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REVIEW ARTICLE

Sexually transmitted diseases: microbiology and management

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Introduction

As we enter a new millennium, age-old problems of infectious diseases continue to plague us. Very few have been eliminated; many – e.g., tuberculosis – are increasing even faster than the terrifying increase of human populations. Such diseases are often inflated by that very increase – through overcrowding, poverty and environmental degradation. The end of the last millennium has also seen an unprecedented maelstrom of new or emergent diseases. Many of these, too, may have arisen in the context of modern social trends. Perhaps the most nightmarish is HIV disease. Unknown before the last two decades of the twentieth century, this currently incurable virus already infects >50% of the ordinary young adult population in parts of sub-Saharan Africa and is spreading rapidly, especially in the poorer and more socially unstable parts of the world.

Nevertheless, HIV is potentially one of a group of the most controllable diseases – sexually transmissible diseases (STDs). These – unlike tuberculosis, which is transmitted *via* the most fleeting social intercourse on a billion aerosols – require the most intimate contact between human beings for their transmission. Even under these conditions, HIV is not nearly as transmissible as some other STDs, e.g., hepatitis B or gonorrhoea. It is the co-factor effect of other STDs that largely explains the infectivity and prevalence of HIV.

The prevalence of STDs – 333 million cases per annum [1] – has driven the HIV epidemic. Controlling STDs, by reinforcement of syndromic management without any other interventions of sophisticated diagnostic techniques, reduced the rate of HIV increase in the celebrated Mwanza trial [2]. Even before this trial had been published, the World Bank estimated that STDs, often easily treated, often incapacitating if untreated and principally affecting the most economically productive section of society – young adults – was the most 'cost-effective' of medical interventions [3].

Antimicrobial treatment of some STDs is becoming increasingly problematic. Some strains of gonorrhoea and chancroid are now resistant to all the antibiotics generally available in poorer countries. HIV rapidly develops resistance to the multitude of ever more expensive antiviral agents (and their combinations) that are being developed to treat it. However, the vast proportion of STDs world-wide are not treated at all [4]. This is affected by the cost of treatment, the subclinical nature of many STDs and the reluctance of individuals to seek treatment. Equally, sexual contact between individuals is inherently difficult to regulate, driven as it is in part by atavistic instinct and taboo. The same degradation of the human environment that has promoted the resurgence and spread of many infectious diseases has also enhanced STDs.

On 6 February 2000, a dedicated group of speakers and an enthusiastic audience met at the School of Tropical Medicine, Liverpool, to spend a day discussing new methods of investigating, understanding and treating STDs as well as social factors underlying various STDs in a number of countries. The following is a synopsis of the meeting.

Finally, a story is told of Julius Nyerere: when his advisers were in dispute about priorities in development for Tanzania, he told them about the baby millipede who complained to his mother that he could not decide which of his legs to move first. 'Move all of them!' was her reply. The complexity and variety of STDs are

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immense, it seems likely that strategies to control them, e.g., mass treatment, vaccination, contact tracing of behaviour change, will succeed only if used in a multifaceted approach which combines technology with humanity.

THE MANAGEMENT OF STDs FROM VENEREOLOGY TO SEXUAL HEALTH: NEW OPPORTUNITIES AND NEW THREATS

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At the beginning of the last century the Royal Commission on Venereal Diseases (VD) produced an enlightened document which led to the Public Health (Venereal Diseases) Regulations (1916) [5]. This formed the basis for clinical services for VD in the UK and resulted in a clinic system in which patients had open access and free treatment. Confidentiality was guaranteed and there was to be no notification by name. However, for epidemiological purposes the number of patients with each disease would be reported quarterly. Proper supporting laboratory facilities for appropriate tests were provided and medical students were instructed in the practical aspects of venereology. For the staff, there was now a career structure to follow. These basic principles still apply in the clinic system today.

The clinics were highly stigmatised, but for those in trouble it was perceived as a safe place to go for proper professional advice and treatment, with confidentiality built into the system. The doctors and nurses working in the clinic showed great expertise in administering the then available treatments and in dealing with their many complications. All this was before the modern vogue for counselling, but individual patients were treated with great sensitivity, while practical issues about spouses, partnerships outside of marriage, future liaisons, effects on children and even the insurance system were dealt with in the clinics on a daily basis [6].

In the post World War II era, penicillin dramatically changed the face of VD. By the early 1950s, the incidence of syphilis and gonorrhoea fell to an all time low and some authorities predicted that they might be treated out of existence [7]. However, neither the spirochaete nor the gonococcus must have read these reports, because there is now new concern about the increasing incidence of both these diseases [8].

With the decline of traditional VD, physicians working in the clinics could now pay attention to other 'STDs'. The associated advance in laboratory technology has facilitated this work. To reflect this change in workload most venereologists changed their name to genitourinary physicians. With the emergence of AIDS in the early 1980s, new money flowed into the system, improving the infrastructure of genitourinary medicine clinics [9]. Most of the old- fashioned basement clinics have now gone to be replaced by modern departments. This, along with media publicity, has done much to remove the stigma of STDs although much remains to be done. Genitourinary physicians should be ideally placed to lead sexual health because:

- We have in place a clinic system, offering confidential, open access in every health authority in the country and with an established system of confidential networking between clinics. The speciality links easily with microbiology, epidemiology and public health. These are all important in STD control.
- Genitourinary physicians are good at taking sexual histories. This is a great opportunity to educate other colleagues.
- Genitourinary physicians are experts at examining the genitals of both sexes in a structured way.
- Genitourinary physicians, because of their everyday clinical experience, can explain to patients the risks connected with unprotected sex and are able to place this advice in a practical context.
- Genitourinary physicians are used to sexuality in its many shapes and do not start with the assumption that everyone is 'straight'.
- Virtually all genitourinary physicians are trained in family planning.
- Genitourinary physicians are used to seeing victims of sexual assault and handle these patients with sensitivity.
- Genitourinary physicians are experienced in seeing patients with non-infective genital disease as well as those many patients who worry about their genitals (and their sexuality) but who have no organic disease.

And yet in spite of all these advantages, the clinic system is under threat mainly due to funding issues. Primary care groups (PCGs), who will soon control all the funds as they become Primary Care Trusts, may not be aware of the full range of clinical activities of their local genitourinary medicine department, because of open access and confidentiality. Each year almost one million new cases are dealt with by genitourinary physicians in the UK.

