CLINICAL MICROBIOLOGY REVIEWS, July 2011, p. 498–514 Vol. 24, No. 3
0893-8512/11/$12.00 doi:10.1128/CMR.00006-11

Mycoplasma genitalium: from Chrysalis to Multicolored Butterfly

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INTRODUCTION

Mycoplasmas are the smallest prokaryocytes capable of self-replication. They belong to the class *Mollicutes* (meaning soft skin) and have evolved regressively by genome reduction from Gram-positive bacterial ancestors, namely, certain clostridia. The term "mollicute" is sometimes used trivially to describe any organism in the class. The term "mycoplasma" might be used best to describe any member of the genus *Mycoplasma* (within the family *Mycoplasmataceae* and order *Mycoplasmatales*) but is also used, as here, in a trivial way to refer to any organism within the class.

Properties that distinguish mycoplasmas from eubacteria have been presented elsewhere (207). Genetic information is provided by a genome that in the case of *Mycoplasma genitalium* is the smallest one known for a self-replicating organism, i.e., 580 kb, and is estimated to code for fewer than 500 genes. It was this very small genome size that prompted Craig Venter and colleagues to construct the genome of *M. genitalium in vitro* as the initial step in creating a bacterial cell controlled by a chemically synthesized genome (59). Confining the number of structural elements, metabolic pathways, and components of protein synthesis to an essential minimum places mycoplasmas closest to the concept of "minimum cells" (140). They have adopted a parasitic mode of life, obtaining from the host many

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TABLE 1. Some features of *Mycoplasma* species of human origin

Species	Yr first isolated or named	Primary site colonized		Metabolism of:		Considered pathogenic
		Genital tract	Respiratory tract	Glucose	Arginine	
M. hominis	1937	+			+	+
M. fermentans	1952	+?		+	+	+
U. urealyticum[a]	1954	+				+
M. salivarium	1955		+		+	
M. primatum	1955		+		+	
M. pneumoniae	1962		+	+		+
M. orale	1964		+		+	
M. buccale	1965		+		+	
M. faucium	1965		+		+	
M. lipophilum	1974		+		+	
M. genitalium	1981	+		+		+
M. pirum	1985	+		+		?
M. spermatophilum	1991	+			+	?
M. penetrans	1991	+		+	+	?
M. amphoriforme	2005		+	+		?

[a] Metabolizes urea uniquely. In 2002, it was divided into *U. urealyticum* and *U. parvum.* ?, not certain.

nutrients that they cannot synthesize, and are fastidious in their growth requirements due to the small genome, a feature seen especially in the case of *M. genitalium*. The need for a molecular approach for the study of this and other mycoplasmas has been felt, particularly as classic genetics could not be applied due to difficulties in cultivation as well as the use of the UGA codon to encode tryptophan instead of the universal stop signal. Tools used for the investigation of nucleic acids, genes, and proteins have been applied not only for the characterization of mycoplasmas but also for studying their taxonomic and phylogenetic properties.

The 16 mycoplasmal/ureaplasmal species that are considered to be of human origin are listed sequentially in Table 1 according to their first report of discovery or naming. Most are considered to be commensals in either the respiratory or urogenital tracts, with at least four, including *M. genitalium*, showing pathogenic properties. As information about *M. genitalium* and the diseases that it causes has accrued, there have been reviews at different stages of this evolution (97, 98, 192, 195, 214). The current review is an attempt to bring the topic up-to-date.

HISTORY OF THE DISCOVERY OF *M. GENITALIUM*

During studies of acute nongonococcal urethritis (NGU) in the 1970s, it was apparent that some men responded to tetracycline therapy despite the failure to detect bacteria in the urethra (214). In addition, dark-field microscopy of fresh urethral smears from a few men with NGU, some of whom were infected by chlamydiae, ureaplasmas, *Mycoplasma hominis*, and other microorganisms, sometimes revealed motile spiral forms (214). These were not *Treponema pallidum* but to some extent resembled spiroplasmas in appearance, that is, motile helical organisms belonging to the genus *Spiroplasma*, which infect plants and insects. This prompted the notion that there might be a human counterpart of the plant spiroplasmas. In view of this, urethral swabs from 13 men with NGU attending the sexually transmitted disease (STD) clinic at St. Mary's Hospital, Paddington, London, United Kingdom, in 1980 were collected in sucrose-phosphate transport medium containing 10% heat-inactivated fetal calf serum. These specimens were transported in liquid nitrogen by one of us (D.T.-R.) to J. G. Tully's laboratory at the National Institutes of Health, Bethesda, MD, where they were inoculated into SP4 medium (220). This procedure had been designed for and was especially conducive to the isolation of spiroplasmas and also mycoplasmas. Spiroplasmas were not isolated, but after the medium had been incubated at 37°C for about a month, specimens from two of the men yielded two strains, G-37 and M-30, of a glucose-fermenting mycoplasma (221). These strains and a third one were recovered in the laboratory of D.T.-R. from the same specimens after they had been refrozen and transported back to the United Kingdom (214). Strains G-37 and M-30 were found to be closely related but different serologically from all other known mycoplasmas, a finding which resulted in the proposal that they should be regarded as belonging to a new species, *M. genitalium* (222), the 11th species of human origin to be isolated (Table 1).

SOME EVENTS IN THE "FALLOW" PERIOD

Subsequent to the isolation of *M. genitalium* from the male urethra, there was an interval of about 10 years before sensitive and reliable detection techniques were developed (see below) to show that infection by *M. genitalium* is the cause of various STDs, hence the title of this review. During the "fallow" period, attempts to repeat the original observation were made by many researchers, for example, Samra et al. (174), but without success. In the laboratory of D.T.-R., specimens from other patients with NGU, as well as men with gonorrhea and those without urethritis when they were seen at the STD clinic, were examined by using SP4 medium (201). The latter, however, was not the same batch as that used earlier. Subculturable color changes occurred with specimens from 7 of 22 men with NGU, 2 of 17 men with gonorrhea, and 2 of 20 men without urethritis, and some of these changes were shown later by PCR to be consistent with the presence of *M. genitalium*. Prior to this, however, the color changes could be regarded only as presumptive evidence for the existence of *M. genitalium*, because specific identification became impossible when many of the

color changes did not occur after the media had been stored frozen, and furthermore, the initial color changes had taken 1 to almost 5 months to occur upon the incubation of the media at 37°C. Clearly, it is not practical to undertake recovery attempts under such circumstances, and therefore, efforts were made to improve the growth medium for *M. genitalium*. It was possible to show, using a laboratory-passaged strain of *M. genitalium*, that, for example, fetal calf serum was superior to horse serum when incorporated into Edward-type medium (50) and that the addition of glutamine to SP4 medium that had been stored at 4°C improved its performance considerably (193). However, these and other attempted improvements did not produce a medium that was as sensitive as that used for the very first isolation of *M. genitalium*. During this period, when the detection of *M. genitalium* seemed virtually impossible, other approaches were taken to study the mycoplasma. Thus, a microimmunofluorescence test was developed for measuring antibodies (52), and the effects of the inoculation of subhuman primates were assessed (204).

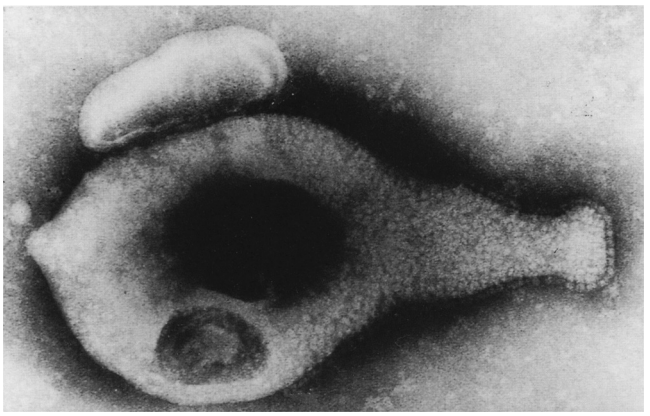

FIG. 1. Transmission electron micrograph of *M. genitalium* negatively stained with ammonium molybdate. The characteristic flask shape and the terminal truncated portion with extracellular small projections are shown. The organism size is presented in the text (original magnification, ×120,000). (Reprinted from reference 222.)

