The localisation of treponemes and characterisation of the inflammatory infiltrate in skin biopsies from patients with primary or secondary syphilis, or early infectious yaws

H J H Engelkens, F J W ten Kate, Jubianto Judanarso, V D Vuzevski, J B H J van Lier, J C J Godschalk, J J van der Sluis, and E Stolz

Abstract

Objective—To study the localisation of treponemes and to analyse the inflammatory infiltrate in biopsy specimens from patients with primary or secondary syphilis, or early infectious yaws.

Materials and methods—Skin biopsies originating from human lesions of primary (29x) or secondary (15x) syphilis (Rotterdam), or early yaws (18x) (West Sumatra) were studied. Different histochemical and immunohistochemical detection methods were used in this study.

Results and conclusion—The histochemical silver staining method according to Steiner revealed the presence of *T. pallidum* in all cases of primary syphilis studied. In 10 out of 14 cases of secondary syphilis, treponemes were demonstrated. With an immunofluorescence staining technique (IF) using anti-*T. pallidum* antiserum raised in rabbits (a-Tp), *T. pallidum* was demonstrated in 28 out of 29 cases of primary syphilis, and in 14 out of 14 studied cases of secondary syphilis. The silver staining method and IF showed identical localisations of *T. pallidum* (mainly in the dermal-epidermal junction zone or throughout the dermis). Using a-Tp antiserum in the indirect immunofluorescence technique, *T. pertenue* could be demonstrated in the dermis more often than with Steiner silver staining. However, epidermotropism of *T. pertenue* in yaws specimens was remarkable, compared with more mesodermotropism of *T. pallidum*; numbers of *T. pertenue* in the dermis were limited in all specimens. The dermal inflammatory infiltrate in primary and secondary syphilis was composed mainly of lymphocytes and plasma cells. In most cases more T (CD3 positive) cells than B (CD22 positive) cells were present. Regarding T cell subpopulations, in primary syphilis, T helper/inducer (CD4 positive) cells predominated in 86% of cases. In secondary syphilitic lesions, numbers of T helper/inducer cells were less frequent than or equal to T-suppressor/cytotoxic (CD8 positive) cells in 60% of cases. Remarkably, in yaws specimens the inflammatory infiltrate consisted mainly of IgG, but also IgA and IgM pro-

ducing plasma cells. T or B lymphocytes were scarce, which is in sharp contrast with findings in syphilitic lesions.

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Introduction

Sexually transmitted syphilis, caused by *Treponema pallidum* subspecies *pallidum* (*T. pallidum*) is still a major worldwide threat. In Europe and the United States syphilis has not yet been eradicated.¹⁻³ In many developing countries this treponemal infection is highly prevalent.⁴ In the AIDS era, the classical sexually transmitted ulcerative diseases such as syphilis deserve renewed interest, because these may facilitate the transmission of HIV infection.⁵⁻⁷ In the 1980s only a few articles were published on the histopathological aspects of syphilis. The wide variety of possible microscopical changes in secondary syphilis, analogous to the variety seen in the clinical expression of the disease, was stressed.⁸⁻¹¹ One recent study by Tosca *et al* focused on composition of the inflammatory infiltrate before and after antibiotic treatment was given.¹⁰

Yaws (framboesia tropica), caused by *Treponema pallidum* subspecies *pertenue* (*T. pertenue*), is a chronic nonsexually transmitted treponematosis of childhood occurring in rural remote regions with tropical, humid climates.¹² Specifically in West and Central Africa, a dramatic re-emergence of yaws was recently reported.¹³⁻¹⁵ Yaws has also become resurgent in several countries in Southeast Asia.¹⁶⁻¹⁸ From the 1950s onwards, studies of the histopathological findings in early yaws have been scarce.^{19,20} Conclusions of older studies were based on material obtained from a limited number of patients. To our knowledge, analysis of the inflammatory infiltrate in yaws has never been addressed before. In this article we investigate and compare the localisation of spirochetes in skin biopsies from patients suffering from primary or secondary syphilis, or from early infectious yaws. An analysis of the inflammatory infiltrate in these specimens was performed.

