

Primary and secondary syphilis, 20 years' experience 3: diagnosis, treatment, and follow up

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SUMMARY The methods of diagnosis (dark ground microscopy and serology), treatment, and follow up of 946 patients with primary and 854 with secondary syphilis who presented to a London STD clinic between 1965 and 1984 were reviewed retrospectively. On dark ground microscopy spirochaetes typical of *Treponema pallidum* were seen in 673 (78%) of 884 patients with primary syphilitic chancres. Of the patients with primary syphilis, 137 (14.5%) had negative serology results at presentation. Eight (0.9%) of the patients with secondary syphilis had negative results at presentation, but seven of these gave positive results one month later. Procaine penicillin was the treatment used most, and erythromycin the commonest alternative. The Jarisch-Herxheimer reaction occurred more often after treatment with penicillin than with erythromycin or tetracycline ($p < 0.005$). In most patients the Venereal Diseases Research Laboratory (VDRL) test showed a consistent fall in titre after treatment; a small proportion, however, continued to give positive results (some at a high titre) with no other evidence of reinfection or treatment failure.

In the first two parts of this study we reviewed the epidemiological and clinical features of patients seen at the Middlesex Hospital between 1965 and 1984 with primary and secondary syphilis.^{1,2} In this part we consider the diagnosis, treatment, and follow up of the same group of patients.

The inability to culture *Treponema pallidum* in the laboratory means that clinical evaluation, dark ground microscopy to show treponemes in clinically suspect lesions, and serological tests are the methods used to diagnose syphilis. The numerous serological tests available may be divided into those with non-specific reactivity, such as the Venereal Disease Research Laboratory (VDRL) test, and those with specific reactivity to treponemes, such as the *T pallidum* haemagglutination assay (TPHA) and the fluorescent treponemal antibody absorption (FTA-ABS) test.

Penicillin, first used to treat patients with syphilis by Mahoney *et al* in 1943,³ continues to be the drug of choice. Measures of treatment success include

the disappearance of treponemes from lesions and changes in serological titres after treatment.⁴

Patients and methods

We reviewed retrospectively^{1,2} the notes of all patients with primary or secondary syphilis who attended this department of genitourinary medicine between 1965 and 1984. Information recorded included the results of dark ground microscopy, (primary syphilis only), results of syphilis serology tests before and after treatment, the type of treatment given, and whether the patient had a Jarisch-Herxheimer reaction (exacerbation of skin lesions, fever, and malaise) afterwards. During the 20 years of the study five different serological tests were used. These were the Wasserman reaction (WR), the Reiter Protein Complement fixation test (RPCFT), the Venereal Diseases Research Laboratory (VDRL) test, the Fluorescent treponemal antibody absorption assorted (FTA-ABS) test, and the macroscopic *T pallidum* Haemagglutination assay (TPHA).

We used the χ^2 test for statistical analysis.

Results

We analysed the notes of 946 patients with primary and 854 with secondary syphilis.

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Table 1 Results of dark ground microscopy by site of lesion in 864 patients (838 men, 26 women) with primary syphilis

Site of lesions	No positive/No tested (%)
Genital	476/619 (76.9)
Anal/rectal	189/236 (80.1)
Oral	8/9 (88.8)

DARK GROUND EXAMINATION - PRIMARY SYPHILIS

Of dark ground examinations carried out on 838 men and 26 women patients, 673 (77.9%) gave positive results. Dark ground positivity was not related to the site of the lesion (table 1) or to the sexual orientation of the patient.

SEROLOGICAL TESTS (table 2)

Of 939 patients with primary syphilis tested in the VDRL, 661 (70.4%) gave positive results, most (415 (62.8%)) at a titre of 1/8 or less. Positive results were found in 487/650 (74.9%) patients in the TPHA and 495/539 (91.8%) in the FTA-ABS. In 49 the FTA-ABS was the only positive result at presentation. Of the 163 patients with negative TPHA results initially, 95 were also tested in the FTA-ABS and VDRL: positive results were seen in 62 (65.3%) of them in the FTA-ABS and 30 (31.6%) in the VDRL tests ($p < 0.001$). Of 137 (14.5%) patients with primary syphilis who had no positive serological test results at presentation, 55 (40.2%) gave positive results during a mean follow up time of 9.4 months.