We await with interest the report of the 'Sexual Health Strategy Group' from the Department of Health. With the recent increase in all forms of STDs, the emergence of antibiotic-resistant strains and the relentless threat of AIDS it is more important than ever that we not only maintain but strengthen the clinic system for clinical STD services [10]. The presence of most STDs has been shown to increase the relative risk of the acquisition of HIV [2]. Perhaps the most important single public health action to contain HIV spread is to adequately control STDs. The corollary is certainly

true, 'if we do not control STD spread we will not control HIV no matter what other public health measures we may take'.

Conclusion

- What started as venereology has changed its name to sexual health; but the patients remain the same, having the same anxieties about sex and its consequences and worrying about their partners.
- The disease profile has changed dramatically with new STDs and the emergence of antibiotic resistance, while old-fashioned VD has not gone away.
- The basic principles of clinical care remain unchanged. We need to preserve and strengthen the clinic system of STD control. We will neglect this at our peril. If we do not keep the genital tract 'clean' there will be no sexual health either for the individual or the nation.

BACTERIAL VAGINOSIS: DIAGNOSIS, MICROBIOLOGY AND MANAGEMENT

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Introduction

Bacterial vaginosis (BV) is a clinical syndrome of unknown aetiology characterised by an overgrowth of vaginal anaerobes and variable degrees of depletion of the normal *Lactobacillus* spp. population. Symptomatic women report an offensive, fishy smelling discharge, which is most marked after unprotected intercourse or at the time of menstruation. The diagnosis is usually made clinically based upon the composite (Amsel) criteria (Table 1) [11]. Approximately 50% of women with BV appear to be asymptomatic. Many studies in the last decade have established that BV is a risk factor for a host of obstetric, gynaecological and neonatal complications, including miscarriage, preterm birth and post-partum endometritis. In the western world, BV is the leading cause of abnormal vaginal discharge. In an unselected population, the prevalence rate is 10–20% [12], but this may reach 36% in women attending STD clinics and 28% in those seeking elective termination of pregnancy (TOP) [13]. It is probably commoner in women with sexually transmitted infections but has been reported in virgin women and may be particularly common in lesbian women [12]. It is associated with black race and IUCD use in many studies. The condition often arises spontaneously around the time of menstruation and may resolve spontaneously mid-cycle [14]. Our lack of understanding of the aetiology is reflected in our inability to prevent relapse after antibiotic treatment.

Table 1. Amsel's (composite) criteria for the diagnosis of BV in clinical practice

- vaginal pH >4.5
- release of a fishy smell on addition of alkali (10% potassium hydroxide)
- a characteristic discharge on examination
- presence of 'clue cells' on microscopy

Diagnosis

Amsel criteria

BV is diagnosed by detecting at least three of four composite criteria (Table 1). These arose from the original description of 'Haemophilus vaginitis' by Gardner and Dukes in 1955 [15]. They recognised the typical thin homogeneous discharge, elevated vaginal pH and the fishy smell. Moreover, they described the appearance, on wet mount examination of vaginal fluid, of epithelial cells covered with so many small bacteria that the border was fuzzy. They called them 'clue cells', as their presence was a clue to the diagnosis. They associated a small gram-variable coccus – '*Haemophilus vaginalis*', ultimately renamed *Gardnerella vaginalis* – with the condition. Subsequently, other anaerobic or facultative species were found in association with *G. vaginalis*. Pheifer and colleagues described the KOH or 'whiff' test as an aid to diagnosis in 1978 [16]. At a symposium in 1983, the term bacterial vaginosis was adopted. This recognised that many anaerobic or facultative bacteria are present and that classical signs of inflammation are absent.

These criteria remain the mainstay of diagnosis for clinical practice. They are simple to perform in an 'office' setting and, apart from the outlay for the microscope, require minimal materials. However, they are subjective, and each of the composite criteria may be misleading. Recent studies have concluded that there is a continuum from normal lactobacillus-dominated flora through to 'severe BV', with an intermediate category [17]. The limitations of the Amsel criteria reflect this, as the system attempts to diagnose a dichotomy between BV and normal. As other diagnostic methods are assessed by comparison with the Amsel criteria it is not surprising that not one of them achieves 95% sensitivity and specificity, as the 'gold standard' is itself imperfect.

Microbiology

The organisms most commonly associated with BV are *G. vaginalis, Prevotella* (often described generically as *Bacteroides*) spp., *Mobiluncus* spp. and *Mycoplasma hominis*. High concentrations of *G. vaginalis*, >100-fold greater than normal, are found in up to 95% of women with BV, but it was also found in >50% of women without BV, so that culture has a poor specificity. Quantitative culture, showing high concen-

trations, correlates better with BV in research studies, but culture should not be used for routine diagnosis. The reported prevalence of other organisms often reflects the sensitivity of the culture method for the specific organism. For instance *Fusobacterium* spp., peptostreptococci and non-viridans streptococci have also been associated with BV.

Biochemical tests

BV produces many biochemical changes in vaginal fluid. Anaerobic bacteria produce trimethylamine and polyamines such as putrescine or cadaverine, which are associated with the fishy smell. There is an increase in the ratio of succinate to lactate [18, 19]. Many bacterial enzymes are detectable including sialidase [20, 21] and proline aminopeptidase [22]. These can be measured by techniques such as gas chromatography, HPLC or by biochemical assays. Simple assays have been developed for these, and some are now becoming commercially available. A proline aminopeptidase test was found to have a sensitivity of 79% and specificity of 95% [23]. Another test in development looks for high concentrations of *G. vaginalis* through the use of oligonucleotide probes. Some of these tests may be useful for detecting virulence co-factors rather than just diagnosis. For instance, sialidase has been identified as an additional risk for preterm birth [24].

Gram's stain

The gram-stained vaginal smear has been compared with the composite criteria in several studies. Typical lactobacilli are large gram-positive rods, with blunt ends. In contrast, *G. vaginalis* is usually a gram-negative coccus, although described as a gram-variable coccobacillus. *Mobiluncus* spp. are also easily recognised as curved rods with pointed ends. *Mob. mulieris* bacilli are longer than *Mob. curtissi*. On wet mount they are highly motile by means of their central flagella.