Materials and methods

Syphilis

Biopsy specimens were taken from untreated skin lesions of 44 patients who presented with

Department of Dermatology and Venereology, University Hospital Rotterdam-Dijkzigt and Erasmus University Rotterdam, the Netherlands
H J H Engelkens
J J van der Sluis
E Stolz

Department of Pathology, Academic Medical Centre, University of Amsterdam, the Netherlands
F J W ten Kate

Department of Dermatology and Venereology, Medical Faculty, University of Indonesia, Jakarta, Indonesia
Jubianto Judanarso

Department of Pathology, University Hospital Rotterdam-Dijkzigt and Erasmus University Rotterdam, the Netherlands
V D Vuzevski
J C J Godschalk
J B H J van Lier

Correspondence to: H J H Engelkens, MD, Department of Dermatology and Venereology, University Hospital Rotterdam - Dijkzigt, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

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clinical symptoms of early infectious syphilis at the Department of Dermatology and Venereology, University Hospital Rotterdam-Dijkzigt, the Netherlands, between August 1984 and January 1990, and gave permission for a biopsy. Blood samples of all patients reacted positively in one or more of the following tests: the Venereal Disease Research Laboratory (VDRL) test, Rapid Plasma Reagin (RPR) test, fluorescent treponemal antibody-absorbed (FTA-ABS) test and *Treponema pallidum* haemagglutination assay (TPHA) (at the first or second visit) and/or dark-field examination of exudates of lesions showed the presence of treponemes. A diagnosis of primary syphilis was made in 29 patients (3 women and 26 men). The mean age was 34.3 years (range 21–54 years). In 15 patients (8 women and 7 men) a diagnosis of secondary syphilis was made. In this group the mean age was 34.1 years (range 18–55 years). Clinical manifestations have been described previously.¹¹ The biopsies were sent immediately to the Department of Pathology. All samples were cut into two equal parts. One was fixed in phosphate-buffered 4% formaldehyde solution, and paraffin-embedded. The remaining part was snap-frozen in liquid nitrogen-cooled isopentane and stored in liquid nitrogen for immunohistochemical studies. At the time of the biopsy, the serostatus for antibodies against HIV was unknown in all patients. To study the presence and localisation of treponemes in the biopsies, the histochemical silver staining method according to Steiner²¹ and immunohistochemical methods were used, and analysis of the inflammatory infiltrate was performed.

Yaws

Skin biopsies from 18 patients, five girls and 13 boys, suffering from yaws in rural regions in West Sumatra, Indonesia (November 1988) were studied. The mean age of the patients was 7.4 years (range: 1.5–13 years). An overlap between the primary and secondary stages of yaws was typical,¹² and no distinction between these stages could be made. In all patients biopsied, a diagnosis of early infectious yaws was made on clinical and epidemiologic grounds, proven by reactive serologic tests (VDRL, TPHA, FTA-ABS) and/or positive dark-field examination of the exudate of skin lesions, and positive Steiner silver staining. One part of biopsied tissue was fixed in phosphate-buffered 4% formaldehyde solution. For immunohistochemical studies, another part was frozen immediately, kept in dry ice and transported in dry ice from Indonesia to the Netherlands. To study the localisation of treponemes, results of Steiner silver staining were compared with immunohistochemical methods. Analysis of the inflammatory infiltrate was performed.

Routine staining of all specimens was performed with haematoxylin-azophloxin (H&A). In the H&A slides, depending on the total number of inflammatory cells, the infiltrate was graded as mild (a small number), as

Figure 1 The silver staining according to Steiner demonstrates the presence of *T. pallidum*, located perivascularly (primary syphilis).

dense (a large number), or as moderate (when the total number of inflammatory cells was in between the other two categories).

The composition of the inflammatory infiltrate was analysed on slides from frozen parts of the biopsies, using commercially available polyclonal and monoclonal antibodies against immunoglobulins, T-lymphocytes, T-lymphocyte subpopulations and B-cells.

The sections were tested with commercially available polyclonal antibodies against immunoglobulins (IgG, IgA, IgM, (Immuno de Beer Medicals B.V., Kallestad)), C1q, and β_2 a (Centraal Laboratorium van de Bloedtransfusiedienst van het Nederlandse Rode Kruis). Furthermore, an antiserum against the pathogenic Nichols strain of *T. pallidum*, raised in rabbits, was used (rabbit anti-*T. pallidum* antiserum (a-Tp)). Positive and negative controls were included.