CHARACTERISTIC FEATURES OF *M. GENITALIUM*

Biological and Physical Features

Some of the characteristics of *M. genitalium* are shown in Table 1 and include the following: (i) a genome size of 580 kb; (ii) a guanine-plus-cytosine content of 32%; (iii) metabolism of glucose but not arginine or urea; (iv) very slow growth but more rapid growth upon repeated subculturing; (v) production of some "fried-egg"-like colonies in an atmosphere of nitrogen with 5% CO_2; (vi) frequent bottle shape with a terminal rodlike structure; (vii) adherence to glass and plastic surfaces and to various human and animal cells mainly by an *M. genitalium* attachment (adhesin) protein (MgPa) (88) of 140 kDa; (viii) invasion of epithelial cells, with evidence of nuclear localization; (ix) gliding motility; and (x) inhibition of growth by tetracyclines, fluoroquinolones, or macrolides. As stated above, *M. genitalium* metabolizes glucose but not arginine or urea (214, 221, 222). Thus, in medium containing glucose and phenol red as a pH indicator, its growth causes a reduction in pH (color change from red to yellow), which is useful for its detection. Growth is optimal at 37°C, and colonies on agar develop best in an anaerobic atmosphere of nitrogen with 5% CO_2. It is interesting that *M. genitalium* was isolated originally in medium from which thallous acetate had been omitted, a chemical that had often been incorporated into mycoplasmal media to suppress bacterial contaminants. Subsequently, *M. genitalium* was shown to be susceptible to thallous acetate (214, 222), whereas *Mycoplasma pneumoniae* is not. Dark-field microscopy of *M. genitalium* cultures shows small coccoid bodies, but details cannot be resolved. However, by electron microscopy, several mycoplasmas, of which *M. genitalium* is one, can be seen to have specialized structures at one or both ends (115). Thus, *M. genitalium* is predominantly flask or bottle shaped (214, 221, 222), with a prominent truncated terminal portion (Fig. 1). The dimensions have been calculated (222) to be as follows: a length of 0.6 to 0.7 μm and widths of 0.3 to 0.4 μm at the broadest part and 0.06 to 0.07 μm at the tip. In addition, small projections (7 to 8 nm) (Fig. 1), similar to but somewhat coarser than those on myxoviruses, may be seen extending distally from the tip of *M. genitalium* (221, 222) for about 40 to 60% of its length and may facilitate attachment.

Transmission electron microscopy of sections of the organisms shows the characteristic triple-layered membrane, 7.5 to 10 nm wide, the middle layer of which is less electron dense than the other two. In addition, the terminal truncated portion exhibits an internal rodlike structure (193, 222) (Fig. 1) similar to that seen in *M. pneumoniae*.

The terminal structure of *M. genitalium* is composed of at least seven proteins, of which two (MgPa [also known as MG191], of 140 kDa [88] and P110 [also known as MG192]) are needed for adherence in collaboration with accessory proteins, such as the MG218 and MG317 proteins (156, 169). By use of a ferritin-labeled monoclonal antibody to the *M. genitalium* 140-kDa adhesin protein, it has been shown that it clusters on the terminal portion of the organism (88). Furthermore, it is an immunodominant protein (154, 189, 190). Erythrocytes do not attach to colonies of *M. genitalium* when the organisms of which are mutants that do not produce the 140-kDa protein (146). This is a further illustration of the way in which this protein is involved in adherence, an important first step in producing pathogenic changes (see below).

Despite a size-limited genome, *M. genitalium* still possesses sufficient genomic makeup to be actively motile (197). The MG200 and MG386 genes are involved in this (168), and the specialized terminal structure seems important, as the organisms exhibit gliding motility in which they move tip first. Many of them move in circles, often but not exclusively in a clockwise direction. The speed averages about 0.1 μm per second, which is slower than that recorded for *M. pneumoniae* but faster than that recorded for two other human species, *Mycoplasma amphoriforme* and *Mycoplasma pirum* (70).

Genetic Structure

Despite the fact that *M. pneumoniae* and *M. genitalium* are structurally and, to some extent, antigenically related, they are not, of course, genomically the same. *M. genitalium* has the smallest genome size of all the mycoplasmas (580 kb) (49);

the genome of *M. pneumoniae* is larger (816 kb) (75), and for comparison, the genome sizes of *Chlamydia trachomatis* and *Escherichia coli* are 1,450 kb and 4,700 kb, respectively. The guanine-plus-cytosine (G+C) contents of *M. pneumoniae* and *M. genitalium* are different, 39 mol% and 32 mol%, respectively. However, there is an unevenness of the G+C distribution along the genome. In the case of *M. genitalium*, as indicated, the G+C content of the genome is 32 mol%, but the G+C content of its rRNA genes is 44 mol%, and that of its tRNA genes is 52 mol% (49, 76).

The very small genome size of *M. genitalium* was an important factor in its selection for sequencing. The sequence of the entire genome was made possible by the application of the whole-genome shotgun sequencing strategy, based on the random fragmentation of genomic DNA into small fragments of about 2 kb, followed by their cloning and sequencing, with the complete sequence being reported in 1995 (49). It is interesting that all the proposed open reading frames (ORFs) of the *M. genitalium* genome are contained in the larger genome of *M. pneumoniae*, with the latter containing specific genes not detected in *M. genitalium* (76).

Before the events mentioned above, the MgPa adhesin gene was cloned and sequenced (32) and was found to contain 4,335 nucleotides coding for a protein of 140 kDa. This is different from the P1 adhesin gene of *M. pneumoniae* (170 kDa) (88, 160) but has some shared properties (154), a finding in agreement with the result of an independent study (90). Homology is such that about 48% of the coding sequence of the adhesin gene of *M. pneumoniae* is 60 to 70% similar to the sequence of the MgPa gene.

Replication

The mode of replication of mycoplasmas was once a matter of dispute, but classic binary fission is now regarded as the means of replication. *M. genitalium* is not an exception in this regard. Although the flask-shaped morphology of *M. genitalium*, mentioned above, tends to dominate, other morphological forms can probably be attributed to the fact that cytoplasmic division is not always synchronous with genomic replication. Many of the smaller and aberrant-shaped cells have probably not received sufficient genetic material and are unable to replicate (170).

Although binary fission is the key factor in replication, there is no clear understanding of the factors which coordinate the process. In eubacteria, the FtsZ protein is localized to the site of septation and forms a constriction ring, the Z ring, between the dividing cells. The *ftsZ* gene has been found in mycoplasmas, including *M. genitalium* (49), indicating that it is a highly conserved and ubiquitous gene fulfilling a key role in prokaryotic cell division. However, it has been shown by gene replacement that the *ftsZ* gene is not essential and that *M. genitalium* can manage feasible cell divisions and cytokinesis using the force generated by its motile machinery (125). Of the additional genes associated with cell division in eubacteria, *ftsY* has been identified in both *M. genitalium* and *M. pneumoniae* (76). The genome size appears not to correlate exactly with the ability of a mycoplasma to replicate *in vitro*. Thus, some mycoplasmas with a small genome are not difficult to culture (170). However, as indicated above, this is not true in the case of *M. genitalium*. Perhaps, this can be accounted for, at least in part, by this mycoplasma and *M. pneumoniae*, also slow to replicate, lacking all the genes involved in amino acid synthesis (49, 76), making them totally dependent on an exogenous supply.