Systems for interpreting gram-stained smears have been used by Spiegel *et al*. [25], Nugent *et al*. [26] and Thomason *et al*. [27]. Most of these scoring systems show a high sensitivity, >90%, but low specificity, 70–90%, when compared with Amsel criteria. In pregnant women we described an intermediate category of gram-stained smear in which there was a mixture of lactobacilli and other morphotypes, corresponding to the intermediate score on the Nugent scale [28]. Preliminary results of a microbiological investigation of the intermediate flora and BV indicated that there is little difference in the bacterial species isolated from women with gram-stained smears categorised as intermediate or BV but there was a distinct order in which different species increased in numbers [17]. Gram-staining has the advantage that it allows recognition of the intermediate flora and storage of slides that subsequently can be evaluated independently in research studies. Similar scoring systems have been used to interpret Papanicolaou-stained vaginal [29] or cervical smears [30], but no standardisation of methodology has been agreed.

Management

Because BV follows a relapsing remitting course in many women, the value of treating asymptomatic BV has not been established. There is also no evidence that treatment reduces the prevalence of BV in a community [31]. Therefore, treatment should be prescribed for control of symptoms and in circumstances in which it might prevent complications of a procedure or pregnancy.

Treatments

Antibiotics with good anti-anaerobic activity should be effective treatments for BV. Thus, metronidazole, clindamycin and co-amoxiclav are obvious choices. There are no large trials of co-amoxiclav, which is not licensed for this indication. Theoretically, an antibiotic which is not active against lactobacilli, such as metronidazole, might facilitate a more rapid restoration of vaginal flora than one which is active against lactobacilli, such as clindamycin. On the other hand, clindamycin has better activity against *M. hominis, Mobiluncus* spp. and *G. vaginalis* than metronidazole.

The standard treatment for BV is a course of oral metronidazole. The precise dosage and duration varies, but 400 mg twice a day for 5 days is adequate. It is difficult to compare between treatment studies that use different methodologies [32]. The cure rate immediately after treatment with metronidazole is up to 95%, but after 4 weeks this falls to 80% in open label studies and to <70% in blinded studies. The cure rate after oral placebo treatment is only 5%. A meta-analysis concluded that a single 2-g dose of metronidazole is as effective as 5- or 7-day regimens [33]. This might represent a balance between slightly greater efficacy of 5- or 7-day regimens against better compliance with single dose treatments [34].

Topical treatments with intravaginal clindamycin 2% cream, or metronidazole 0.75% gels are licensed for the treatment of BV. Efficacy is similar to oral metronidazole [34, 35].

Male partners

Four double-blind placebo-controlled trials have failed to show any difference in relapse rates of BV following treatment of male partners with metronidazole, tinidazole [35] or clindamycin 150 mg four times per day [36]. In women with recurrent BV, many physicians advocate screening the partner for STDs but this is not based on prospective studies.

Unwanted effects

Oral metronidazole use is associated with well-recognised side-effects of nausea, a metallic taste and intolerance of alcohol. Allergic rashes occur occasionally. Initial concerns about potential teratogenicity of metronidazole have not been substantiated [37]. However, there remains a potential for mutagenicity [34]. Clindamycin taken orally can induce rashes and occasionally pseudomembranous colitis. Approximately 10% of women develop symptomatic candidosis following treatment for BV.

Treatment in pregnancy

BV is associated with second trimester miscarriage and preterm birth. Several studies have evaluated the value of screening and treating BV to prevent adverse pregnancy outcome. Unfortunately, the results have been variable.

Use of intravaginal preparations is attractive to reduce the incidence of side-effects and the potential for teratogenicity. Once infection is established in the uterus, intravaginal treatment is unlikely to be sufficient to prevent progression to preterm birth. Thus, topical treatment might work best in the first trimester of pregnancy. Two studies reported non-significant trends for women receiving clindamycin cream to have a greater rate of preterm birth or low birth weight infants than those receiving placebo [38, 39]. In contrast, a multicentre UK study has shown a 50% reduction in preterm birth for clindamycin cream with borderline statistical significance (R. F. Lamont, personal communication).

In women with a high risk of preterm birth two studies have shown a benefit for oral treatment for BV, albeit that one was a subgroup analysis. In one study of 80 such women with BV, oral metronidazole treatment, 250 mg tds for 7 days, of women with BV between 13 and 20 weeks gestation produced a 50% reduction in preterm birth compared with placebo treatment [40]. A second study used combined treatment with metronidazole and erythromycin for women with a high risk of preterm birth [41]. In the subgroup of 258 women with BV there was a reduction in preterm birth from 49% in the placebo-treated group to 31% in the antibiotic-treated group. There was no benefit from treatment in women who did not have BV. A large Australian study showed a small non-significant trend for a benefit of using short course metronidazole 400 mg bd for 2 days, repeated after 1 month if BV was still present [42]. Subgroup analysis showed a reduction in preterm birth in the treatment group, particularly those with a prior preterm birth who adhered to the medication. A large multicentre study in the USA randomised 1953 women, who were between 16 and 24 weeks gestation, to receive two 2-g doses of metronidazole or placebo, followed by a second treatment between 24 and 30 weeks gestation [43]. Preterm delivery occurred in 12.2% of women in the metronidazole group and 12.5% of women in the placebo group.

On the basis of these studies we cannot conclude that antibiotic treatment of BV in pregnancy has been shown universally to reduce the incidence of preterm birth. BV has been associated with plasma cell endometritis [44]. To optimise treatment of pregnant women the treatment may need to be directed at endometrial rather than vaginal infection. Furthermore, an evaluation is needed of treatment administered as early as possible in pregnancy, followed by retreatment of relapses to establish whether antibiotic treatment will improve pregnancy outcome. Current data support a benefit for high-risk pregnancies, although the largest randomised study showed no benefit even in this subgroup [43].

Other potential indications for screening and treatment

Termination of pregnancy

Women infected with *Chlamydia trachomatis* who undergo elective TOP have a high risk of developing endometritis and pelvic inflammatory disease. BV also confers an increased risk and may be present in nearly 30% of such women [13]. A double-blind placebo-controlled trial from Sweden demonstrated that the risk of endometritis, in women who did not have chlamydia, was reduced from 12.2% in placebo-treated women to 3.8% of women prescribed oral metronidazole before termination [45].

Other gynaecological surgery

BV has been associated with vaginal cuff cellulitis, wound infection and abscess formation after hysterectomy. No randomised trials have been performed to investigate the value of screening and treatment before such surgery. Similarly, the potential role for BV in infections following IUCD insertion, hysteroscopy or dilation and curettage, has not been studied systematically.