The indirect immunoperoxidase (IIP) method was performed with an optimal dilution of the monoclonal antibody; the presence of T-lymphocytes (CD3, pan-T), helper/inducer T-lymphocytes (CD4 (T_H)), suppressor/cytotoxic T-lymphocytes (CD8 (T_C)) and B-lymphocytes (CD22, pan-B) (Becton Dickinson) was studied. Positive and negative controls were included.

Results

Localisation of treponemes

Primary syphilis. The Steiner silver staining method demonstrated the presence of treponemes in 28 out of 29 biopsy samples from

Figure 2 Primary syphilis. Many treponemes in the dermis (rabbit anti-*T. pallidum* antiserum (a-Tp)).

Figure 3 Many *T. pertenue* organisms are detected (Steiner staining method).

patients with primary syphilis; one specimen did not contain enough tissue to allow silver staining to be performed. In two cases only a few treponemes were detected, in both cases located in the dermis. A moderate number of treponemes were observed in 14 cases, in most cases located in the dermal-epidermal junction zone. In the dermis most treponemes were seen perivascularly, sometimes in the walls of papillary blood vessels; in six out of these 14 cases treponemes were located in the dermis only. Large numbers of treponemes were demonstrated in 12 specimens, again mostly in the dermal-epidermal junction and the perivascular areas (fig 1). With immunofluorescence using a-Tp (fig 2), treponemes were visualised in 28 out of 29 specimens, mostly in the dermis (perivascularly) or dermal-epidermal junction. In one case a-Tp did not show treponemes: however, in the formaldehyde-fixed counterpart of this biopsy many treponemes were demonstrated in the dermis with Steiner silver staining. Only occasionally were microorganisms visualised with anti-IgG, C1q, and β_1a .

Secondary syphilis. Steiner silver staining revealed the presence of treponemes in 10 out of 14 cases studied, with only a few treponemes in five, a moderate number in two, and a large number in three cases. In eight

Figure 4 Yaws: numerous treponemes are visualised in the epidermis, using a-Tp.

Table 1 Results of immunoperoxidase staining of primary (n = 29) and secondary (n = 15) syphilis biopsy specimens; CD3 (pan-T) versus CD22 (pan-B) positive cells

	Primary syphilis	Secondary syphilis
Pan-T > Pan-B	25	13
Pan-B > Pan-T	0	0
Pan-T = Pan-B	0	1
Unknown	4	1

specimens treponemes were mainly observed in the dermal-epidermal junction zone or throughout the dermis, frequently located perivascularly. In two specimens treponemes were mainly observed in the epidermis, reaching the surface.

With a-Tp antibodies, treponemes were visualised in all 14 specimens studied, again mostly in the dermis (perivascularly) or dermal-epidermal junction. In the four Steiner-negative cases, few treponemes were detected using a-Tp, in the dermis (2x) or in the dermal-epidermal junction (2x). In one case *T. pallidum* was observed in the epidermis with anti-IgG.

Yaws

In 18 of 18 cases Steiner staining revealed the epidermal location of *T. pertenue*. In two of 18 biopsy specimens no dermal tissue was present. In only one of the other 16 cases, in which a large number of treponemes were present in the epidermal layers, a few microorganisms were also noted focally in the papillary dermis. In the epidermis the microorganisms were regularly observed in

Figure 5 Primary syphilis: helper/inducer T cells (CD4) (a) are more numerous than suppressor/cytotoxic T cells (CD8) (b). Immunoperoxidase staining, 160 x.

Figure 6 Secondary syphilis: more T (CD3 positive) cells (a) than B (CD22 positive) cells (b) are present in the infiltrate. Immunoperoxidase staining, 160 x.

band-like pattern, sometimes in clusters (fig 3). In the frozen material used for immunofluorescence detection techniques, the epidermis was absent in one biopsy, the dermis in another one. In all biopsies covered by an intact epidermis (17x), many *T. pertenue* organisms were detected in the epidermis. In 16 out of 17 biopsies treponemes were found in the dermis. Numbers in the dermis were small: *T. pertenue* was distributed focally, solitarily or in small clusters. Treponemes were observed most frequently using a-Tp (fig 4). Besides with a-Tp, treponemes were also frequently observed with C1q. With anti-IgG, IgM, IgA and β_1a , the presence of treponemes was observed only occasionally. In some slides the presence of *T. pertenue* was doubtful, owing to strong background staining of other structures resembling treponemes.