PATHOGENESIS

Adhesion

Adhesion is a complex process, and as mentioned above, several proteins, apart from MgPa, are key in the attachment of *M. genitalium* to the surface of various eukaryotic cells (20) and are an essential feature in its pathogenicity. Notable is adherence to glass and plastic surfaces, to epithelial cells (222), as well as to spermatozoa (186) and erythrocytes. The adsorption of erythrocytes ("hemadsorption") onto the surface of mycoplasma colonies on agar (222) is an illustration of the latter. Although the adherence of *M. genitalium* has been shown most consistently with guinea pig and sheep erythrocytes (7), adherence to human erythrocytes also occurs. Sialic acid receptors on erythrocytes are involved, as the adsorption of human erythrocytes (type O) to colonies of *M. genitalium* is abolished if the erythrocytes are first treated with neuraminidase. The binding to colonies that have developed under anaerobic conditions is greater than that to colonies grown aerobically and most extensive if the colonies have developed anaerobically in the presence of pyruvate, mannitol, and hemin (7).

M. genitalium has also been shown to adhere by the terminal tip structure to Vero monkey kidney cells *in vitro* (101) and also to Hep-2 cells. In the latter case, monospecific antibody only against the exposed C-terminal part of MgPa blocked cytadsorption (190). In addition, a similar attachment to the cilia, as well as the surface, of Fallopian tube epithelial cells in organ culture has been observed (29). Attachment to Fallopian tube cells could be inhibited either by treatment of the organism with trypsin, which removes active parts of the MgPa protein, or by preincubating the organism with a monoclonal antibody raised against the MgPa protein. Whether *M. genitalium* uses long-chain sialo-oligosaccharides on host cells as receptors, as does *M. pneumoniae*, is unknown.

A family of repetitive DNA elements with homology to the MgPa adhesin gene has been characterized (167). These repetitive elements, designated MGPar, have been illustrated schematically elsewhere (218). The reciprocal recombination of some of these sequences with those of MgPa and P110 genes contributes to the heterogeneity of the resulting proteins. Such DNA sequence divergence of the MgPa and P110 adhesion genes among strains of *M. genitalium* has been shown to be extensive (98, 130), with intrastrain heterogeneity being frequent (93). Such antigenic variation not only provides an efficient mechanism for optimizing adhesion, which is crucial for obtaining essential nutrients and, hence, for the survival of *M. genitalium*, but also helps to avoid the host's immune response and promote persistence (98).

Motility and Cell Invasion

As mentioned previously, *M. genitalium* exhibits gliding motility (70) and possesses proteins involved in this activity, two of which are motility specific (168). Because there is probably insufficient genomic material to cater for frivolous activities, the assumption is that motility is important, perhaps as a means of penetrating the mucous layer covering mucosal epithelial cells and enabling the mycoplasma to attach to and invade the cells. Whether a surface protein of *M. genitalium*, glyceraldehyde-3-phosphate dehydrogenase, which binds the organism to mucin (1), enhances or retards invasion is unknown. With regard to cell invasion, this has been demonstrated for several mycoplasmas (198). *M. genitalium* is an example (31), with there being evidence of rapid attachment and entry with nuclear localization (8, 142, 224). Not all cells in a population seem to be susceptible to invasion. Indeed, electron microscopic observations have indicated that *M. genitalium* becomes intracellular in only about 10% of Vero cells infected *in vitro* (101). Cell entry seems to be mediated by the specialized tip structure. In one study, in which *M. genitalium* came into contact with human lung fibroblasts (146), the plasma membrane of the cells appeared to be forced inward to form a cup or depression. The membrane pockets resembled clathrin-coated pits, suggesting that the mycoplasma might adhere to and enter the cells by a site-directed, receptor-mediated event resembling cell entry by chlamydiae. Ninety-six hours after invasion there was a lysis of the lung fibroblasts, accompanied by a large number of mycoplasmas in the milieu. Overall, the intracellular location might protect the mycoplasmas from the effects of the host immune system and also antibiotics, promoting the establishment of latent or chronic infection, in other words, enhancing pathogenicity (see below).

Toxin

A unique ADP-ribosylating and vacuolating *M. pneumoniae* toxin (MPN 372) that elicits pathological changes has been described (111), and subjects testing positive for the toxin experienced worse respiratory disease than those who did not (155). Whether a similar toxin might be produced by *M. genitalium* is unknown. However, MG-186, a calcium-dependent membrane-associated nuclease of *M. genitalium*, has been identified (121) and was shown to have the capacity to provide *M. genitalium* with the ability to degrade host cell nucleic acids as a source of nucleotide precursors for growth and for pathogenic processes.

Immunological Responses

Immunological reactions may contribute to the pathogenicity of *M. genitalium*. It is known that the damage caused by *M. pneumoniae* is to a large extent immunologically mediated, being a secondary cellular overresponse of the immune system to a primary infection (194). The same could apply to *M. genitalium*, although it is also known that an acute inflammatory response, dominated by polymorphonuclear leukocytes (PMNLs), occurs as a result of a primary infection by this mycoplasma. This has been shown best by the experimental inoculation of the genital tracts of both male and female subhuman primates (204, 213, 223). Furthermore, cultured human vaginal and cervical epithelial cells *in vitro* have been found to be susceptible to *M. genitalium*, resulting in rapid cellular invasion; as a consequence of the immunogenic protein MG-309 activating NF-kappaB via Toll-like receptors, proinflammatory cytokines (interleukin-6 [IL-6], IL-8, and others) were secreted (141, 142). This provides an insight into how acute inflammatory responses might be activated with their damaging sequelae. The pattern of cytokine secretion was consistent with the recruitment and stimulation of monocytes and macrophages in the vaginal and cervical epithelial mucosa. Phagocytosis by macrophages was an effective way of killing *M. genitalium*, but localization within the cells may provide *M. genitalium* with a means of survival by being protected from cellular immune responses, thereby facilitating the establishment and maintenance of infection (142).

In addition, autoimmune phenomena of various kinds occur after infection by *M. pneumoniae* (10). The close biological similarity between this mycoplasma and *M. genitalium* raises the possibility that autoimmune-stimulated pathology could develop in response to infection by the latter. Furthermore, as *M. genitalium* and *M. pneumoniae* share various antigens that induce some serological cross-reactivity (94, 122, 124, 203), it is plausible that resistance to genital tract infection with *M. genitalium* might occur as a consequence of antibody induced by a previous respiratory infection with *M. pneumoniae*, particularly as the latter infection is seen at an early age and is therefore likely to be experienced first. Because of the difficulty of assessing this proposition with humans, it was evaluated experimentally in a mouse model (200). In this study, mice susceptible to infection by *M. pneumoniae* were protected completely by a previous respiratory infection with this mycoplasma. However, such a respiratory infection did not provide any immunity against a vaginal infection with *M. genitalium*, suggesting that infection of the human respiratory tract by *M. pneumoniae* is unlikely to protect against infection of the genital tract by *M. genitalium*. On the other hand, whether a prior human infection with *M. pneumoniae* might, through cellular immunological means, make infection with *M. genitalium* more severe is plausible but unknown.

Hormones

The response of small laboratory animals to genital challenge with *M. genitalium* is dependent on prior hormone treatment. Thus, the treatment of female mice and hamsters with progesterone was found to be a prerequisite for the establishment of genital tract colonization with *M. genitalium*, which could then be maintained for several weeks (53). Treatment with estradiol failed to induce colonization, although partial effectiveness has been found by others (143). It is unknown if different animal strains, inoculum sizes, and inoculation methods could account for the divergent observations. Whether different hormones could stimulate cell receptors to which the organisms become attached as a means of facilitating colonization is unknown, as is the influence of hormone changes in the human situation.