HIV and STDs

HIV has spread rapidly through sub-Saharan Africa, south-east Asia and South America in the last two decades. Initial reports identified genital ulcer STDs as co-factors for transmission. An early study from Thailand reported an association with BV [46]. A large trial in Uganda of periodic presumptive treatment at a population level did not show a significant reduction in HIV acquisition associated with such treatment at 10-monthly intervals [31]. BV, which had a very high prevalence in this population, emerged as a co-factor for HIV acquisition [47]. A study of pregnant

women from Malawi reported BV to be associated with HIV acquisition during pregnancy and the post-natal period [48].

Self-help

BV probably arises in response to a variety of stimuli. Vaginal douching and the use of shower gel, bubble bath and shampoo should be avoided. In small studies, neither yogurt nor *L. acidophilus* have provided relief beyond the next menstrual period [32]. It is sensible to use condoms with new sex partners to protect against acquisition of many infections, possibly including BV. Although a woman may have several recurrences of BV over the course of several months it usually regresses following repeated treatments [14]. The concept of recolonising the vagina with strains of lactobacilli that produce large amounts of H_2O_2 to prevent relapse after treatment is being investigated.

Conclusions

A 5-day course of oral metronidazole remains the mainstay of treatment for symptomatic women with BV. Up to 30% of women treated for BV will relapse within 1 month of treatment. Intravaginal preparations of metronidazole or clindamycin have similar efficacy. They may have fewer adverse effects but are more expensive. On current data from trials, women with a history of second trimester loss or idiopathic preterm birth should be screened and treated with metronidazole if BV is found, early in the second trimester of pregnancy. We have insufficient data on the value of screening all pregnant women and on the value of clindamycin tablets at present. Women undergoing elective TOP should be screened for BV (and *C. trachomatis*) and treated with metronidazole. We need improved strategies to prevent relapse after antibiotic treatment.

APPLICATIONS OF GENETIC TYPING TO *NEISSERIA GONORRHOEAE*

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Introduction

Neisseria gonorrhoeae is the causative agent of the sexually transmitted infection gonorrhoea. It is a fastidious organism which is an obligate human pathogen. However, unlike some of the other causes of sexually transmitted infections, it is possible to cultivate the organism *in vitro* and hence to use typing methods to follow the epidemiology of this infection. Typing methods for gonococci have been used to monitor temporal changes, follow antibiotic resistant strains, identify clusters and follow transmission chains.

Phenotypic methods

Historically, the phenotypic methods of auxotyping (A) [49] and serotyping (S) [50] have been used as epidemiological tools. Auxotyping discriminates between strains on their nutritional requirement by using chemically defined media that lack individual amino acids such as proline, arginine, hypoxanthine, uracil, methionine and histidine [49]. Serotyping was initially performed with polyclonal antibodies but became more widely used with the description of a panel of 12 monoclonal antibodies in 1984 [50]. The antibodies are used in a co-agglutination test and the pattern of reactivity designates the organisms firstly into either an IA or IB serogroup and then into a serovar.

The phenotypic methods have been used extensively over the last 15 years to address epidemiological questions [51]. When these two independent characters are used alone their discriminatory ability can be low but used in combination they can be highly discriminatory. However, this approach has two problems: firstly, in most populations, a few A/S classes predominate, despite the large number of classes that have been described, and secondly, these methods have subjective endpoints and can have a variable reproducibility over time [52].

Genotypic methods

Genotypic methods have been developed for *N. gonorrhoeae* in an attempt to give greater discrimination between certain auxotypes and serovars and to give a more reproducible and reliable method than serotyping. Auxotypes such as arginine-, hypoxanthine- and uracil- (AHU) requiring, which are often serovar IA-1/2, are considered to be largely clonal and to originate from a common source [53]. However, serovars such as IB-1 are thought to be more heterogeneous and to consist of multiple genotypes. Methods that have been used to reflect the genotype include plasmid analysis, restriction endonuclease fingerprinting, hybridisation with specific probes such as rRNA, amplification by PCR with primers to arbitrary or repetitive sequences, pulsed-field gel electrophoresis (PFGE) and sequencing of specific genes [54].

The large number of techniques that have been described, together with the absence of an internationally accepted method, indicate that interpretation of genotyping of *N. gonorrhoeae* may be difficult. *N. gonorrhoeae* is unique in that it is highly competent for horizontal gene exchange throughout its life cycle. Extensive recombination is thought to occur, particularly during mixed infections *in vivo*, resulting in a

non-clonal or panmictic population [55]. For typing purposes, this genetic diversity can result in a high level of discrimination between strains dependent on the technique or gene chosen. The ultimate discrimination may be achievable in that each gonococcal strain may appear unique unless part of a short transmission chain. The level of discrimination can be measured in any population by using Simpson's Index of Diversity; when the Discrimination Index (DI) equals 0 then all isolates appear indistinguishable and when the DI equals 1 all isolates appear different [56].

Genotypic methods will vary in their discriminatory ability largely dependent on the gene chosen. Plasmid analysis, restriction endonuclease fingerprinting and ribotyping are likely to be less discriminatory because of the relatively small number of plasmids present and the conserved nature of the rRNA, whereas PFGE, sequencing of specific genes and typing of the hypervariable *opa* genes will be highly discriminatory. Therefore, it is essential that the question to be addressed and the level of discrimination required should be carefully considered before the technique is chosen. For instance, if temporal changes over many years are to be monitored, it is necessary to choose a technique that reflects low levels of genetic diversity which are relatively stable such as ribotyping. However, if sexual networks and transmission chains are of interest, then it is necessary to use a gene exhibiting high levels of genetic diversity over short periods of time to give fine discrimination, such as the *opa* genes.

Applications of genotypic methods

Plasmid analysis of antibiotic-resistant strains of *N. gonorrhoeae* is an example of a technique which can be used at different levels of discrimination and can also be used to monitor strains over time. *N. gonorrhoeae* can carry a number of plasmids: cryptic plasmid of 2.6 MDa; penicillinase-encoding plasmids of which the most common are of 2.9, 3.05, 3.2 and 4.4 MDa; conjugative plasmid of 24.5 MDa and TetM/conjugative plasmid of 25.2 MDa [57]. Analysis based on this approach was applied to clinical isolates of penicillinase-producing *N. gonorrhoeae* isolated from patients attending the Genitourinary Medicine Clinic at St Mary's Hospital, London, between 1995 and 1999. Analysis of the types of penicillinase-encoding plasmids demonstrated that the most prevalent type was the 3.2-MDa plasmid, which is thought to have originated in 'Africa' and was found in 60% of isolates. The 4.4-MDa plasmid, which originated in 'Asia', was found in 30% of isolates and the 2.9-MDa plasmid was found in only 10% of isolates. Analysis of these isolates for the presence of the conjugative and TetM/conjugative plasmids showed that the 3.2 + 24.5-MDa combination was found in 25% of isolates, 3.2 + 25.2-MDa in 28% of isolates and 4.4 + 25.2-MDa in 20% of isolates, demonstrating a greater degree of discrimination. Analysis of plasmid type over time showed that isolates carrying the 3.2-MDa penicillinase plasmid have decreased in number between 1995 and 1999 whereas isolates carrying the 2.9-MDa plasmid have increased in prevalence (C.A. Ison, unpublished data).

