Observations on syphilis in Addis Ababa

2. Prevalence and natural history

P. S. FRIEDMANN* AND D. J. M. WRIGHT

From the Department of Pathology, Royal College of Surgeons of England and the Department of Microbiology, Charing Cross Hospital, London

SUMMARY Sera from various groups were tested for syphilis by cardiolipin, fluorescent treponemal antibody-absorbed (FTA-ABS), and treponemal haemagglutination (TPHA) tests. The proportion of positive results, 12.7%, obtained from an unselected urban population suggested that the prevalence of the disease had declined since 1953. The probable explanation is the widespread use of penicillin. Late manifestations of syphilis are much rarer in Ethiopia than would be predicted from the high incidence at the infectious stage and, if present, they affect the cardiovascular system. These findings confirm old observations. Lymphocytes from Ethiopians with early syphilis did not proliferate when cultured with *Treponema pallidum* *in vitro*, in contrast with cells from patients with cardiovascular syphilis. These findings differed from observations made previously on patients in England with early syphilis.

Prevalence of syphilis

Surveys in the past have shown that syphilis is a common disease in Ethiopia. In 1952 Ferreira-Marques (1964) found that an average of 48% of sera gave positive results in cardiolipin tests, Venereal Disease Research Laboratory (VDRL), and Klmer tests; while Buck and Spruyt (1964) using VDRL and fluorescent treponemal antibody-200 (FTA-200) tests showed that 31% of sera from an unselected population gave positive results.

The current study was undertaken to re-assess the prevalence of syphilis and formed part of a search for people with late forms of the disease. The serological tests used were the VDRL slide test with carbon antigen and the fluorescent treponemal antibody test at a dilution of 1/200 (FTA-200). They were done in accordance with the manual of the National Communicable Disease Centre (1969). The only exceptions were sera collected at the Venereal Disease Centre where the slide VDRL and the less sensitive tube Meinicke tests were used.

Of 800 new patients seen at the centre, 48 (6%) had signs of infectious early syphilis and 195 (24.4%) gave positive results to screening tests done

locally. Since it was possible that such tests were not very sensitive, sera were brought to London to be checked by the fluorescent treponemal antibody-absorbed (FTA-ABS) test (Wilkinson, 1972) and the *Treponema pallidum* haemagglutination (TPHA) test (Johnston, 1972). Two sera which gave positive results to screening tests at the Venereal Disease Centre gave false positive results in London, but 209 of 601 sera reported as negative in Ethiopia were found to be positive (Table 1). Thus 402/796 (50.5%)

Table 1 Results of screening tests on 796 sera done at the VD Centre, Addis Ababa, compared with confirmatory tests done at Charing Cross Hospital, London

VDRL screening test		Confirmatory tests				No. positive
		TPHA	FTA-ABS	+	-	
+	195	186	4	3	2	193
-	601	156	45	8	392	209
						Total 402

24.4% of screening tests were positive, compared with 50.5% of confirmatory tests.

were actually positive. Positive TPHA results, in the absence of a reactive FTA-ABS or VDRL, were found in 45/796 (5.7%) of sera. This was interpreted as indicating that reactivity in the TPHA test persists

*Reprints from Dr P. S. Friedmann, Department of Dermatology Royal Victoria Infirmary, Newcastle upon Tyne NE1

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longer than that in the FTA-ABS test and that the patients must have had an earlier syphilitic infection. Although the proportion of infectious cases among those with syphilis—48/402 (12%), seems much lower than the 45% reported for England (Felton, 1973), our figure is not strictly comparable since an unknown number of patients presented themselves as 'new' although they had been treated previously.