RELIABLE DETECTION OF *M. GENITALIUM*

As a consequence of the difficulty of culturing *M. genitalium*, several workers made efforts to develop DNA probes for this mycoplasma (172). One of these probes was used to examine genital specimens from men in several clinical categories (81). There was no significant difference between the prevalence of *M. genitalium* in men with chlamydia-positive or chlamydia-negative NGU and that in men who had gonococcal urethritis or no urethritis. It was reported, however, that the mycoplasma was present more frequently in homosexual men than in heterosexual men and, furthermore, that there was a significantly increased prevalence in individuals who had persistent or recurrent NGU. In general, however, DNA probes were insufficiently sensitive to be useful.

Two groups (106, 162) took a different approach, and each one developed a PCR that was several orders of magnitude more sensitive and coming into vogue in the late 1980s as a means of detecting microorganisms. These groups, who amplified different fragments of the MgPa adhesin protein, showed that as little as 10^{-15} g of *M. genitalium* DNA could be detected, corresponding to fewer than 10 organisms. Moreover, the results of the testing of genital specimens by the two different PCR assays were comparable (34). The initial success of the use of PCR soon prompted other investigators (15, 33) to use the technique and yet others to devise technical modifications (41, 132, 232, 233), use a multiplex PCR (135), target the 16S rRNA gene of *M. genitalium* (42, 102), and use another nucleic acid amplification test, transcription-mediated amplification (TMA), with success (69, 89, 230). TMA, specific for *M. genitalium*, is an assay for research only, developed by Gen-Probe, Inc., and is unavailable commercially as yet (218), as is a multiplex test for *C. trachomatis*, *Neisseria gonorrhoeae*, and *M. genitalium* developed by Bio-Rad, which has not yet been validated to the point where it has FDA approval. In recent years, the development of real-time PCR has led to the development of a number of sensitive tests with less risk of amplicon contamination and with the ability to quantitatively measure the *M. genitalium* DNA load in specimens (16, 24, 36, 69, 100, 109, 188, 231). With more knowledge of the sequence variation between strains (218), in particular of the MgPa gene, it has become clear that some assays applied primers that could not be expected to react with all *M. genitalium* strains (130, 178). Furthermore, as many specimens carry a very low load of *M. genitalium* DNA (100), the choice of amplification assay and nucleic acid extraction method may greatly influence the detection sensitivity.

As another approach to diagnosis, Jensen and colleagues used a strategy involving the PCR assay to isolate *M. genitalium* from urogenital specimens (67, 104). Vero cell cultures were inoculated with the specimens, and mycoplasmal growth was monitored by PCR technology; when the latter provided evidence of multiplication, the cell culture material was subcultured onto mycoplasma medium. In this way, 20 isolates of *M. genitalium* were recovered and shown to be genotypically distinct (218). Since then, 15 new isolates have been obtained.

It has been possible with these various approaches to realistically look at the relationship between *M. genitalium* and various clinical conditions and to study further aspects of this mycoplasma.

Best Specimens for Examination

The type of specimen required for the optimum detection of *M. genitalium* has received some attention. In one study (99), first-void urine specimens from either men or women had a sensitivity of 95% when tested in a PCR assay, and they outperformed swab specimens, although for women, urine supplemented with a cervical specimen was superior in sensitivity. In a later study (230), vaginal specimens provided greater sensitivity than cervical or urine specimens. However, we believe that there is insufficient information to make a firm recommendation regarding specimen type. In the case of *N. gonorrhoeae* and *C. trachomatis*, self-obtained vaginal swabs have been recommended (79) and should be explored more for *M. genitalium*. Without question, the performance of different specimen types will depend on the method of nucleic acid extraction. With a very low *M. genitalium* DNA load in a significant proportion of the specimens (100), the concentration of the specimen by centrifugation may be essential. Of course, epididymal fluid, prostatic biopsy, and tubal specimens should be examined when deemed appropriate, but no systematic studies of the performances of these specimen types have been presented. The processing of specimens before freezing, particularly those from women, appears to be important in maintaining a high detection sensitivity (22).

PREFFERED ANATOMICAL SITE OF COLONIZATION BY *M. GENITALIUM* AND EVIDENCE FOR SEXUAL TRANSMISSION

M. genitalium has been detected in human urogenital, respiratory (6, 33), and rectal specimens (208). The latter initially raised the question of whether there was a preference for the intestinal tract, a notion supported by the fact that mycoplasmas that have the same structural configuration as *M. genitalium* have been found in the genital and intestinal tracts of cattle (60) and also swine. However, there is now overwhelming evidence, based on numerous detection studies, that the human urogenital tract is the preferred site of colonization.

Moreover, the results of a seroepidemiological investigation (227), as well as studies of sexual partners, strongly indicated that *M. genitalium* is sexually transmitted. Thus, a high rate of concordance of *M. genitalium* has been noted for partners (2, 46, 47, 113, 215, 216); even more convincing has been the concordance of *M. genitalium* genotypes in infected couples (78, 131). In addition, as in the case of *M. pneumoniae*, it is clear that *M. genitalium* is able to spread hematogenously from the primary site of colonization, as shown with experimentally infected subhuman male primates (223), therefore providing the opportunity to invade other sites, such as joints.

RELATIONSHIP BETWEEN *M. GENITALIUM* AND DISEASE IN MEN

Acute Nongonococcal Urethritis

Since *M. genitalium* was isolated initially from men with acute NGU, it is not surprising that further clinical studies focused on this condition. In numerous studies (2, 9, 14, 19, 21, 24, 30, 35, 40, 47, 55, 58, 74, 80, 84, 92, 95, 105, 108, 113, 118,

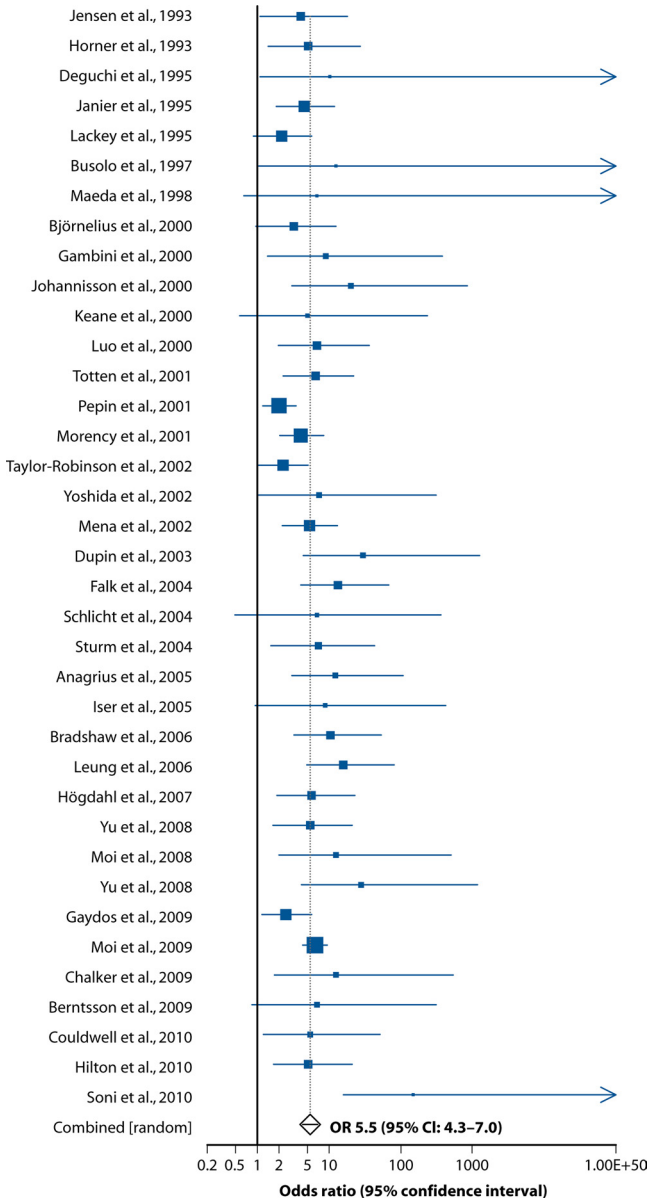

FIG. 2. Association between *M. genitalium* and acute NGU in men. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from published studies of PCR positivity. References correspond to reference numbers 2, 9, 14, 19, 21, 24, 30, 35, 40, 47, 55, 58, 74, 80, 84, 92, 95, 105, 108, 113, 118, 120, 128, 133, 144, 147, 149, 153, 164, 176, 182, 185, 211, 217, 232, 234, and 235.