Opa-typing is an example of a technique that detects diversity in a hypervariable gene and can give fine discrimination [58] allowing the study of sexual networks and transmission chains. This approach has been used in a social, epidemiological and microbiological study of isolates from patients attending two Genitourinary Medicine Clinics in London and Sheffield [59]. Gonococcal isolates were collected from consecutive patients over a 1-year period and detailed demographic data were collected at extended interviews and blinded from the microbiological study. In London, both approaches revealed a heterogeneous population with a small number of sexual pairs or triplets. In this population opa-typing was highly discriminatory with a DI of 0.996. In Sheffield, linked epidemiological and microbiological data were available for 120 cases. The epidemiological data identified small clusters with 57% of cases apparently unlinked. In contrast, opa-typing divided the population into larger clusters of which the largest consisted of 18 and 43 cases, respectively, with only 21% of cases having unique profiles. The DI for opa-typing in Sheffield was 0.847. The data obtained from the London study confirmed previous work that opa-typing is a highly discriminatory technique. The presence of large clusters and a less diverse population in Sheffield raised the possibility that the large microbiological clusters had identified linked patients that were not obvious through epidemiological data alone because patients were unable or unwilling to identify all their contacts. This was supported by the highly significant correlation of the opa-typing with the epidemiological data. Moreover, in short transmission chains with named contacts, opa-types were often concordant. The characteristics of patients within the two main clusters suggested that when used together, the epidemiological and microbiological approaches have identified endemic gonorrhoea in Sheffield.

Discordance between the microbiological analysis and the epidemiological data did occur on occasions and may result either from dense parts of the network where patients had multiple partners and hence different sources of infection, or alternatively it may reflect natural evolution of the *opa* genes. High levels of discrimination are mostly easily produced by studying diversity in hypervariable genes and consequently there will be greater rate of change than exhibited by more stable or conserved genes. The rate of change of *opa* genes in a transmission chain is not known but in the Sheffield study *opa* profiles were detected that were unchanged over a 1-year period. In the subsequent 1-year period changes were detected in the prevalence of these two clusters resulting in the loss of one of the clusters after 2 years.

Conclusion

Genetic typing for gonorrhoea has proved to be highly discriminatory and the microbiological clusters are often larger than the epidemiological clusters. However, opa-typing has not proved sufficiently discriminatory to provide an estimate of distance in a transmission chain. Opa-typing produces a banding pattern for comparison and this may not be sufficiently sensitive for this purpose. However, it is possible that DNA sequencing may be of more value for this purpose as has proved possible in other infections such as HIV [60].

Molecular typing has enhanced our ability to study the epidemiology of infectious diseases. Highly discriminatory techniques, such as opa-typing for *N. gonorrhoeae*, can identify variation that changes over relatively short time periods and can be extremely useful in a specific geographical location. These techniques will be of less value for global epidemiology where changes over longer time periods are of interest and then it is more appropriate to use a technique that identifies variation that changes more slowly. In conclusion, it is unlikely that a single molecular technique will be developed that can be used for studying all aspects of the epidemiology of gonorrhoea. However, a range of techniques of differing discriminatory ability has already been described and the choice of technique should be driven by the question to be addressed.

EPIDEMIC SYPHILIS IN RUSSIA AND THE NEWLY INDEPENDENT STATES OF THE FORMER SOVIET UNION: TRENDS, ORIGINS AND PRIORITIES FOR CONTROL

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Introduction

Political, economic and social changes in the Newly Independent States (NIS) of the former Soviet Union have had a profound impact on the health of these populations. Furthermore, the new 'openness' has allowed the wider scientific community to access, for the first time, unique social and health statistics previously treated as State secrets. This review describes some historical and contemporary features of the epidemiology and control of syphilis in the NIS showing that during the 1990s these countries have experienced major epidemics of this infection. The origins and implications of these, as well as the prospects for their control, are discussed.

Trends in occurrence

With glasnost, historical data describing syphilis occurrence in the territories of the former USSR have become available to the wider scientific community for the first time. These show that rates of syphilis occurrence in the early 20th century were of the same order of magnitude as those observed in the USA [61]. In Russia in 1921, the notification rate was 550 per 100 000 [62]. With the introduction of penicillin and a rigorous public health control system this fell to 2.45 by 1963 increasing to a new peak of around 30 in the mid-1970s before declining again to <10 by the late 1980s [62]. It is now clear that subsequently, the NIS have experienced major epidemics of syphilis [63, 64]. Table 2 is based on data from the World Health Organization Regional Office for Europe and illustrates the scale of these epidemics, which are about 10 times larger than those reported from the USA in the early part of this decade [65]. By 1996, notification of new cases of syphilis in the Russian Federation had risen 48-fold over 1989 levels to reach 263 per 100 000 total population. Across the NIS, the epidemic has affected

Table 2. Rates of notification of new cases of syphilis in the Newly Independent States

	Notification rates of new cases of syphilis (per 100 000 population)						
State	1990	1991	1992	1993	1994	1995	1996
Armenia	3.7	7.1	9.0	9.8	12	12	–
Azerbaijan	2.7	4.0	6.0	7.8	–	–	
Belarus	2.7	5.1	12	31	72	149	210
Estonia	3.4	7.4	11	23	57	70	70
Georgia	13	13	13	12	16	16	–
Kazakhstan	1.5	2.1	3.5	8.2	33	123	231
Kyrgyzstan	2.0	2.1	2.5	4.4	22	33	137
Latvia	4.8	8.1	10	32	59	91	117
Lithuania	2.5	7.0	10	18	59	87	99
Moldova	16	20	47	83.3	116	173	200
Russian Federation	5.4	7.2	13	34	86	172	263
Tajikistan	1.6	1.6	2.9	5.8	8.3	20	12
Turkmenistan	4.6	5.4	6.3	8.3	15	23	28
Ukraine	6.0	10	18	35	69	119	144
Uzbekistan	1.8	1.9	2.5	4.4	11	25	24

men and women equally and has comprised, predominantly, infectious forms of the disease. Rates shown in Table 2 obscure even higher levels of infection among younger people: in 1996 the rate of notification of new cases of syphilis in young women aged 18–19 years in Russia exceeded 1 per 100 [64]. The epidemics are not confined to particular areas of the NIS but are widely distributed, although their timing varies from place to place [66]. Whilst rates in Western European countries have generally remained well below 10 per 100 000, these countries are beginning to see cases of syphilis which are linked to infection acquired in the NIS.

