presence of inflammatory changes and the isolation of Chlamydia. Furthermore, the clinical signs associated with the presence of Chlamydia in the conjunctiva, genital tract, and rectum may closely resemble each other.

In early studies large amounts of the urethral epithelial cells to be tested were obtained by a curette.[102 104] This made the study of a control group impracticable. A miniature endo-urethral swab has been devised[129] which can be passed to the bulb of the urethra in men, and results using this atraumatic method to collect material for culture in irradiated McCoy-cells are as good as those using a urethral curette. This method will permit the study of a control group of men and repeated tests of the urethra to assess the results of treatment of chlamydial urethritis in male patients.

Genital Reservoir of Chlamydial Infection

Non-gonococcal urethritis (NGU) is becoming increasingly common. In England and Wales in 1970, 48,550 cases of NGU were reported in men, compared with 54,717 cases of gonorrhoea in men, women, and children.[57 58] If the equivalent infections in women are considered probably the incidence of non-gonococcal genital infection in men and women must be even greater than that of gonorrhoea. About 90% of NGU in men is NSU. In a joint study, carried out at the Whitechapel Clinic of The London Hospital and the Institute of Ophthalmology, eight cases of gonococcal ophthalmia neonatorum were seen over a period in which 44 cases of ophthalmia neonatorum due to TRIC agent were seen. Factors concerned in this ratio include the incidence of each infection in the community, the relative clinical silence of genital infection due to TRIC agent (so that parents tend to remain untreated), and the longer incubation of ophthalmia neonatorum due to TRIC agent than that due to gonorrhoea.

Hence a considerable proportion of "non-specific" genital infection is related to Chlamydia. The new developments will enable us to begin to define how big this proportion is; to study control groups; to determine if any of the Chlamydia are non-pathogenic in the eye, genital tract, or elsewhere; and to study further special forms of disease such as Reiter's disease, abacterial pyuria, proctitis, and salpingitis. Thus there is evidence already that salpingitis commonly occurs in the mothers of babies suffering from ophthalmia neonatorum due to TRIC agent.[103 130] The culture of specimens obtained at laparoscopy should show whether Chlamydia is present in the affected fallopian tubes or not. Such studies will lay the foundations for defined assessment of treatment for disease due to Chlamydia.

It would be surprising if there were no other agent concerned as a cause of NSU; therefore it will be of particular interest to test for other agents those patients in whom efficient tests (cell culture and immunological studies) for Chlamydia have given negative results.

Persistence of Treponemes after Treatment

E. M. C. DUNLOP

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Treponeme-like forms have been found by workers in France, the United States of America, Italy, and Britain in material from patients suffering from late syphilis, even after large amounts of antisyphilitic treatment; they have also been found after the treatment of early syphilis. The organisms have been recovered from lymph nodes, aqueous humour, cerebrospinal fluid, brain, arteries affected by temporal arteritis, and bone. The subject has been reviewed.[51–56]

Syphilis in England and Wales

Syphilis is a very well-controlled disease here,[57 58] unlike gonorrhoea and non-gonococcal genital infection; thus the number of reported cases of infectious syphilis was only 1,628 in 1970, compared with the 4,986 cases in 1939. Nevertheless, in the 25 years starting in 1946 over 178,000 cases of acquired and congenital syphilis were reported. If the number of persons treated during the war is added it is clear that there are many people in this country who know that they have received treatment for syphilis. If unnecessary doubts are raised now about the clinical effectiveness of treatment this will cause ill-founded anxiety, fear, and the reopening of long-closed problems for many people.

The London Hospital, Moorfields Eye Hospital, Institute of Ophthalmology
E. M. C. DUNLOP, M.D., F.R.C.P., Consultant Venereologist

Are they Treponema pallidum?

The fundamental question is whether treponeme-like forms found after the treatment of syphilis are *Treponema pallidum*. If they are, they may be virulent, avirulent, or of low virulence. Alternatively, these forms may be artefacts, natural filaments, or other treponemes. Thus Wilkinson[59] reported that glass filaments could resemble treponemes, while Montenegro *et al.*[60] concluded that some structures previously reported as treponemes by their group were artefacts but that others were "incontrovertible" treponemes.

Treponeme-like forms may be seen on microscopical examination of a specimen from a patient or from an animal that has been inoculated with such a specimen. They may be seen in wet preparations by darkfield microscopy, which allows their characteristic motility to be recognized, or in fixed material which may be stained with silver or by a fluorescent antibody method. Experienced observers who have looked for "persistent treponemes" have reported the presence of structures morphologically typical of *T. pallidum* in fixed preparations. Nevertheless, if other structures can closely resemble *T. pallidum*, conceivably some may be indistinguishable on morphological grounds. But artefacts could not show true motility in wet preparations. Motile treponeme-like forms have been seen by different observers in aqueous humour and in cerebrospinal fluid. Thus Wilkinson[61] found such forms in wet darkfield preparations of spinal fluid in six cases; in three the forms were motile but, perhaps not unexpectedly, did not show the vigorous movement that is shown by treponemes freshly obtained from the lesions of early syphilis.