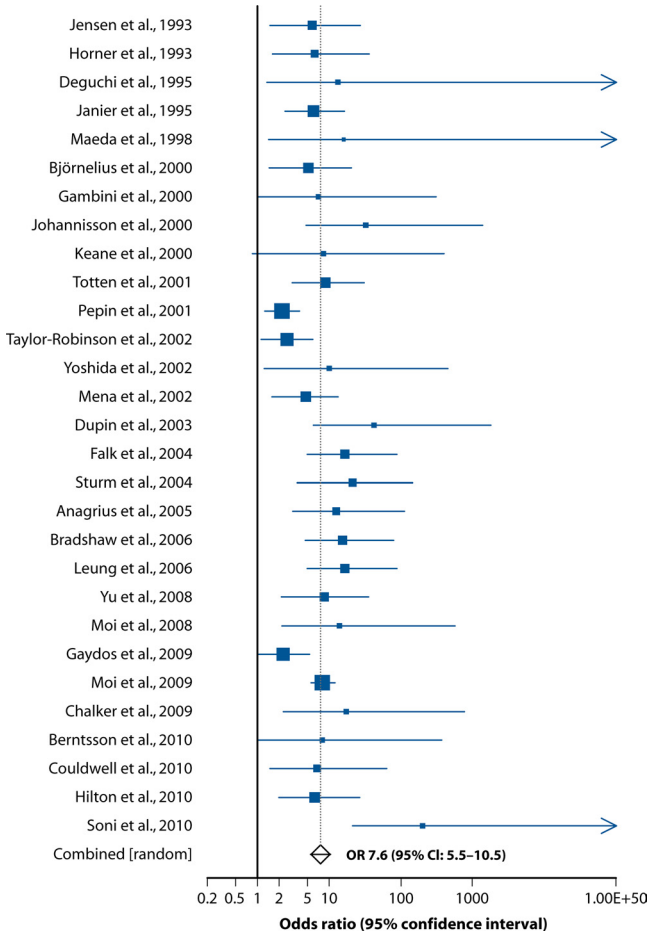

FIG. 3. Association between *M. genitalium* and acute nonchlamydial NGU. Odds ratios and 95% confidence intervals were calculated from published studies of PCR positivity. References correspond to reference numbers 2, 9, 14, 19, 24, 30, 35, 40, 47, 55, 58, 74, 84, 95, 105, 108, 113, 120, 133, 144, 147, 149, 164, 182, 185, 211, 217, 232, and 235.

120, 128, 133, 144, 147, 149, 153, 164, 176, 182, 185, 211, 217, 232, 234, 235) in which microscopy has been the dominant feature in making the diagnosis, *M. genitalium* has been strongly and almost uniformly associated with acute NGU (Fig. 2). In one study (211), in which the diagnosis was based on clinical symptoms and signs only, the association with *M. genitalium* was weaker, probably because some of those subjects recorded as not having NGU had microscopic evidence of disease. Overall, *M. genitalium* has been detected in the urethras of 15 to 25% of men with symptomatic NGU, compared to about 5 to 10% of those without disease. Among STD clinic populations, about 90% of *M. genitalium*-infected men have microscopic evidence of urethritis, and about three-quarters report symptoms, with a complaint of discharge being more common than in NGU of other etiologies (228). Indeed, there is evidence that *M. genitalium* is more closely associated with symptomatic than with asymptomatic NGU (14, 82, 87). Furthermore, the development and use of quantitative PCR assays for *M. genitalium* have shown greater *M. genitalium* DNA loads in urine from men with NGU than in urine from those without the disease (98, 100).

It is noteworthy that the association between mycoplasma and disease is even stronger for acute nonchlamydial NGU (NCNGU) (2, 9, 14, 19, 24, 30, 35, 40, 47, 55, 58, 74, 84, 95, 105, 108, 113, 120, 133, 144, 147, 149, 164, 182, 185, 211, 217, 232, 235) (Fig. 3), with the mycoplasma being found in more than one-third of men with such disease, indicating that *M. genitalium* and *C. trachomatis* act as separate causes of the condition. There have been few attempts to measure *M. genitalium* antibody responses; these have met with some but limited success (98, 189, 201, 205). The separation between the occurrences of *M. genitalium* and *C. trachomatis* in NGU helps to answer the

TABLE 2. Fulfillment of criteria required to determine whether *M. genitalium* or *C. trachomatis* causes NGU[a]

Criterion	Fulfillment of criterion for:	
	M. genitalium	*C. trachomatis*
Detection significantly more often than in controls for:		
Acute NGU	++++	++++
Chronic NGU	+++	+
Homosexual NGU	+++	+++
Larger no. of organisms than in controls	+++	++
Antibody titers and responses more often than in controls	+	++
Effective microbiological and clinical response to therapy	++++	++++
Reproduction of disease in inoculated subhuman primates	++++	+++
Reproduction of disease in inoculated human volunteers	ND	ND
Wide geographic involvement	++++	++++
Disease prevented by natural or exptl immunity	ND	+

[a] ++++, excellent; +++, good; ++, moderate; +, poor; ND, not determined. The second to eighth criteria relate mainly to acute NGU.

question of whether *M. genitalium* is truly a cause; it argues against the notion that the mycoplasma is significantly associated with acute NGU due to it merely being an invader of tissue damaged by some other agent that is the real cause of NGU. Furthermore, the changes seen after the experimental inoculation of the urogenital tract of subhuman primates (204) were in keeping with those seen for acute NGU. These changes were shown best by the inoculation of the urethras of male chimpanzees (213, 223), at which site an acute inflammatory response dominated by PMNLs occurred in most animals, accompanied by a late-developing antibody response. Indeed, the results of these animal experiments are an important component of the extended version of Koch's postulates (191), the fulfillment of which signifies that a microorganism is a cause of NGU. They are fulfilled almost as adequately by *M. genitalium* as they are by *C. trachomatis* (Table 2). Some of the criteria for defining a causal relationship and their fulfillment by *M. genitalium* have also been discussed previously (85, 96, 98, 210).

Chronic NGU

Persistent or recurrent NGU following an acute attack was noted by Hooton et al. (81) to be associated with *M. genitalium*, as mentioned above. Since then, *M. genitalium* has been found in up to 40% of men presenting with chronic disease after treatment with doxycycline (209, 229). Indeed, in several clinical studies (36, 82, 83, 134, 205, 229), a strong correlation was found between *M. genitalium* infection and persistent or recurrent NGU, probably due to tetracyclines and, more recently, azithromycin (17, 18) eradicating *M. genitalium* from only a subset of the patients (12, 46). Other aspects of treatment are discussed below.

Balanoposthitis

Inflammation of the glans penis (balanitis) and inflammation of the prepuce (posthitis) frequently occur together (balanoposthitis). In one study (86), *M. genitalium* was associated significantly ($P = 0.01$) with balanitis and/or posthitis in 114 men with acute symptomatic NGU. This association persisted when there was a control for *C. trachomatis*, which was not involved. Further studies are merited, particularly those that focus on men who have urethritis and those who do not.