Inflammatory infiltrate

Primary syphilis. In 28 H and A specimens, the inflammatory infiltrate was located in all layers of the dermis, particularly perivascular-

ly. The infiltrate was described as dense in 21, moderate in five and mild in two specimens. The infiltrate consisted of lymphocytes and plasma cells (in highly variable numbers) in all cases, admixed with histiocytes in nine and polymorphonuclear leucocytes in 18 cases.

With anti-IgG, anti-IgM and anti-IgA conjugates, plasma cells stained positively in 17 of 29 (59%), 20 of 29 (69%) and 21 of 29 (72%) of cases, respectively; numbers of positive cells were highly variable. No plasma cells were observed in four cases. In most cases there was a preponderance of T lymphocytes in the dermal inflammatory infiltrate: more T (CD3 positive) cells than B (CD22 positive) cells were present in 25 of 29 biopsies of primary syphilis. In four cases this ratio was unknown (see table 1). Study of T cell subpopulations demonstrated that in 20 out of 29 biopsies (69%), helper/inducer T cells (CD4) were more numerous than suppressor/cytotoxic T cells (CD8) (fig 5). In six cases T helper/inducer cells were about equal to T suppressor/cytotoxic cells (21%), and in three, T helper/inducer cells were less common than T suppressor/cytotoxic cells (10%). (See table 1).

Secondary syphilis. In secondary syphilis, the density of the inflammatory infiltrate and the distribution of inflammatory cell types were highly variable, dense in nine, moderate in four and mild in two specimens. In all biopsies of secondary syphilis lymphocytes and plasma cells predominated. However, plasma cells were only scarce in two biopsy specimens. The predominantly lymphoplasmacellular infiltrate was admixed with small amounts of histiocytes, neutrophils, and in one case with eosinophils.

Plasma cells stained positively in six out of 15 (40%) with anti-IgG antiserum, in 12 of 15 (80%) with anti-IgM antiserum, and in 12 out of 15 (80%) with anti-IgA antiserum, numbers of plasma cells being highly variable. In two cases immunofluorescence did not reveal the presence of plasma cells. It was demonstrated that in biopsies from secondary syphilis lesions also, T cells predominated in the infiltrate (fig 6) in most (13 out of 15) cases (table 1). However, numbers of positive cells were highly variable. Study of T cell subsets showed that in six out of 15 biopsies (40%) T helper/inducer cells were more numerous than T suppressor/cytotoxic cells. In four cases T helper/inducer cells were about equal to T suppressor/cytotoxic cells (27%), and in five cases, T helper/inducer cells were fewer in number than T suppressor/cytotoxic cells (33%) (see table 2 and figure 7).

Yaws

With H&A staining, in the yaws specimens an infiltrate composed of plasma cells and lymphocytes was observed in all 16 cases studied. Histiocytes were present in five cases and polymorphonuclear leucocytes were seen in

Figure 7 Secondary syphilis: helper/inducer T cells (a) are less numerous than suppressor/cytotoxic T cells (b). Immunoperoxidase staining, 250 x.

two. In addition, eosinophils were present in the infiltrate in four cases. The inflammatory infiltrate in the deeper dermis consisted mainly of plasma cells. In one case a mild infiltrate was observed; a moderate infiltrate was seen in seven and a dense infiltrate in eight cases.

With anti-IgG, anti-IgM and anti-IgA conjugates, plasma cells stained positively (fig 8) in specimens of all 18 cases. The numbers of plasma cells were highly variable. In most cases it was obvious that with anti-IgG the largest number of plasma cells gave a positive reaction. Only in a few cases was a weak staining of small groups of CD3, CD22, CD4, and CD8 positive cells observed in the

Figure 8 With immunofluorescence, using anti-IgA, many plasma cells are demonstrated in a biopsy sample of yaws.

Table 2 Results of immunoperoxidase staining of primary (n = 29) and secondary (n = 15) syphilis biopsy specimens: T cell subpopulations (CD4 (T_h) versus CD8 (T_c) positive cells)

	Primary syphilis	Secondary syphilis
T _h > T _c	20	66
T _h < T _c	3	5
T _h = T _c	6	4
Unknown	0	0

dermis. In most cases no B- or T- lymphocytes were observed.