The presence of virulent *T. pallidum* may be shown by the experimental infection of animals. The importance of a typical

infectivity test in the rabbit was emphasized by Turner *et al.*[53] But, though the course of syphilis in the rabbit after infection with material from patients suffering from early syphilis is well known, that following inoculation with material from patients with late syphilis is little known. Collart[62] reported that even in primary and secondary syphilis only eight of 15 transfers of infectious material to rabbits gave positive results. In particular, a negative classical infectivity test should be interpreted with caution after the inoculation of material from a patient suffering from late or treated syphilis.[63-65]

Rabbits may be infected by *T. cuniculi*, while monkeys may also harbour treponemes—so animals used for inoculation must be free from such infection. Disease produced by inoculation with a fully virulent organism should be typical, though probably less virulent organisms may cause milder disease; its final identification as syphilitic rests on finding typical treponemes on darkfield microscopy of the initial recipient animal or of an animal that has received material in a second passage.

Morphologically some persisting treponeme-like forms in material from patients are identical with *T. pallidum*. Animals have been infected with such material by four groups of workers.[64-72] Treponemes were demonstrated in inoculated animals after staining specimens with silver or by a fluorescent antibody method, or by darkfield microscopy of wet specimens, which allowed motility typical of *T. pallidum* to be seen as well as morphological appearance. Hardy *et al.*[72] in a unique study, found virulent treponemes after the treatment of early congenital syphilis in a baby who had died at the age of 22 days. The mother had been treated with 2·4 mega units of benzathine penicillin 10 days before delivery. The baby received large doses of penicillin for 17 days after birth; a non-motile treponeme was found by darkfield microscopy in the spinal fluid at the age of 10 days and another in the aqueous humour after death. Inoculation of rabbits with aqueous humour and with tissue from the eye produced testicular lesions due to a strain of *T. pallidum* that was penicillin-sensitive and highly virulent to rabbits. This is the first report of the recovery of undoubted *T. pallidum* from a case of treated early syphilis.

Hence, in a few cases at least, treponeme-like forms found after treatment are *T. pallidum*.

How Does T. pallidum Survive?

Treponemes have been found after dosages of penicillin sufficient to maintain much higher concentrations of penicillin than the 0·03 U/ml regarded as fully treponemacidal. Nevertheless, a strain of *T. pallidum* resistant to penicillin has yet to be described. A number of factors may be concerned.

Stage of Disease.—In late syphilis the infection is relatively inactive; hence some organisms may survive because they are resting and so may be insusceptible to treatment. However, the organism recovered by Hardy *et al.*[72] was obtained after the treatment of early congenital syphilis; it was highly pathogenic to rabbits and was sensitive to penicillin.

Microbial Persistence.—McDermott[73] used this term in drawing attention to the fact that some organisms are able to survive attack by antibiotics to which they are sensitive. Thus treatment failure occurs in a few patients after the treatment of early syphilis with penicillin.

Site of Infection.—Smith *et al.*[74] reported a failure rate of 21% after the treatment of asymptomatic neurosyphilis with benzathine penicillin by injection compared with 10·5% for other preparations of penicillin. Because of the low levels of penicillin that are produced in serum by the former it seems that effective treponemacidal levels may not be attained in the spinal fluid and eye. Goldman *et al.*[75] confirmed that aqueous benzylpenicillin and benzathine penicillin, when administered by intramuscular injection, do not readily enter the eye. Though levels of penicillin and of ampicillin in serum and eye may be increased by the administration of probenecid, conditions in the eye may be such as to favour persistence of treponemes.[72] Persisting treponemes have been found in other sites, particularly in lymph nodes,[64-68] which must be reached by treponemacidal concentrations of antibiotics.

Intracellular Forms.—By electron microscopy[76-78] *T. pallidum* has been observed in macrophages, plasma cells, fibroblasts, lymphocytes, neutrophils, and a Leydig cell. Treponemes in phagocytic cells undergo change, though in fibroblasts they appear unchanged.[76 77] Possibly organisms do survive within some types of cells. While treponemacidal levels of antibiotics are readily attained in serum, relatively little is known about the levels attained within cells.

"Zone Phenomenon" of Eagle.—Penicillin acts on growing organisms. Tipper and Strominger[79 80] have shown that low concentrations of the penicillins acting on *Staphylococcus aureus* cause the production of cell walls deficient in peptide cross-linkages; high concentrations rapidly inhibit growth so that defective cell walls are not produced. This may explain the fact that the killing rate of low concentrations of penicillin on *Staph. aureus* was higher than that of high concentrations (the "zone phenomenon" of Eagle). Whether this applies to *T. pallidum* is unknown.