Only eight (0.9%) of the 854 patients diagnosed as having secondary syphilis did not have a positive serological result at presentation, and seven of them gave positive results when reassessed at follow up one month later. The VDRL test gave positive results in 841/853 (98.6%), 758 (90.1%) of whom had titres of 1/8 or more. Positive results were found in 550/552 (99.6%) in the FTA-ABS test and 607/623 (97.4%) in the TPHA.

TREATMENT

Table 3 shows that penicillin was used to treat most (1601/1781, 89.9%).

Intramuscular procaine penicillin was the treatment used most often for primary and secondary syphilis, (for 792/932 (85%) patients with primary and 741/849 (87.3%) with secondary infection. Benzathine pen-

Table 3 Treatment of 1781* patients with primary or secondary syphilis comparing penicillin and non-penicillin regimens (figures are numbers (percentages) of patients treated with given regimen)

	Procaine or benzathine penicillin	Non-penicillin (erythromycin or tetracycline)
Primary (n = 932)	827 (88.7)	105 (11.3)
Secondary (n = 849)	774 (91.2)	75 (8.8)

*Treatment not known or combination of antibiotics used for 19/1800 patients.

icillin was used in only 26 (2.8%) of the patients with primary and 28 (3.3%) of those with secondary syphilis. Nine patients with primary and five with secondary syphilis received a combination of benzathine and procaine penicillin. Two non-penicillin drugs were used, erythromycin in 176/1781 (9.9%) and tetracycline in only four (0.2%). The most usual reason for non-penicillin treatment was a history of allergy (in 126 (7%) patients). Table 4 shows that the Jarisch-Herxheimer reactions, when recorded, were significantly ($p < 0.00005$) more common in patients treated with penicillin (455/721 (63%)) than erythromycin or tetracycline 22/76 (29%).

FOLLOW UP

The figure shows titres at which serum samples showed positive results in the VDRL at various times after treatment. No significant differences were found comparing VDRL titres in patients treated with penicillin or non-penicillin. After six months 30% (282/939) of patients who had been treated for primary syphilis were still VDRL positive, 2.6% (81) of them at titres greater than 1/8. At 18 months 140 (14.9%) still gave positive results.

Six months after treatment 55% (465/846) of those treated for secondary syphilis still gave positive results, and at 18 months the figure was 32% (270). (The VDRL titre was less than 1/8 in most, but 17 (4%) patients remained VDRL positive at the end of 18 months with titres of 1/16 or more).

Discussion

In patients with primary syphilis 78% (673/864) of the chancres were found to be dark ground positive. Reasons for false negative results include recent local

Table 2 Results of serological tests at presentation in 1800 patients with primary or secondary syphilis (figures are numbers (percentages) positive/numbers tested)

Diagnosis	Wasserman reaction	Reiter protein complement fixation test	Venereal Diseases Research Laboratory	Treponema pallidum haemagglutination assay	Fluorescent treponemal antibody-absorption
Primary (n = 946)	210/291 (72.2)	176/289 (60.9)	661/939 (70.4)	487/650 (74.9)	495/539 (91.8)
Secondary (n = 854)	239/241 (99.2)	232/240 (96.7)	841/853 (98.6)	607/623 (97.4)	550/552 (99.6)