Chronic Prostatitis

Despite the fact that *M. genitalium* is involved in chronic NGU, there is sparse evidence that it is associated with chronic prostatitis. Thus, in one study (37), it was not detected by use of a PCR on transperineally derived prostatic biopsy specimens taken under ultrasound control from 50 patients with chronic abacterial prostatitis. In another study (116), *M. genitalium* was detected by a PCR assay of prostatic biopsy specimens from 5 (4%) of 135 men, and in yet another study (136), *M. genitalium* was detected in semen from 2 of 18 men with chronic abacterial inflammatory prostatitis, compared to none of 20 controls, which is insufficient evidence to suggest any significant association.

However, it is possible that the detection of *M. genitalium* becomes thwarted by previous bouts of antibiotic therapy and still plausible but, of course, speculative that an early infection might set in motion immunological processes that culminate in chronic prostatitis.

Acute Epididymitis

Clinical experience as well as the detection of *M. genitalium* in a few patients during an antibiotic trial (44) indicated that *M. genitalium* may be a cause of acute epididymitis in some patients. An undoubted causal involvement is certainly true in the case of *C. trachomatis* (38) and, by analogy, might well be so for *M. genitalium*. To firmly establish this, epididymal fluid should be examined whenever possible in addition to urine and/or urethral swabs (38).

DISEASE IN WOMEN

Nongonococcal Urethritis

There is evidence for an association between *M. genitalium* and urethritis in women attending STD clinics (2, 48, 80, 148). The observations have been made mainly in Scandinavia, where examination of urethral smears from women is a part of routine STD examinations, and the numbers of these infections are few compared with those in men. It is clear that further studies are warranted, as it is not yet fully clear to what extent *M. genitalium* is involved in symptomatic or asymptomatic pyuria or in the so-called "urethral syndrome" (dysuria and frequency in women with apparently sterile urine).

Bacterial Vaginosis and Vaginitis

The detection of *M. genitalium* organisms in women by PCR came before they were associated with NGU in men. Thus,

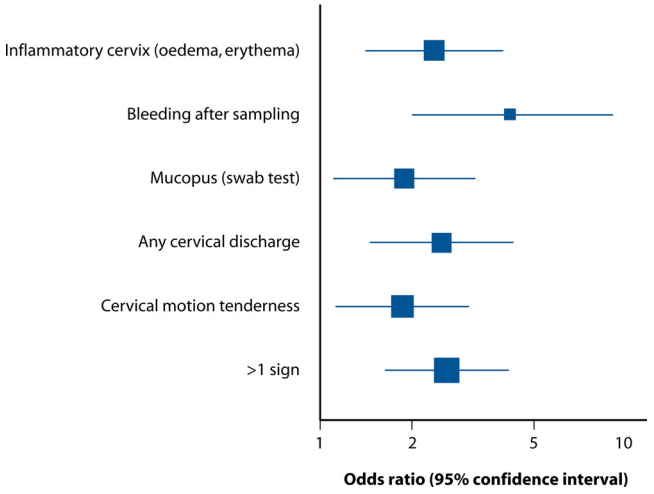

FIG. 4. Association of *M. genitalium* with cervicitis depending on the criterion used for defining cervicitis. (Data from reference 163.)

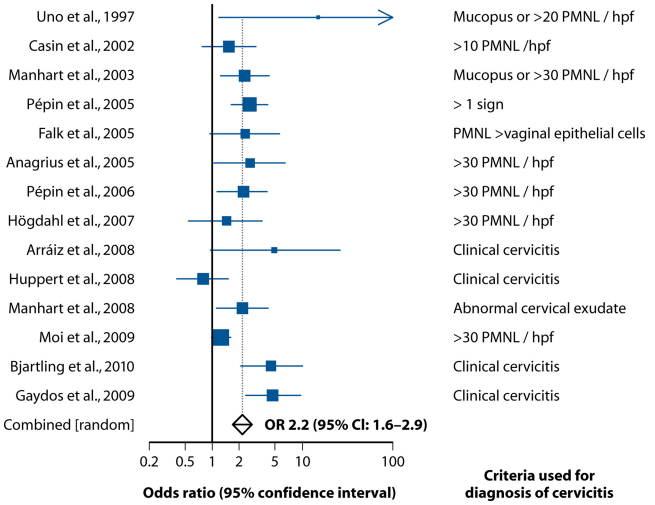

FIG. 5. Association between *M. genitalium* and cervicitis. Odds ratios and 95% confidence intervals were calculated from published studies of PCR positivity. hpf, high-power field. References correspond to reference numbers 2, 4, 11, 23, 48, 57, 80, 89, 137, 139, 148, 163, 165, and 225.

they were first detected in the lower genital tract of about one-fifth of women attending an STD clinic at St. Mary's Hospital, London, United Kingdom (161), and in cervical samples from 5 of 74 women in Copenhagen, Denmark (106). However, unlike *M. hominis*, which is very strongly, if not causally, associated with bacterial vaginosis (BV) (173) in which inflammatory cells are absent, the association of *M. genitalium* with BV is controversial. In three studies (114, 119, 137), there was no evidence that *M. genitalium* played any part in BV, while in a fourth study (158), the presence of *M. genitalium* in women was independently associated with BV, being more common in women with BV than in those without the condition. Clearly, this does not necessarily mean that there is a causal relationship, but the issue needs to be resolved.

Gonococcal and chlamydial infections are not known for causing inflammation of the vagina in sexually mature women. However, aerobic vaginitis with aerobic bacteria has been described (39), and infection of vaginal cells *in vitro* (142) and skin cells in balanoposthitis (86) by *M. genitalium* raises the intriguing question of whether it might cause vaginitis *in vivo*.

Cervicitis

Because the cervix is easily accessible, it can be examined both clinically and microbiologically without difficulty. Therefore, evidence that *M. genitalium* is or is not a cause of cervicitis should be straightforward. The only difficulty lies in the fact that there is no standard definition of cervicitis (45). Diagnosis has been based by some investigators only on overt clinical signs (mucopurulent discharge, cervical friability, erythema, and bleeding after sampling) and by others only on the number of PMNLs per microscope field of discharge. Some of the latter have regarded >10 cells as being important, and others have regarded no fewer than 30 cells as being important. A few investigators have used a combination of the clinical and microscopic criteria. The effect that the use of different overt signs to define cervicitis has on its association with *M. genitalium* was pointed out by Pepin et al. (163) (Fig. 4). While the observations are of value, they do not cover the relationship between PMNLs and *M. genitalium*. Therefore, it is difficult to make direct comparisons with the results of other studies (see below) in which PMNL counts, with or without overt signs, or overt signs alone have been used to diagnose cervicitis and to seek an association with *M. genitalium*. The first evidence of an association came from a Japanese study, reported in 1997 (225), in which *M. genitalium* was detected in the cervices of 5 (9%) of 57 women with cervicitis but in none of 79 women without the condition. Subsequently, the results of other studies (2, 4, 11, 23, 48, 57, 80, 89, 137, 139, 148, 163, 165, 225), shown in Fig. 5, to a large extent attest to *M. genitalium* having a significant role in causing cervicitis. Indeed, in a recent study (129), *M. genitalium* was the only genital mycoplasma/ureaplasma regarded as causing cervicitis.

Vaginal inoculation of marmosets, squirrel monkeys, and chimpanzees with *M. genitalium* resulted in the development of antibody responses and PMNLs in vaginal smears (204). Although not specifically determined, the cervix was a possible source of the inflammatory cells. This was the site of infection, and not the vagina, in *M. hominis*-infected mice (51), but the ability to infect human vaginal cells *in vitro* (142) means that the vagina cannot be excluded as a source.