Results of serological tests done on 701 of the patients were analysed in relation to the age of the patient (Table 2). There was a progressive increase in the proportion of people with positive serological

Table 2 Age related incidence of positive serological tests for patients attending the VD Centre

Age (years)	No. tested	VDRL	Confirmatory* tests	Positive %*
10-14	25	0	3	11.5
15-19	158	30	56	35.4
20-24	196	49	93	47.4
25-29	116	33	68	58.6
30-34	66	22	42	63.6
35-39	40	15	27	67.5
40-44	36	15	23	63.9
45-54	38	13	28	73.7
55+	26	6	17	65.4
Total	701	183	357	50.9

*TPHA or FTA-ABS

results up to the age of 30-34 years, after which the number remained fairly constant. This finding makes it unlikely that childhood treponemal infection accounts for the serological reactivity in these patients. The proportion of people with positive results in each age group does not merely reflect a simple relationship with sample size. The distribution of people with positive results in each age group is significantly different from those giving negative tests ($\chi^2 = 55.27$, $P < 0.001$). The ratio of positive VDRL results to confirmatory tests was constant for all age groups. This may imply that even the older patients seen at the centre had early syphilis.

In addition to the highly selected group of patients seen at the centre, other groups of people were

Table 3 Results of serological tests for syphilis on samples from various groups of people in Ethiopia

Nature of population	No. tested	Positive (%)		
		VDRL	FTA-200	TPHA*
St Paul's Hospital (Mothers in labour)	337	12.7	10.9	ND
Amanuel Hospital (Lunatic asylum)	111	10.1	ND	10.1
Alert Hospital (Patients with leprosy)	73	4	ND	4
Contacts of leprosy (Patients in provincial area (Gurage))	250	0.4	ND	0.8

*Performed at Charing Cross Hospital, London
ND Not done

examined (Table 3). These were an unselected group of women from the general population who were admitted to one of the larger obstetric units (St Paul's Hospital), inmates of the Amanuel Mental Hospital, and patients with leprosy at the Alert Hospital. Sera that had been collected in the provincial area of Gurage as part of a survey of contacts and families of people with leprosy were also tested.

Of 337 mothers and babies (cord blood) tested, 12.5% of VDRL results and 10.9% of FTA-200 results were positive. Sera from the four people which reacted in the VDRL test alone did so only weakly. No child of the 37 mothers who were serologically positive had clinical features of congenital syphilis and only three of their sera gave positive results when examined for IgM by the FTA-200 (IgM-FTA-200) test.

A substantial number of the inmates of the Amanuel Hospital were short-stay, young neurotics, psychotics, or criminals admitted for psychiatric assessment before sentence. The average age of patients tested was 35 years (range 14-60). The medical director was confident that there were no cases of neurosyphilis among the 700 patients. Serological tests done on 111 patients yielded 12 positive results. Nine of the patients with positive results and a further 16 from other hospitals who also had positive results consented to lumbar puncture; no abnormality was found in any sample of cerebrospinal fluid.

Three patients with leprosy gave positive results to the VDRL test. It has been suggested that in Ethiopia false positive VDRL test reactions are commonly associated with such diseases as leprosy, and indeed in one survey as many as 15% of people with leprosy were found to give false positive reactions (Buck and Spruyt, 1964). However, we did not find any false positive VDRL reactions in our group of 73 patients with leprosy.

Of 250 sera from the Gurage region, only one gave a positive VDRL reaction while two gave positive results to TPHA tests. As would be expected the incidence of syphilis was lower among the more isolated rural population of that region.

The steady decline in the prevalence of syphilis in Addis Ababa as shown by the results for our unselected group, the mothers at St Paul's Hospital, is most probably attributable to the advent of penicillin, which became available there in 1953.

Clinical patterns of syphilis

EARLY INFECTION

Determination of the length of the incubation period was difficult. The duration of infection before attendance was longer than is seen in this country.

For example, 12 patients with primary syphilis had lesions for an average of 18 days, and 15 patients with secondary syphilis had rashes for an average of 35 days before attendance. Multiple primary lesions, often with kissing symmetry on adjacent areas of scrotum or thigh, were common. The most frequent and often the only secondary manifestations were perineal condylomata (Fig. 1). Pustular secondary rashes, mixed papulopustular forms, annular papulonecrotic (Fig. 2), and follicular rashes were often observed; pityriasiform rashes were seen occasionally. Palmar and plantar syphilides, mucosal involvement, generalised lymphadenopathy, and alopecia were all rare. Herxheimer reactions tended to be severe.