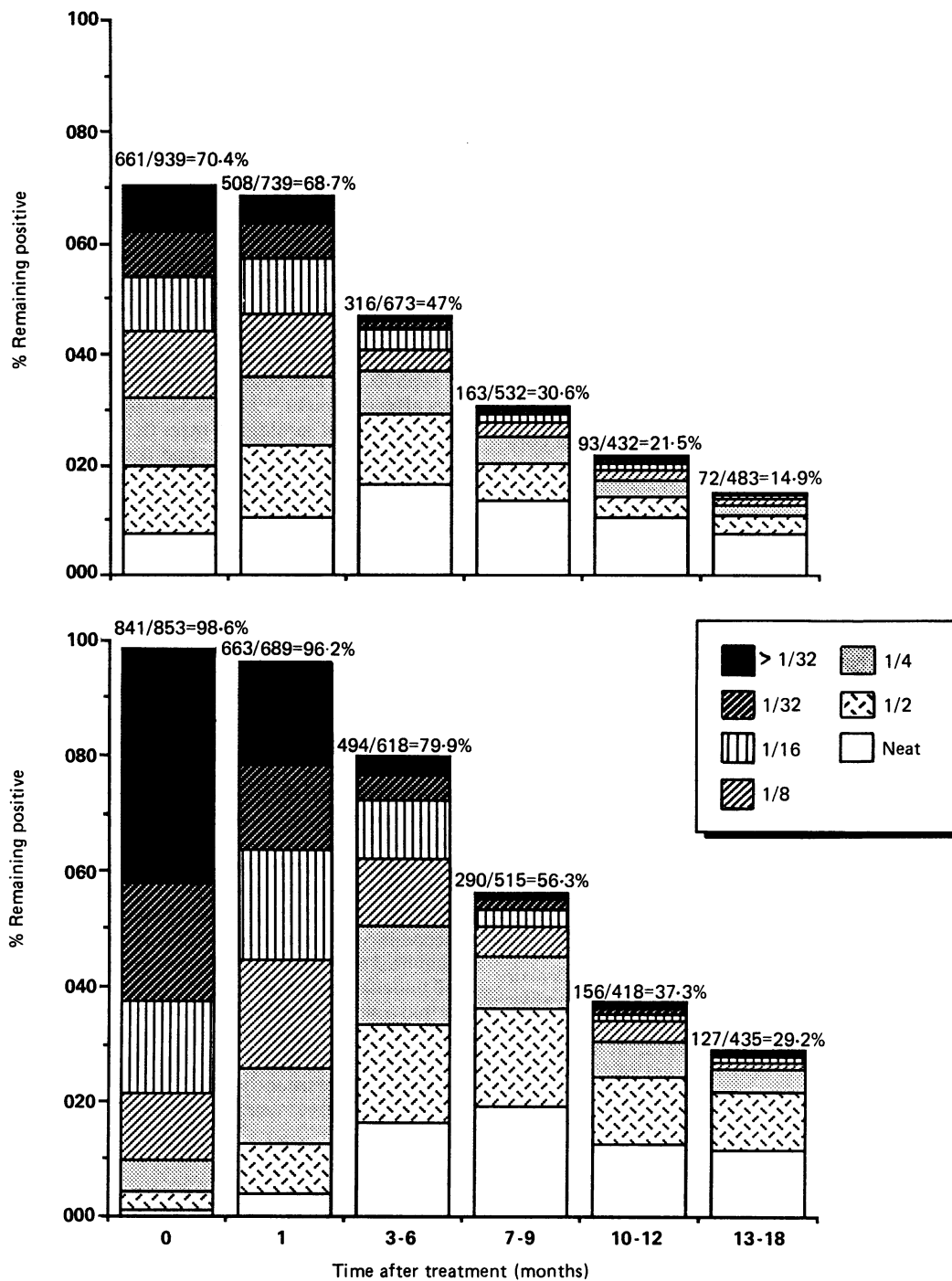


Fig Changes in titres at which serum samples gave positive results in the VDRL test at various times after treating (top) 939 patients with primary syphilis and (bottom) 854 with secondary syphilis.