Whereas the recent syphilis epidemics in the USA are reported to have been focused on marginalised and impoverished communities [67], it is more difficult to develop an adequate picture of the socio-economic distribution of infection in the NIS. This is because the standard occupational groups do not reflect the important divisions, and rapid fluctuations in these, created by a growing mass of unemployed, political and economic migrants and refugees, as well as emerging entrepreneurial classes. However, our recent examination of the statistics of one dermatology clinic in a Russian city has revealed an increase in the proportion of cases of syphilis diagnosed in unemployed people between 1985 and 1995 from 18% to 50.4% (A. M. Renton, unpublished data).

The significance of these syphilis epidemics lies not only in the high levels of morbidity caused by the infection, but in their potential impact on the dissemination of HIV within the population. There is good evidence that syphilis, along with other sexually transmitted diseases (STD), significantly enhances the transmission of HIV in populations [2, 68, 69]. The conjunction of these syphilis epidemics with significant changes in sexual behaviour in NIS countries and emerging epidemics of injecting drug use and injection-acquired drug-related HIV [70] could produce epidemics of sexually acquired HIV in the NIS which are many times larger than those observed in Western European countries [71, 72]. These could have a significant negative influence on HIV epidemiology in Europe as a whole.

Origins of the epidemics

We must largely rely on anecdotal evidence to form hypotheses linking political, social and economic developments to changes in both sexual behaviours and the effectiveness and patterns of usage of health services [64]. Market reforms have coincided with the creation of major differentials in income, standards of living and conditions of work [73] as well as health sector reform. Official GDPs declined substantially in several countries, creating poverty and reducing Governments' resource bases for funding health services and other social infrastructure [74]. Industrial restructuring has increased workforce mobility and increased unemployment, especially among women [75]. Opening of borders has allowed a massive increase in migration both within the region and between the region and other countries. These changes are believed to have had a profound impact on both sexual behaviour and the STD control system [76].

Systematic studies of changes in sexual behaviour and attitudes are largely lacking, but a number of recent changes can be discerned which are likely to have contributed to the epidemics. International travel has increased considerably, with increased opportunity for sexual contact, perhaps with prostitutes, and in areas with higher HIV and STD rates. Internal migration has increased with a general casualisation of sexual relationships and, in some countries, a rapid growth in formal and informal prostitution. A rapid decrease in the age at first sexual intercourse has been described in Russia, with convergence towards average ages commonly described in European and US populations. There is also believed to have been an increase in child and adolescent prostitution. Increasing commerce between East and West has led to a rapid penetration of sexually orientated products, images and advertising and pornography has become widely available through sex shops and other outlets. The emphasis on individual choice and consumerism, the glamorisation of sexuality and the diffusion of sexual imagery are thought to have led to a profound shift in sexual mores and lifestyles, especially among young people.

The traditional system of STD surveillance and control of STD in the USSR was centred around a nationwide clinical Dermatovenereology Service (DVS) directed by the central Soviet Ministry of Health [76]. The service provided free diagnosis and had legal powers to force those infected to undergo treatment and to identify sexual contacts for tracing, and these were frequently used. Names of infected persons could, in certain circumstances, be passed to other government agencies and employers. There was an extensive programme of active screening and case-finding in clinically and occupationally defined groups. Diagnostic testing was reasonably well validated, although treatment of syphilis required hospitalisation and prolonged treatment with penicillin injections [64, 77, 78]. Surveillance of STDs was achieved through mandatory universal notification by physicians of newly identified cases. While the NIS have largely retained the old DVS structures since the political break-up of the Soviet Union, major changes have taken place within these. With people less willing to suffer the stigma and sanctions of the old service, there has been rapid growth in use of private sector STD treatment (often of poor quality), and of self-treatment, which is likely to have increased the average duration of infectivity (L. I. Tichonova, personal communication). In many countries, the dermatovenereology services now run a large number of anonymous dermatovenereology clinics

(ADVCs) (in parallel with and often in the same premises as the old service), where people can seek anonymous testing within the state system in exchange for payment. However, when syphilis is diagnosed patients are usually required to identify themselves, and the cost for investigation and treatment of syphilis may exceed $US 100 [77]. In reality, the levels of confidentiality may be very poor. Although ADVCs offer modern outpatient treatment for syphilis with benzathine penicillin, in some regions up to 50% of patients are still managed in hospital as inpatients.

The introduction of paid ADVCs has radically altered the system. In recent years Governments have often provided less than half of the funds indicated in agreed budgets, and while the old-style free service still operates, state sources represent only a fraction of the total funds received by the DVS. ADVCs provide a service in which each item is costed and charged directly to the patient. Which diagnostic tests are performed, and which treatment is prescribed may be determined by the patient's ability or willingness to pay. This system leads to wide variations in the quality of the clinical service received. In particular, those without money or insurance (traditionally those most at risk of STD) still face the barrier of the old named service. As the social acceptability of the authoritarian approach and named contact tracing further declines it may be expected that for those unable to afford the ADVCs, the time to presentation and treatment may actually increase.

There have also been attempts to move towards more integrated sexual health services. There has been *ad hoc* collaboration with other sectors such as family planning and women's consultation centres, and outreach and peer education projects to access sex workers, gay men and injecting drug users are beginning to be designed and implemented, but these continue to run into problems arising from the *de facto* criminalisation of these groups.

Prospects for control

It is tempting to see the way forward primarily in technical terms but this would be to ignore obstacles presented by practical reality. National authorities in the NIS recognise that control can be achieved only through combining sexual health promotion activities with the achievement of early detection and effective treatment of cases. They also recognise that the latter can be achieved only by providing confidential and affordable services which patients trust and that the use of legal sanctions is no longer desirable or effective.

