000		Case 2 of Steinberg and Immergut (1945)

TABLE III
INCUBATION PERIOD AND STAGE OF SYPHILIS DEVELOPING AFTER THE TREATMENT OF GONORRHEA WITH
PENICILLIN (PREVIOUSLY REPORTED CASES)

Time in days from		Probable incubation period in days	Units of penicillin given	Clinical notes	Authors
last exposure to penicillin treatment	penicillin treatment to clinical lesion				
31	25	56	100,000	Maculo-papular syphilide. Blood test positive.	Atcheson (1945)
	33		100,000	Ulcer of frenulum.	Van Horn and Dakin (1944)
	35		125,000	Primary chancre.	Steinberg and Immergut (1945)
	49		125,000	Maculo-papular syphilide. Blood test positive.	Steinberg and Immergut (1945)
13	69	82	100,000	Penile ulcer appeared 51 days after treatment.	Osmond (1945)
3	89	92	200,000	Primary chancre.	Frankland (1946)
7	65	72	200,000	Primary chancre. Blood test positive 5 days before positive D.G.	Batchelor, Donald, and Murrell (1946)
6	52	58	360,000	Primary chancre.	Batchelor, Donald, and Murrell (1946)
5	72	77	200,000	Primary chancre.	Batchelor, Donald, and Murrell (1946)
6	74	80	200,000	Seen 5 weeks later with florid secondary syphilis.	Batchelor, Donald, and Murrell (1946)

syphilis, though suspected, was never confirmed. In the series by Batchelor and others (1946) 3 cases appear inadmissible. In case 1, after at least 700,000 units penicillin, they report, "First appearance noted of indurated sore at urinary meatus, and of a scar in the coronal sulcus." In case 2 penicillin was given on May 22, and yet on May 23 they observe, "Indurated lesion on under surface of penis." In view of the domestic complications involved in case 6, it is extremely unlikely that the patient's statement is reliable.

The remaining case reports in which no genital lesions existed prior to penicillin administration are presented in Table III. In most of these cases, clinical and serological evidence of syphilis appeared well within three months of penicillin therapy. In very few cases has there been unchallengeable proof of delay beyond this period, and in these cases penicillin in amounts of 200,000 units or more was given.

Although the apparent incubation period in all the cases, where obtainable, is very variable, what is of interest is the large number in which the appearance of the first clinical lesions occurred approximately 4 to 6 weeks after penicillin. One might be led to conclude that any spirochaetes remaining after penicillin therapy develop as though they were a fresh inoculum at that time. Magnusen and Eagle's (1945) work on experimental syphilis in rabbits gives some support for this view.

In a few cases, a syphilide appeared as the first clinical sign more than 3 months after treatment. There is no necessary causal relationship in this, for "syphilis d'emblée" is well-known, and many cases have been seen amongst troops who never received penicillin, and who are notoriously bad observers of genital lesions, especially when these are painless and hidden by the prepuce.

Finally, amongst many thousands of cases under post-penicillin surveillance for gonorrhoea, none have been seen in which blood tests negative at 3 months became positive at 6 months without there being either an intermediate exposure or a vaccine inoculation which would account for it. In these latter cases the serological test was weakly positive and variable.

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Conclusions

There is no evidence that penicillin, in amounts up to 150,000 units, delays the appearance of syphilis for more than 3 months after treatment. Unnecessary psychological trauma and little benefit will accrue in extending surveillance beyond this period.

Where larger doses of penicillin are given, surveillance may require to be prolonged, but insufficient data is available to serve as a guide to its duration, since this is probably related to the amount of penicillin used.

Anyone administering penicillin, and particularly any practitioner assuming the responsibility of treating gonorrhoea with penicillin, should submit to careful examination any existing genital lesion, however little it may conform to the classical picture of a specific ulcer.

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