Pelvic Inflammatory Disease

Inflammation ascending beyond the cervix, i.e., pelvic inflammatory disease (PID), like most genital tract diseases, does not have a single cause (72, 183) and is more difficult to diagnose than cervicitis. Clinical examination alone may give a false impression, but laparoscopy is helpful in providing a more accurate diagnosis and in enabling upper tract specimens to be taken. However, although the specificity of laparoscopy is high, the sensitivity is not optimal, and endometritis without salpingitis may be missed. In the absence of upper genital tract sampling, the detection of pathogens in the cervix has often been used as a proxy in etiological studies of PID. Indeed,

M. genitalium organisms in the cervix have an opportunity to invade the upper genital tract and cause PID, and in women with clinical signs of upper tract infection, as many as 60% of those with *M. genitalium* detected in cervical specimens also had positive detections from endometrial biopsy specimens (63). PID comprises endometritis and/or salpingitis, and studies of these anatomical sites of infection are discussed below.

Laparoscopy is not often undertaken, and two studies (180, 181) in which *M. genitalium* was associated with PID were based on clinical examination alone and did not make the finer anatomical distinction; in a third longitudinal study (158), there was only a trend in the direction of PID being associated with *M. genitalium*. In a study of women presenting for termination of pregnancy in New Zealand (119), there was a high rate of *M. genitalium* infection (9%) based on self-taken vaginal swabs. This is important because *M. genitalium* has been associated significantly with PID occurring after termination of pregnancy (11).

Endometritis. In an early study (91) on endometritis, *M. genitalium* was reported to have been detected in endometrial biopsy specimens from women with clinically suspected PID, but it is not possible to assess whether there was a significant relationship between detection and disease. On the other hand, in another study (26), *M. genitalium* was found to be strongly associated with acute endometritis, being detected in 9 (16%) of 58 women with histologically diagnosed endometritis but in only 1 (2%) of 57 women without endometritis.

Salpingitis. There have been few studies in which the Fallopian tubes have been examined at laparoscopy. In one study (27), *M. genitalium* was detected in the cervix/endometrium of 9 (7%) of 123 women with acute salpingitis but in only a single tube, and in another study (D. Taylor-Robinson, J. S. Jensen, H. F. Svenstrup, and C. M. Stacey, unpublished data), *M. genitalium* was detected in only 1 tube of 22 women with salpingitis.

Further evidence for *M. genitalium* causing PID is (i) the ability of the organisms to adhere to Fallopian tube mucosal epithelial cells in organ culture (29) and to affect the cells and cause ciliary damage (5), (ii) the production of endometritis and salpingitis experimentally in several subhuman primate species (151, 202, 204) and hydrosalpinx formation in mice (143), (iii) the association of tubal factor infertility with a previous infection with *M. genitalium* (25), and (iv) the demonstration of *M. genitalium* antibody responses in one-third of women with acute PID (150), a finding disputed by some investigators (110, 123). In summary, the overall supportive aspects have led to the conclusion that *M. genitalium* is one of the causes of PID (62).

Reproductive Disease in Women

In relation to pregnancy outcome and as discussed above, there is evidence that *M. genitalium* alone or in combination with other microorganisms causes some cases of PID. As this disease damages Fallopian tubes (5), there is a small chance that such a prior mycoplasmal infection could be responsible for an ectopic pregnancy. However, a serological study provided no support for this (110).

In consideration of the poor pregnancy outcomes of spontaneous preterm labor (SPTL) and preterm birth (PTB), which have been shown to occur for women with BV (71), six studies (56, 112, 117, 127, 159, 179) suggested that *M. genitalium* was unlikely to be responsible for such outcomes, whereas in two other studies (43, 77), it was reported to be a significant independent risk factor for SPTL and PTB. Clearly, this controversial matter needs resolution.

M. hominis is considered to be responsible for some cases of maternal fever after a normal delivery or abortion (212), but the role, if any, of *M. genitalium* has not been assessed.

DISEASE IN BOTH MEN AND WOMEN

Infertility

M. genitalium organisms have been shown to adhere by their terminal structure to the head, midpiece, and tail of human spermatozoa *in vitro* and in sufficient numbers affect their motility (186). Whether this could reduce male fertility *in vivo* is unknown. It is feasible, however, that spermatozoa that are still motile and carry organisms could deliver them to the upper reaches of the female genital tract. Given that *M. genitalium* is known to cause PID, it would be reasonable to assume that this could result in tubal damage and occlusion and subsequent infertility. In one early study (152), antibody to *M. genitalium* was not associated with abnormal salpingographic findings. On the other hand, two seroepidemiological studies (25, 187) have shown an association with tubal factor infertility, with 17 to 22% of women with this condition having *M. genitalium* antibodies, compared to 4 to 6% of women with normal tubes.

C. trachomatis did not seem to be involved, as, serologically, the association of *M. genitalium* with infertility was independent of *C. trachomatis* (187, 189). However, despite this finding, the use of serology as a means of assessing the role of *M. genitalium* in female infertility is not straightforward. It may seem to be a way of relating prior infection with current or long-standing infertility, but there is a chance that women who have had a prior infection could also be at a higher risk for infection by STD organisms other than *C. trachomatis*, which might cause the infertility. Certainly, the use of PCR for organism detection has to be questioned, because a current or recent infection detected in this way, probably through cervical swabbing, may have nothing to do with infertility, which is unlikely to be of recent origin. It is therefore difficult to interpret the results of a study (61) in which *M. genitalium* was detected more frequently in cervical swabs from infertile women than in cervical swabs from healthy fertile women.

Arthritis

Sexually acquired reactive arthritis (SARA) or the less common Reiter's disease, in which conjunctivitis also develops, occurs in men who have or have recently had NGU and less often in women. A case of adult conjunctivitis in which *M. genitalium* was detected has been described (13), but this was not part of Reiter's disease. However, *M. genitalium* has been detected by PCR technology in the knees of 2 of 13 patients with arthritis, one of whom had Reiter's disease and the other of whom had seronegative rheumatoid arthritis (206). In addition, clinical experience indicates that reactive arthritis occurs occasionally in patients with *M. genitalium* genital tract infec-

tions, suggesting that further, more detailed studies would be profitable. Experimentally, *M. genitalium* was recovered from the blood of two of six chimpanzees infected in the urethra (223). Clearly, hematogenous spread may result in joint infection, and this was seemingly the only way in which the knees of female mice became involved following the intravaginal inoculation of *M. genitalium* (143). *M. genitalium*, together with *M. pneumoniae*, was reported to have been recovered from the joints of a patient with pneumonia and subsequent polyarthritis (219). However, the strain recovered had a genotype that was indistinguishable from the G37 type strain (78, 131), so it may represent laboratory cross-contamination. Whether *M. genitalium* is involved in septic arthritis occurring in hypogammaglobulinemic patients, as are other mycoplasmas (54), has not been established. *M. genitalium* has also been reported to have been detected with or without *Mycoplasma fermentans* and with or without *C. trachomatis* in 9 (35%) of 26 "deranged" temporomandibular joints considered possibly of a reactive nature (73). This is surprising and needs confirmation.

Infection in Homosexual Men and in Immunodeficient or Immunosuppressed Patients

During the course of the 30 years since *M. genitalium* was first isolated, it has been detected in homosexual men (208), but there has been little information, until recently, about the influence of HIV infection. About a decade ago it was reported that more than 50% of men who had AIDS but no urethritis were *M. genitalium* positive in the urethra but that only about 10% of those who were HIV positive without AIDS had the mycoplasma in the urethra (195). Furthermore, the CD4 cell count had no influence on the mycoplasmal infection. It was suggested that *M. genitalium* was unlikely to be a mucosal pathogen. This view is, of course, untenable in the light of other studies, some of which have been mentioned above. Interestingly, another group (126) failed to detect *M. genitalium* in urine from 54 HIV-positive patients. More recently, it was reported (182) that *M. genitalium* was found much more frequently at both urethral and rectal sites of HIV-positive homosexual men than at urethral and rectal sites of those who were HIV negative. Furthermore, urethral infection was associated significantly with symptoms (dysuria), but there was no association between rectal infection and anorectal symptoms and signs, an observation that has been confirmed (D. Taylor-Robinson, P. Benn, C. Carder, and J. Boman, unpublished data). A lack of an association with proctitis seems illogical and warrants further examination in view of the ability of *M. genitalium* to damage other mucosal areas.