But the development of services on these lines is very difficult to achieve even where national authorities have the will. The actual development of services is driven by a number of competing forces among which the desire to modernise is but one. The need to generate income to keep the service running is of key importance and drives the service towards activities for which patients can be charged and away from likely more cost-effective activities in health promotion and patient care. Furthermore, persistence of the old DVS ideology means that the interests of the individual are seen as secondary to the needs of society as a whole, and this is used to justify the often insensitive way in which people are treated, as well as the lack of confidentiality which still characterises much of the service. Therefore, an effective strategy to achieve the control of STD in the NIS will need to find ways to modify these forces and the way they interact to drive the development of control interventions towards the technical shape which all our experience suggests will be effective.

Conclusion

The epidemics of syphilis in the NIS have major implications for health in the region, and, in particular, threaten to fuel a substantial epidemic of sexually transmitted HIV infection. Sexual health professions, agencies and research groups world-wide should consider the contribution they could make through exchange programmes, training activities and collaboration in demonstration projects. These must address ethical standards and the principles and practice of confidentiality as well as technical aspects of interventions and the sharing of experience of working in the field with young people, gay men and sex workers.

RECENT ADVANCES ON DONOVANOSIS

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Interest in donovanosis has increased considerably in the last decade with major advances in microbiology and treatment and the conviction that the disease is now eradicable from its Australian reservoir. The extraordinary diversity of clinical manifestations of this disease has long been known but recent case reports continue to stress the ease with which this rare infection may be overlooked by clinicians unfamiliar with its diverse extragenital manifestations.

The classical form of donovanosis comprises a primary ulcerative genital lesion which spreads to regional lymph nodes whence it then tends to spread into the overlying skin to produce secondary ulceration. The diagnosis is made by recognising intracellular organisms (Donovan bodies) in Giemsa-stained material taken from lesions. This technique was first used in India by Donovan, who examined material from an unusual oral lesion from a boy who worked on his

ward. The most important recent research has been conducted in Durban, South Africa and in northern Australia. The disease has additional endemic foci in South and Central America, India and Papua New Guinea.

In 1999 [79], evidence was put forward to justify changing the name of the causative organism from *Calymmatobacterium granulomatis* to *Klebsiella granulomatis*. This was based on sequencing the *phoE* and 16S ribosomal RNA genes and demonstrating close homology with *K. pneumoniae* and *K. rhinoscleromatis*. The data obtained indicate that the organism should be classed either as a sixth species of *Klebsiella* or a fourth subspecies of *K. pneumoniae*. The homology with *K. rhinoscleromatis* is particularly interesting because this organism gives rise to a granulomatous inflammation of the upper airways which shows remarkably close histological appearances to donovanosis. These advances in the taxonomy of the organism that causes donovanosis were made possible by recent success in growing the organism in tissue culture. This was achieved in Durban by decontaminating specimens with a cocktail of amikacin, vancomycin and metronidazole and subsequent culture in human peripheral blood mononuclear cells. In Darwin, successful culture in HEp-2 cells has been reported [80]. It has been suggested that the inability of *K. granulomatis* to grow on simple media is linked to the lack of the sucrose transporter gene (*scrA*) found in other *Klebsiella* species [81]. Another spin-off from the molecular studies of *K. granulomatis* has been the development of PCR methods to assist diagnosis [82]. Donovan bodies are often difficult to find and PCR products may be demonstrated in patients with typical lesions but negative for Donovan bodies.

A recent letter to the *Medical Journal of Australia* [83] highlights some of the unusual cases of donovanosis seen over the past 8 years in northern Australia where the diagnosis was delayed. The list includes:

- A 7-month-old male child with cervical lymphadenopathy and failure to thrive
- An 8-year-old girl with a lesion of a tooth socket
- A woman who underwent hysterectomy for suspected carcinoma of the cervix which proved to be a lesion of donovanosis
- A woman presenting with infertility who had donovanosis lesions of the cervix and vaginal vault
- Two women who presented with psoas abscess
- One woman who presented with perinephric abscess
- A case of spinal cord compression due to donovanosis [84].

These cases re-emphasise the fact that donovanosis can be transmitted at birth from an infected mother [85] and that women are particularly prone to haematogenous dissemination if untreated cervical lesions are torn during childbirth. Confusion with malignant lesions has been reported many times, as well as the development of squamous carcinoma at the site of old or chronic lesions of donovanosis.

Important new agents introduced in the treatment of donovanosis include azithromycin, ceftriaxone and fluorinated quinolones [86]. Of these the most impressive results have been with azithromycin. A recent trial [87] in Australia compared a once-weekly dose of 1 g with a daily dose of 500 mg. The results were excellent with both schedules and the weekly schedule offers a major advance in view of serious problems with compliance experienced in the past. Large numbers of patients have been treated with azithromycin in Australia, including patients with unusually severe or extensive disease and patients who had failed on previous regimens [88, 89].

A proposal to eradicate donovanosis from Australia by the year 2003 was formally adopted recently. A recent article [90] in the *Australia and New Zealand Journal of Public Health* sets out a framework for eradication which includes setting up a co-ordinating structure, dialogue with aboriginal community leaders, education for the community and for health workers, provision of drugs and diagnostic support, improved surveillance, operational research and liaison with neighbouring Papua New Guinea, which contains an important reservoir of infection. The prospects for eradication elsewhere in the world are more bleak. The disease tends to affect the poorest and most disadvantaged communities and it is much more difficult to envisage an efficient case-finding and treatment approach that could work in the crowded slums of Indian cities. Despite these difficulties previous experience has demonstrated the feasibility of conducting large-scale case-finding and treatment campaigns for donovanosis in difficult field conditions. In the 1920s, M. U. Thierfelder and his wife trained Javan bird-of-paradise hunters to administer intravenous trivalent antimonials on alternate days to large numbers of the Marind-anim tribe of Dutch South New Guinea who became infected through ritual homosexual and heterosexual practices [91]. This successfully controlled the disease.

TROPICAL INFECTIONS THAT MIMIC SEXUALLY TRANSMITTED DISEASES

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A range of tropical infections may occasionally mimic sexually transmitted diseases (STDs) but the two that do so most commonly are schistosomiasis and filarial infections.