Discussion

Hitherto no rigorous morphological, serological, immunological or genetic differences have been described to distinguish between the causative agents of yaws and syphilis. There have been, however, distinctive clinical, epidemiological and geographical features.¹²⁻¹⁴ In previous work, the epidermotropic character of *T. pertenue* was obvious, in contrast to the more mesodermotropic character of *T. pallidum*.¹¹⁻²⁰ It was hypothesised that this difference could be held responsible for the different clinical and pathological findings in lesions of venereal syphilis and yaws, and the milder course of the latter disease.¹¹⁻¹⁹ In this study, with Steiner silver staining as well as with a-Tp using immunofluorescence, it was demonstrated that *T. pallidum* was primarily located in the dermis or dermal-epidermal junction. We noticed that with the Steiner silver staining method, the epidermotropism of *T. pertenue* was obvious. Hardly any treponemes could be demonstrated in the dermis. However, using a-Tp antibodies, *T. pertenue* could also be demonstrated in the dermis in nearly all specimens. These microorganisms located dermally were nevertheless only scarce, in contrast to the large numbers of treponemes in the epidermal layers, thus confirming the epidermotropic character of *T. pertenue*. Immunoglobulins or complement components could rarely be demonstrated in relation to the treponeme organisms.

Histopathologically, in many studies the inflammatory infiltrate in early syphilis and yaws has been characterised as mainly lymphoplasmacellular. Nowadays, the availability of specific monoclonal antibodies can be used to characterise exactly the composition of the infiltrate. In this study it became clear that plasma cells were the predominating cells in the infiltrate in a large majority of cases of primary as well as of secondary syphilis: B lymphocytes and plasma cells were less frequent. In most cases of primary syphilis, in this predominantly T cell infiltrate, the T helper/inducer cells were more frequent than suppressor/cytotoxic cells. However, in secondary syphilis biopsy samples the ratio of T helper/inducer and T suppressor/cytotoxic cells was approximately equal or reversed in more than half of the cases. Our findings are comparable with those of Tosca *et al*, who demonstrated that in primary lesions T-

Figure 9 Many plasma cells in the inflammatory infiltrate of yaws (methyl green pyronin staining).

helper lymphocytes were more numerous than T-suppressor lymphocytes, while in secondary lesions T-suppressor lymphocytes predominated.¹⁰ The increased numbers of T-suppressor lymphocytes in the secondary stage lesions of syphilis may result in the natural shutdown of the early vigorous immune response following clearance of most of the treponemes from the lesions, ushering in the latent stage.

In contrast with these findings, however, in yaws specimens hardly any T and B lymphocytes were detected. We found that plasma cells were by far the most important constituent of the inflammatory infiltrate in early infectious yaws. With immunofluorescence it was observed in the yaws cases that IgG producing plasma cells were the most numerous, but IgA and IgM producing plasma cells were also present in all specimens. Afterwards, these findings in yaws were histochemically confirmed with methyl green pyronin staining, which again demonstrated the presence of an abundance of plasma cells (fig 9).

In syphilis patients no overlap between the primary and secondary stage lesions, as in yaws, was observed. Unfortunately, the precise duration of the presence of lesions at the time of biopsy, and the HIV serostatus were unclear. Furthermore, to allow a more accurate interpretation of our results, serial sectioning of biopsy material may offer additional information, to eliminate the one-dimensional view of a single section.

A remarkable difference in the inflammatory reaction of yaws and venereal syphilis is presented here. Whether this represents a typical feature of yaws, regional differences of *T. pertenue* strains or influence of transport remains to be seen. Therefore, further study of biopsy samples from patients suffering from syphilis or endemic treponematoses in other regions of the world is recommended for a better understanding of treponemal infection.

The authors thank all patients in West Sumatra and Rotterdam who gave permission for performing a biopsy. We thank the Indonesian authorities for permission to perform our studies on yaws. We gratefully acknowledge the cooperation of the Centres of Disease Control in Jakarta and Padang and the nursing staff in the area of Pariaman, and we thank G.T.Noordhoek and J.van der Stek for their kind help during the investigations. We are grateful to the staff of the Department of Dermato-venereology, University Hospital Rotterdam-Dijkzigt, for collecting the biopsy samples of syphilis patients. The Dutch Organisation for Scientific Research (NWO), The Hague, and the Finsen Foundation, Rotterdam, the Netherlands sponsored our work. The Royal Dutch Airlines (KLM) transported all biopsy specimens free of charge.