CONGENITAL SYPHILIS

Eight per cent of perinatal deaths are caused by congenital syphilis (Demussie, personal communication). In 1975, 49 infants brought to the VD Centre exhibited darkfield positive papular lesions of congenital syphilis. None of the infants was younger than six weeks and most were two to three months old. In one paediatric unit, at least as many cases presented with intercurrent infection or jaundice.

LATE SYPHILIS

Late manifestations and stigmata of congenital syphilis are rare in Ethiopia, a fact previously noted by Guthe (1949) and Ferreira-Marques (1964). In the acquired infection, gummatous and neurological complications were not seen. By contrast, however,

Fig. 1 Secondary syphilis showing well developed condylomata lata.

Fig. 2 Secondary syphilis in Ethiopia showing annular, papulonecrotic lesions.

cardiovascular syphilis was found in adolescents and in older patients. In the heart clinic at the Russian hospital in Addis Ababa, the incidence of cardiovascular syphilis was about 3% of the approximately 500 new patients a year.

We had the opportunity of scanning miniature chest radiographs taken each week in the course of a screening programme for tuberculosis. About one-quarter of suspect films, that is 10 a week, were selected for further appraisal. Patients with possible syphilitic lesions were examined and serological tests performed. In four months, 40 patients were selected because of their chest x rays, sometimes combined with an old history of syphilis. Only two had evidence of aortic incompetence. Severe syphilitic aortic insufficiency was seen at other hospitals. Diffuse widening of the ascending aorta seen on a miniature chest radiograph may not constitute sufficient evidence to support a diagnosis of syphilitic aortitis. However, of the 40 patients, 23 gave positive results to slide VDRL tests and 29 gave positive results in the FTA-200 test. It was not possible to do FTA-200 tests on a further six patients in whom syphilis was suspected although their VDRL reactions were negative. The observation of Vukotich and Giel (1970) that angina and aortic calcification were absent in patients with syphilitic aortitis was confirmed. As so many people with supposed syphilis had negative serological results, it is possible that an idiopathic granulomatous aortitis may exist. It is most unlikely to be

the aortitis described by Isaacson (1961), as that affected the aortic arch in young people. A history of exposure to antibiotics or an estimate of the degree of activity of the disease could not be reliably obtained.

According to popular belief, syphilis was first introduced into Ethiopia by the Portuguese in the sixteenth century. However, Antoine d'Abbadie, a nineteenth century French traveller, records that the elderly people remembered syphilis first making its appearance in Ethiopia in their youth (Pankhurst, 1975). It is, therefore, possible that the severity of the disease may be related to the fairly recent introduction of syphilis to a 'virgin' population. It is also tempting to speculate that syphilis as seen in Ethiopia parallels the flamboyant syphilis of sixteenth century Europe rather than that of today. It may be that the transition from yaws to syphilis which Hudson (1946) suggested might have occurred with the opening of the trade routes, was due not to a change in the spirochaete but to changes in the immune response of the European.

Despite the florid manifestation and high incidence of early syphilis, there is much less late disease than might have been expected from the pattern in Europe.

Immunological aspects

In previous studies of cell-mediated immune reactivity in syphilis, cutaneous delayed hypersensitivity to formalised Nichols strain *T. pallidum* was investigated. The only stage of the disease in which delayed hypersensitivity was regularly found was gummatous syphilis (Barker, 1934; Thivolet *et al.*, 1953).

As part of the present study, cell-mediated immune reactivity in Ethiopians with syphilis was investigated by means of the lymphocyte transformation test (LT test). The test assesses the ability of lymphocytes to proliferate when cultured *in vitro* with antigens to which the patient is sensitive. Evidence is accumulating to suggest that the results of this test correlate with delayed hypersensitivity (Bjune *et al.*, 1976; Fleer *et al.*, 1976). Moreover, delayed hypersensitivity may not be related to protective immunity (Knight Schapiro *et al.*, 1974; Reggiardo and Middlebrook, 1974).