Schistosomiasis

Schistosoma haematobium. It has been known for many years that the adult pairs of this fluke live in the vesical and pelvic venous plexuses and deposit ova

in most pelvic tissues including the genital tract [92], but it has only recently been re-emphasised that these ova are a common cause of symptoms in both men and women [93, 94]. In men, symptoms may include urethritis, dysuria and the presence of visible clumps of ova and pus cells, 'like lumps of bread', in the ejaculate or of haematospermia [95]. These symptoms have become rather common in expatriates returning to the UK after scuba diving in Lake Malawi or exposure to fresh water in other parts of Africa [96]. Chronic prostatitis is another possible complication. In women, a wide variety of symptoms has been postulated including abortion, infertility, ectopic pregnancy, menstrual irregularity, pelvic pain and pelvic inflammatory disease. Of particular importance to the genito-urinary physician is the finding of polypoid and papillomatous lesions and ulcers of the cervix, vagina and labia, which bleed easily. Larger lesions were found to be associated with higher concentrations of schistosome ova. Inflammation of and bleeding from the genital tracts of both men and women have been postulated to increase the risk of transmission of HIV.

The diagnosis of genital schistosomiasis is likely to be considered only if a history of travel to Africa and swimming in fresh water is elicited. In men, examination for ova in semen as well as in urine passed between 10 a.m. and 2 p.m. will help to make the diagnosis [96]. A high eosinophil count is useful in early disease and serological tests for schistosomal antibodies are usually positive 3–6 months after exposure. Diagnosis is important because treatment with praziquantel is straightforward and chronic damage to tissues of the genital tract, bladder and rectum, including the risk of bladder cancer, can be avoided.

Other varieties of schistosomes including *S. mansoni, S. japonicum* and *S. intercalatum* less commonly cause genital lesions.

Filariasis

Bancroftian filariasis in men often presents with pain arising from a swollen spermatic cord (funiculitis). This pain may be felt in the lower abdomen or in the scrotum and is associated with a thick, tender spermatic cord. Attacks may last for several days and recur at intervals [97]. An attack of epidydimo-orchitis is a less frequent event and must be differentiated from attacks of bacterial origin. Such symptoms from early filariasis may be accompanied by tender swelling of regional lymph nodes, retrograde lymphangitis and sometimes fever.

Hydrocoele is the commonest chronic manifestation of bancroftian filariasis in many regions such as East Africa and the presence of many hydrocoeles in the male population should prompt investigation for filariasis. The hydrocoele fluid is usually indistinguishable from that of idiopathic disease but may sometimes contain microfilariae or have a milky white appearance.

Lymph scrotum is an unusual condition in which vesicles appear in the scrotal skin and may discharge fluid with a high protein content that readily becomes secondarily infected.

Elephantiasis of the scrotum resulting from lymphatic obstruction can reach a considerable size and result in gross disability, although surgical management is relatively straightforward. Similar elephantiasis of the vulva also occurs in women.

Chyluria, the passage of milky urine containing chylomicrons, is due to drainage of obstructed lymphatics into the urinary collecting system.

The diagnosis of bancroftian filariasis may sometimes be made by finding microfilariae in blood collected at night, but such microfilariae are very often absent in symptomatic patients. A marked eosinophilia is a helpful pointer in early disease but eosinophil counts decline in late obstructive disease. A simple card test for filarial antigen is very useful in confirming the diagnosis [98].

Onchocerciasis is a filarial infection occurring in tropical Africa and Central and South America. It can cause papular eruptions, itching, inguinal adenopathy, hanging groin, patchy depigmentation and subcutaneous nodules around the pelvis and might be mistaken for scabies. The diagnosis is usually made by finding microfilariae in blood-free skin snips or by microscopy of removed subcutaneous nodules [99].

Guinea worm infection. *Dracunculus medinensis* is a tissue nematode; the females are 50–100 cm in length. Infection presents as a blister, most often on the foot or leg but also quite frequently in the scrotum. The head of the female then protrudes and a milky fluid containing thousands of larvae is produced, especially if the area is immersed in water. Local ulceration, secondary bacterial infection and abscess formation are frequent complications [100]. Eradication programmes and provision of potable water have greatly diminished the incidence of this disease.

Tuberculosis

Tuberculous epididymitis is a relatively uncommon cause of pain and swelling of the testicle. It usually causes a firm to hard craggy swelling of the upper pole of the epididymis and if neglected may lead on to sinus formation and a posterior scrotal ulcer [101]. Haematospermia is a rare presentation [102]. Although the origin is often haematogenous spread there is sometimes concomitant tuberculous renal disease and

cystitis. Involvement of the seminal vesicles and prostate should also be sought. Diagnosis is usually by biopsy, histopathology and culture, although cultures of early morning urine specimens are helpful if the kidneys are involved.

Some unusual causes of perineal ulceration

As described above, schistosomiasis and tuberculosis may cause cracks and ulcers in this area.

Amoebiasis is an unusual cause of ulceration usually spreading from the perianal area in people with uncontrolled amoebic dysentery. Once established in the skin *Entamoeba histolytica* can cause rapidly spreading necrosis, which is halted only by an effective amoebicide such as metronidazole. Ulceration of the penis is also well recorded, usually in homosexuals. Lesions of the cervix in women may mimic cervical carcinoma.

Leishmaniasis acquired in Southern Europe also may attack mucosal surfaces, albeit rarely, and a chronic perianal ulcer from infection with an organism of the *Leishmania donovani* complex has been recorded recently [103]. Metastatic lesions from dermal leishmaniasis may also occur on the genitalia.

Myiasis from fly larvae can cause ulceration in this area. Small boil-like lesions with a central punctum initiated by the eggs and larvae of the tumbu fly, *Cordylobia anthropophaga*, laid on unironed underclothing in Africa or painful lesions caused by *Dermatobium hominis* in Central or South America are most frequently seen [104]. We have recently been involved with the diagnosis of an unfortunate elderly man who presented with scrotal pain and ulceration after a trip to Argentina and was found to have >30 larvae of the new world screw-worm, *Cochliomyia hominivorax*, eating into his scrotum.

Other causes of skin lesions in the genital area

Leprosy plaques are often found in the 'bathing drawers' area; they do not usually itch and the diagnosis is made by finding anaesthesia, enlargement of superficial nerves or the presence of *Mycobacterium leprae* in skin smears.

Larva migrans lesions, usually due to the dog hookworm *Ancylostoma braziliensis*, are quite common on the buttocks or genital areas, especially in persons buried in beach sand in the tropics. The typical serpentine tracks are sometimes difficult to see in this anatomical area as a less specific folliculitis is often predominant. More rapidly moving lesions (*Larva currens*) which typically last for only 24–48 h may be caused by migrating *Strongyloides stercoralis* larvae. In this case there is usually an eosinophilia and stool culture at room temperature for parasites and ELISA antibody tests are diagnostic [105].

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