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those on genital candidiasis and antifungal agents.

Oral and oesophageal candidiasis are well and clearly described, the relatively few paragraphs here on HIV and AIDS reminding us that there are other causes. Diagnosis of oesophageal candidal infection is often difficult without endoscopy but the authors emphasise the valuable empiricism of several days fluconazole. Assessment of response to treatment will often establish a retrospective diagnosis.

Jack Sobel has contributed an excellent succinct chapter on all aspects of genital candidiasis, ranging from theories concerning pathogenesis to practical aspects of diagnosis. He describes his successful use of long term oral ketoconazole in recurrent vaginal candidiasis but most of us in the UK are wary of its toxicity, in particular hepatitis, though this is rare. We prefer various miconazole or clotrimazole regimens and hope that in future years a combination of fluconazole or itraconazole and vaginal therapy will become the successful norm. Sobel correctly states "*the contribution of sexual transmission to the pathogenesis of [Candida] infection remains unknown*". However, there is a statement in an earlier chapter (p. 40), "Genital candidiasis, is usually considered a sexually transmitted disease".

Gerald Bodey, the editor, provides a good summary of antifungal agents in the final chapter. Topical and systemic agents in current use are discussed including amphotericin B, flucytosine, the azoles, ketoconazole and the newer systemics fluconazole and itraconazole.

This text covers the whole field of candidiasis well. It would be a useful addition to a reference library. The book would be enhanced by a chapter on candida infections in HIV and AIDS, including in this a discussion on prophylactic regimens for oral, oesophageal and vaginal candidiasis.

MICHAEL J BALSDON

A Colour Atlas of Diseases of the Vulva. CM Ridley, JD Oriel, AJ Robinson. London, Chapman & Hall, 1992 (Pp 109). £60.00). ISBN 0-412-36520-0.

There has long been a need for an atlas of vulval diseases and the publication of this book is most welcome. Nearly 300 colour photographs are displayed within its covers, showing examples of both common as well as some relatively rare vulval disorders. Approximately 50 of the photographs illustrate histological features, infecting organisms or the skin changes which may accompany vulval disease.

The seven chapters cover the following topics: general principles; infections; non-infective, non-neoplastic conditions; tumour-like lesions and cysts, tumours; miscellaneous conditions; childhood lesions; child sexual abuse. In addition there are helpful lists of diagnoses grouped under broad headings of clinical features and symptoms, and appendices of the histological classification of vulval dystrophy and classification of vulvodynia. The principles of examination of the vulva and possible relevant investigations are briefly discussed, but further practical details would be needed by a practitioner embarking on the investigation of a patient. It would have been helpful to have shown examples of vulval appearance in black and Asian skin in addition to that in white skin.

The range of photographs covering vulval abnormalities is extensive, usually with several examples of the more common disorders. This is clearly an important feature in, for example, lichen sclerosus et atrophicus where the clinical manifestations may be very variable. Vulval soreness and irritation are often initially thought to be due to candidosis, until proved otherwise and so I was somewhat disappointed to find relatively few illustrations of this condition. The quality of the photographs is generally good, but there are some which are out of focus or of an odd colour.

As with many medical colour atlases, striking a balance between the value of the visual content and the written text is a difficult challenge. In this atlas, the text is brief, but does venture beyond points of observation into aetiology and therapy. As a result, therapeutic suggestions are often single and dogmatic.

This is not a book to leave out on your coffee table at home, but it is a most useful book to have at hand in the clinic. It would be best used in conjunction with a more detailed text but certainly has a place in aiding diagnosis or consideration of possible diagnoses. Although the preface suggests that this is a book for genitomedical physicians, gynaecologists and dermatologists, I would also, and perhaps particularly, suggest that it would be a most valuable acquisition in paediatric departments and general practitioners' surgeries.

JANE C STERLING

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Correction

Engelkens H J H *et al*: The localisation of treponemes and characterisation of the inflammatory infiltrate in skin biopsies from patients with primary or secondary syphilis, or early infectious yaws (*Genitourin Med* 1993;69:102-7). In table 2, for cases of secondary syphilis (line $T_h > T_a$), the correct figure is 6 instead of 66.