Lymphocytes from patients with early syphilis in Ethiopia were unresponsive when cultured with the Nichols strain of *T. pallidum* although they did respond normally to tuberculin (Friedmann and Turk, 1977). This was in marked contrast to previous observations that lymphocytes from similar patients in England usually responded to *T. pallidum* (Friedmann and Turk, 1975). Lymphocytes from

Ethiopian patients with cardiovascular syphilis were, however, also reactive.

The differences observed between lymphocyte reactivity of patients in Ethiopia and in England cannot be explained by differences in the test antigens used. Direct comparisons were made in both countries and no gross differences were observed between reactions to an isolate of *T. pallidum* derived from a lymph node of an Ethiopian with secondary syphilis and those towards the usual test antigen (Friedmann and Turk, 1977).

Although Ethiopians lack the cellular hypersensitivity detected by LT tests which was exhibited by their counterparts in Europe, they clearly have protective immune mechanisms. Even before the advent of penicillin, the disease was apparently checked in the latent stage and did not progress to late complications in either congenital or acquired forms (Ferreira-Marques, 1964). Paradoxically, it was only those who developed cardiovascular syphilis whose lymphocytes displayed reactivity *in vitro*. The most likely explanation of our findings is, therefore, that the late manifestations of syphilis result from the tissue-damaging effects of delayed hypersensitivity reactions.

Other diseases in Ethiopians show a similar dissociation between immune and hypersensitive reactions. For instance, leprosy occurs mainly as the 'borderline' form, usually of the more tuberculoid type, which is associated with fairly competent host defences. Delayed hypersensitivity, as detected by the LT test was, however, only present in a few patients (Bjune *et al.*, 1976). Again onchocerciasis is prevalent in parts of Ethiopia. The associated blindness, which is thought to be produced by hypersensitivity reactions, was found to be rare in one endemic area in which it was sought (Oomen, 1967).

There are many factors which may contribute to the differences in clinical pattern and immunological reactivity observed between people with syphilis in Ethiopia and in England. The effects of malnutrition on immune responses in syphilis are unknown, although deficient nutrition, especially in infancy, may alter the cellular immune response in chronic diseases such as tuberculosis (Sinha and Bang, 1976) and leprosy (Skinsnes, 1969). The influence of poor nutrition on the course of syphilis is shown by the predisposition of underweight mothers to give birth to congenitally infected babies. The body weight of 80% of mothers of syphilitic stillborn babies in Addis Ababa was 50 kg or lighter, while no such infants were born to women who weighed more than 59 kg. Miscarriage and still births owing to other causes were also commoner in mothers with low body weight (Demussie, personal communication).

An additional dietary factor which might affect Ethiopians in particular may derive from their staple cereal food. This plant, called *teff*, is not grown on a large scale in any other country.

Concomitant infection with other organisms such as intestinal worms, which are common, may influence host defences, although malaria can be excluded as it is not found in the Ethiopian highlands. Moreover, in Uganda where malaria is prevalent, the proportion of neurosyphilis found in a series of autopsies was 5.2% (Davies, 1947).

In conclusion, it appears that syphilis is still prevalent in Addis Ababa, although it is decreasing, probably because of the widespread use of penicillin. It also appears that, apart from perinatal death from congenital syphilis, serious and dangerous complications of the late forms of the disease are not proportionally represented. The immunological findings would suggest that the infrequent occurrence of the late forms of the disease may be associated with diminished delayed hypersensitivity in the Ethiopian.