Table 4 *Jarisch-Herxheimer reactions in 797 patients with primary or secondary syphilis after penicillin or non-penicillin treatment (figures are numbers (percentages) of patients who reacted/numbers for whom data were available)*

	Procaine or benzathine penicillin	Non-penicillin (erythromycin or tetracycline)	Difference
Primary	217/357 (60.8)	15/42 (35.7)	p < 0.002
Secondary	238/364 (65.4)	7/34 (20.6)	p < 0.00005
All patients	455/721 (63.1)	22/76 (28.9)	p < 0.00005

treatments, recent systemic antibiotic treatment, or excess debris obscuring the view.⁵ Suggestions have been made that false positive results may be obtained from oral or anal lesions because of the presence of saprophytic spirochaetes.⁶ We were unable to find any significant correlation between the site of the lesion and the results of dark field microscopy which contradicts that suggestion.

In patients with primary syphilis the FTA-ABS test is usually the first to give positive results, and the TPHA does so a few weeks later.⁷ This was confirmed by our study, which showed that 92% of patients had positive results in the FTA-ABS test and 75% in the TPHA at the time of presentation. Our finding of 15% of patients giving negative results in all tests at presentation was similar to that reported previously.⁸

It is generally accepted that all patients with secondary syphilis have positive serological markers at presentation.^{9,10} In our patients eight initially gave negative results, although seven gave positive results one month later. The accuracy of the diagnosis in the one who did not seroconvert is doubtful. In this connection the report of a patient with secondary syphilis and coexisting human immunodeficiency virus (HIV) infection is of some interest.¹¹ The results of serological tests were initially negative, but became positive 20 days after presentation, and the authors postulated that HIV had altered the serological response to syphilis. Our study suggests that patients with secondary syphilis occasionally give negative serological test results at presentation. Though the HIV status of our patients is not known, at least some of them were diagnosed before advent of HIV infection.

The observation that the Jarisch-Herxheimer reaction was more common in patients treated with penicillin possibly reflects a more rapid treponemoidal effect of penicillin compared with tetracycline or erythromycin. Erythromycin and tetracycline are bacteriostatic, rather than bacteriocidal; they inhibit the metabolic processes of the organisms, which allows the host defence mechanisms to kill the treponemes.¹² This may result in a slower release of toxic substances into the bloodstream, and hence a reduced incidence of Jarisch-Herxheimer reactions.

The serological response after treatment has been used as a yardstick to assess its efficacy.¹³ In our study 15% of the patients with primary and 29% with secondary syphilis still had positive VDRL test results 13 to 18 months after treatment. No other evidence in these patients suggested treatment failure. In a series of 588 patients with primary and 623 with secondary syphilis Fiumara found complete resolution of symptoms and negative serology test results within one year of treatment in primary and within two years of secondary disease.¹⁴ All the patients had received benzathine penicillin 2.4 MU a week intramuscularly for two weeks or tetracycline 500 mg qds for 12 days. In contrast, other workers have found that up to 3% of patients with primary and 24% of those with secondary syphilis still had positive results in the VDRL two years after treatment.^{15,16} It has been suggested that the higher the initial serological titres the longer the time to return to negative results, and it has been shown that those who have been reinfected have been shown to take longer to give negative results than patients with a first episode of primary or secondary syphilis.¹⁷ Of our 1800 patients, 334 (18.6%), had previously been treated for syphilis,¹ which may account for the differences seen between our study and others.

Of considerable concern are reports of apparent treatment failure after adequate doses of benzathine penicillin had been given to patients with secondary syphilis and coexisting HIV infection.^{18,19} The natural history of syphilis may alter in patients with HIV infection,²⁰ though one study has shown no difference in the serological response to syphilis in men with and without HIV infection.²¹ Patients infected with HIV who develop syphilis need careful evaluation and follow up.

In summary, we have reviewed the diagnosis, treatment, and serological response to treatment in patients attending a central London STD clinic with primary or secondary syphilis during a 20 year period. We have highlighted the importance of dark ground evaluation in all patients suspected of having primary syphilis, the fact that a small percentage of patients with secondary syphilis may give negative results to serology tests at presentation, and finally that a sizeable minority of patients have persistently positive VDRL test results after successful treatment.

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