Importance for the Patient

The successful inoculation of animals in a few cases does not mean that all treponeme-like forms are *T. pallidum*. Also experience of the infectivity test in late syphilis, and particularly treated late syphilis, is small. A positive test shows the presence of *T. pallidum* virulent to the rabbit, but the significance of a negative infectivity test in such a case is less clear. In long-standing syphilis in man, tissue sensitivity may play a major part in the production of disease. Possibly "persistent treponemes" with reduced or no virulence to rabbits[64 66] might produce disease in the human host sensitive to them or to their products. It may also be significant that lesions of syphilis were precipitated in some rabbits by the administration of cortisone.[64-68]

Several studies suggested a relation between the finding of treponeme-like forms and active manifestations of syphilis, such as iritis.[61 81-83] Subsequently the work of the last group at Moorfields Eye Hospital and the Whitechapel Clinic was extended.[84 85] No correlation could be found with activity of iritis; 35 patients with active iritis were tested and treponeme-like forms found in aqueous humour from seven; 37 patients with previous iritis were tested and treponeme-like forms were found in seven. In all, 252 patients were tested, including a control group of 15 patients. Treponeme-like forms were found in one of the control group compared with 42 of 223 patients known to have had treated or untreated treponemal infection. Treponeme-like forms were found only a little more commonly in specimens of cerebrospinal fluid with a cell count of 6 or more (4 of 12) than in specimens with a normal cell count (30 of 227). There was no significant correlation between positive findings and positive results obtained by serological tests (treponemal immobilization test, absorbed fluorescent treponemal antibody test, or tests for reagin. Previous "adequate" antisyphilitic treatment did not influence the results of tests for treponeme-like forms. This study is to be extended to include more control cases.

Ryan *et al.*[86] studied aqueous humour from 153 patients including 48 "controls." In only one case were treponeme-like forms seen; these were in three specimens from a patient with quiescent interstitial keratitis; inoculation of rabbits with this aqueous humour gave negative results. In 16 cases short spiral forms were seen, and in two, large borrelia-like forms. There was no correlation between the finding of these spiral forms and the results of serological tests for syphilis in this study or in that of Whitfield and Wirostko.[83] They found treponeme-like forms in aqueous humour from six of 50 patients suffering from uveitis but not in that from 50 controls. Golden

et al.[87] found motile treponeme-like forms in aqueous humour from one of 47 "control" patients. These did not stain by an indirect fluorescent antibody method; the patient had negative serological tests including the absorbed fluorescent treponemal antibody test.

The finding of treponeme-like forms in material from patients in whose cases even the most sensitive serological tests for syphilis have given negative results does not necessarily mean that these forms are not *T. pallidum*. Seronegative syphilis does occur; monkeys have been infected with material from a seronegative tabetic.[70] Degos *et al.*[62] found motile treponemes at necropsy in the lymph nodes of a seronegative patient who had died from malignant secondary syphilis after having received treatment for 10 days. Nevertheless, if most treponeme-like forms were related to syphilis, it would be reasonable to expect to find a correlation between their presence and positive results from sensitive tests for the diagnosis of the disease. Certainly, treponeme-like forms have been found in some cases in which no definite evidence of treponemal infection could be found despite detailed investigation.

Preliminary Conclusions

Tests of aqueous humour and cerebrospinal fluid for treponeme-like forms give a small yield even in cases of undoubted late syphilis, treated or untreated. In a few cases persisting organisms have been shown to be *T. pallidum* but in most cases their nature is uncertain and so is their significance to the patient.

The search for treponeme-like forms is a time-consuming research procedure that can be undertaken only by experienced microbiologists. Such tests might be made more sensitive, as has been attempted by Chandler.[88] Because identification of the agent by its behaviour in experimental animals is fundamental, and because Collart *et al.*[64 66] have shown reduced virulence of persisting treponemes to the rabbit, further attempts to enhance the sensitivity of experimental animals may give additional information. It is essential that control groups should be studied and any treponeme-like forms should be identified as fully as possible.

The finding of apparently persisting treponemes after the treatment of late syphilis cannot alter the firmly established view of clinicians and epidemiologists[89] that it is only early syphilis, in which moist lesions are produced, that is infectious by sexual contact.

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Clinical Problems

Bilateral Retinoblastoma: A Dominantly Inherited Affection

ARNOLD SORSBY

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Summary

Ten survivors of sporadic bilateral retinoblastoma had 14 offspring, of whom eight were affected, seven of them in both eyes. Other reports from the literature raise the total of similar unselected cases to 19 survivors with a total of 39 offspring, of whom 17 were affected in both eyes and three in one eye.

The high incidence of the bilateral affection in dominantly inherited retinoblastoma—as recorded in the literature—and in the offspring of survivors from sporadic bilateral retinoblastoma, as reported in the present study, establish all cases of bilateral retinoblastoma as a dominant disorder either in transmission or as a new mutation. This disorder, though fully or almost fully penetrant, is not always fully expressed. A small proportion, probably about 5 to 10% of all cases of the much more common sporadic unilateral affection, are in fact incompletely expressed germinal mutations for bilateral retinoblastoma. There is some evidence that histological appearances may distinguish these potentially transmissible unilateral tumours from the mass of unilateral retinoblastoma which have no genetic significance.

Royal College of Surgeons of England, London W.C.2

ARNOLD SORSBY, C.B.E., M.D., F.R.C.S., Emeritus Research Professor in Ophthalmology

Introduction

The designation of retinoblastoma, which has replaced the older name of glioma of the retina, emphasizes the fact that this