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References

- Barker, L. P. (1934). Value of organic luetin in diagnosis and treatment of syphilis. *Archives of Dermatology and Syphilology*, 30, 676-686.
- Bjune, G., Barnetson, R. St. C., Ridley, D. S., and Kronvall, G. (1976). Lymphocyte transformation test in leprosy: Correlation of the response with inflammation of lesions. *Clinical and Experimental Immunology*, 25, 85-94.
- Buck, A. A., and Spruyt, D. J. (1964). Seroreactivity in the Venereal Disease Research Laboratory slide test and the fluorescent treponemal antibody test. *American Journal of Hygiene*, 80, 91-102.
- Davies, J. N. P. (1947). Pathology of central African natives. Mulago Hospital post mortem studies, 5. *East African Medical Journal*, 24, 437-449.
- Felton, W. F. (1973). Estimate of annual incidence of undiscovered syphilis. *British Journal of Venereal Diseases*, 49, 249-255.
- Ferreira-Marques, J. (1964). Contribution à l'étude des maladies vénériennes et cutanées à Addis Ababa. *Dermatologia Tropica*, 3, 139-151.
- Fleer, A., van der Hart, M., Blok-Schut, B. J. T., and Schellekens, P. T. A. (1976). Correlation of PPD and BCG induced leucocyte migration inhibition, delayed cutaneous hypersensitivity, lymphocyte transformation and humoral antibodies to PPD in man. *European Journal of Immunology*, 6, 163-167.
- Friedmann, P. S., and Turk, J. L. (1975). A spectrum of lymphocyte responsiveness in human syphilis. *Clinical and Experimental Immunology*, 21, 59-64.
- Friedmann, P. S., and Turk, J. L. (1977). The role of cell-mediated immune mechanisms in syphilis in Ethiopia. *Clinical and Experimental Immunology*. (In press).
- Guthe, T. (1949). Venereal disease in Ethiopia. *Bulletin of the World Health Organisation*, 2, 85-137.
- Hudson, E. H. H. (1946). *Treponematosis*, p. 112. Oxford University Press: London.
- Isaacson, C. (1961). An idiopathic aortitis in young Africans. *Journal of Pathology and Bacteriology*, 81, 69-79.
- Johnston, N. A. (1972). *Treponema pallidum* haemagglutination test for syphilis. *British Journal of Venereal Diseases*, 48, 474-478.
- Knight Schapiro, C. D., Harding, G. E., and Smith, D. W. (1974). Relationship of delayed-type hypersensitivity and acquired cellular resistance in experimental airborne tuberculosis. *Journal of Infectious Diseases*, 130, 8-15.
- National Communicable Disease Centre (1969). *Manual of Tests for Syphilis* (revised). Public Health Service Publication No. 11. US Government: Washington DC.
- Oomen, A. P. (1967). Clinical manifestations of onchocerciasis. *Ethiopian Medical Journal*, 5, 159-173.
- Pankhurst, R. (1975). Old-time Ethiopian cures for syphilis: Seventeenth to twentieth centuries. *Journal of the History of Medicine and Allied Sciences*, 30, 199-216.
- Reggiardo, Z., and Middlebrook, G. (1974). Delayed-type hypersensitivity and immunity against aerogenic tuberculosis in guinea pigs. *Infection and Immunity*, 9, 815-820.
- Sinha, D. P., and Bang, F. B. (1976). Protein and calorie malnutrition, cell-mediated immunity and BCG vaccination in children from west Bengal. *Lancet*, 2, 531-533.
- Skinsnes, O. K. (1969). *Transactions of the VIIth International Congress on Leprosy*, p. 222. Japanese Leprosy Foundation: Tokyo.
- Thivolet, J., Simeray, A., Rolland, M., and Challut, F. (1953). Etude de l'intradermo-réaction aux suspensions de treponemes formoles (souche Nichols pathogène) chez les syphilitiques et les sujets normaux. *Annales de l'Institut Pasteur*, 85, 23-33.
- Vukotich, D., and Giel, R. (1970). Cardiovascular and neurological findings in Ethiopians with syphilitic heart disease. *Tropical and Geographical Medicine*, 22, 45-52.
- Wilkinson, A. E. (1972). *Laboratory Diagnosis of Venereal Diseases*. Monograph Series No. 1, pp. 18-24. Public Health Laboratory Service: London.