M. genitalium-induced cervicitis (129) has been shown to occur more often in HIV-positive than in HIV-negative women, and the mycoplasma has been found more frequently in endometrial biopsy specimens of women who were HIV positive (91) and to persist longer in HIV-positive women (28). Furthermore, it was noted (139) that women who had a high burden of *M. genitalium* organisms were more likely to shed HIV-1 DNA than were *M. genitalium*-negative women, an observation in keeping with the ability of mycoplasmas to stimulate HIV replication (175) and possibly enhance, as does *C. trachomatis*, the transmission of the virus. This suggestion is also supported by some limited serological data (166). The significant positive association between *M. genitalium* and HIV infection has been further strongly supported by the result of a meta-analysis of 19 eligible studies (157).

TABLE 3. Susceptibilities of *M. genitalium* to various antibiotics compared with those of *M. hominis* and *Ureaplasma* spp.[a]

Antibiotic	Susceptibility of:		
	M. genitalium	*M. hominis*	*Ureaplasma* spp.
Tetracyclines			
Tetracycline	±	+	+
Doxycycline	±	+	+
Minocycline	±	+	+
Macrolides			
Erythromycin	++	−	+±
Clarithromycin	++±	−	+++
Azithromycin	+++	−	+
Lincosamides			
Clindamycin	±	+++	±
Quinolones			
Ciprofloxacin	+	+	±
Ofloxacin	±	+	+
Moxifloxacin	++	++	++
Penicillins	−	−	−
Rifamycins	−	−	−

[a] +++, extremely sensitive (MIC ≤ 0.005 μg/ml); ++, highly sensitive (MIC ≤ 0.05 μg/ml); +, moderately sensitive (MIC ≤ 0.1 μg/ml); ±, weakly sensitive (MIC, 0.5 to 2 μg/ml); −, insensitive. Note that some strains of *M. genitalium* are resistant to macrolides and that some strains of *M. hominis* and *Ureaplasma* spp. are resistant to the tetracyclines (MICs of 2 to >64 μg/ml).

ANTIMICROBIAL SUSCEPTIBILITY, TREATMENT, AND PREVENTION

The *in vitro* antimicrobial susceptibility of *M. genitalium* is quite similar to those of *M. pneumoniae* (68, 171, 196) and *C. trachomatis*. The susceptibility of *M. genitalium* to various antibiotics is outlined in Table 3 and presented in more detail elsewhere (226). Although tetracyclines were used to treat NGU before *M. genitalium* was discovered, they are not the antibiotics of choice for *M. genitalium*-associated disease (12, 145). This was also true for women for whom cefoxitin and doxycycline failed to eradicate endometrial *M. genitalium* (63). As mentioned above, the failure of tetracyclines or older quinolones to eliminate *M. genitalium* from the male urethra (46, 83, 108, 134, 205, 229) sometimes resulted in chronic NGU. However, azithromycin was available for *C. trachomatis* infections and is more active *in vitro* than the tetracyclines, has superior mucosal cell penetration, and could be given effectively as a single dose. In fact, in the empirical treatment of NGU, 1.0 g of azithromycin was at least as effective as 100 mg of doxycycline twice daily for 7 days in bringing about clinical cure (184). When azithromycin was given to *M. genitalium*-positive men with urethritis, the organisms were eliminated from 85% of the patients after a 1.0-g single dose, and chronic disease did not ensue (12). This is in accordance with azithromycin having at least 100-fold more activity *in vitro* against *M. genitalium* than any of the quinolones or tetracyclines (65, 66,

68). Unfortunately, there is now evidence that some strains of *M. genitalium* have developed resistance to azithromycin through mutations in region V of the 23S rRNA gene (103). Single-dose azithromycin therapy for NGU may not be effective (12, 17) and may select for resistance. In fact, in a recent study (177), it was found that a 1.0-g single dose of azithromycin eradicated *M. genitalium* from only 67% of the patients, probably reflecting both preexisting macrolide resistance in the population and the emergence of resistance. In contrast, clearance rates of 96 to 100% have been reported after treatment with 1.5 g azithromycin given over 5 days as 500 mg on day 1 followed by 250 mg once per day on days 2 to 5, at least in a population with a low prevalence of macrolide resistance (12, 46). If this treatment is not effective and there is evidence that chronic disease is developing, administration of a course of moxifloxacin (18, 107), which, of the quinolones, has potent activity against *M. genitalium* (65), should be considered. The exploration of further effective therapy is essential, as strains that are resistant to both azithromycin and moxifloxacin have been detected (J. S. Jensen, unpublished data).

Whether the approach to treatment mentioned above is effective for HIV-positive patients who are more susceptible to *M. genitalium* infection remains to be documented, but it is a clinical impression that these patients respond well to standard treatment. Animal experiments have shown that a fully functioning immune system is required for the elimination, rather than suppression, of mycoplasmas after antimicrobial therapy (199), so systematic studies are warranted.

The prevention of an infectious STD centers around the use of a vaccine and screening of populations for the organism in question to deliver effective treatment. The development of a vaccine for *M. genitalium* might be contemplated in the future, but further information about its overall importance is required first. With regard to screening, the cost-effectiveness of such a procedure has to be considered, as the prevalence of *M. genitalium* in the general population is relatively low. Prevalence figures of 0.7% to no more than 3.3% have been recorded (3, 64, 138, 158, 159), generally 4 to 5 times less than those for *C. trachomatis*, and probably do not justify widespread screening programs. However, the selective screening of individuals who can be considered particularly vulnerable on the basis of certain risk factors (for example, young age, early sexual debut, more than one sexual partner, change of sexual partner, and presenting with symptoms) may be a worthwhile approach. From a diagnostic point of view, we believe that it makes a difference to clinical management to know the etiology of NGU, particularly if the disease recurs or becomes chronic. Also, in areas where there is a high prevalence of macrolide resistance, the detection of sequence-based resistance mutations is helpful clinically. However, until further information is available on this issue, a recommendation that it be undertaken routinely would seem premature.

SUMMARY

A summary of the extent to which *M. genitalium* is considered, on a subjective basis, to be associated with or be the cause of the various diseases highlighted in the text is presented in Table 4. A comparison is made between *M. genitalium* and two other genital tract-orientated mollicutes, namely, *M. hominis*, the first mycoplasma of human origin to be discovered, and *Ureaplasma* species.

TABLE 4. Relationship between *M. genitalium* and disease compared with *M. hominis* and *Ureaplasma* spp.[a]

Condition	*M. genitalium*		*M. hominis*		*Ureaplasma* spp.	
	A	C	A	C	A	C
NGU						
Acute	++++	++++	−		+++	+++
Chronic	+++	+++	−		−	
Balanoposthitis	+++	++	−		−	
Chronic prostatitis	+	+	−		−	
Epididymitis	++	++	+	−	++	++
Reiter's disease/ SARA	++	+	−		++	++
BV	++	−	++++	+	+++	±
Cervicitis	+++	+++	−		−	
Infertility	++	++	−		++	−
Ectopic pregnancy	+	?	+	−	+	−
PID	+++	+++	+++	++	+	−
Postpartum fever	NE		+++	+++	++	−
PTB	++	+	++	−	+++	++
Neonatal conjunctivitis	NE		−		−	
Neonatal respiratory disease	NE		+	?	+++	++

[a] Shown are the chances of the indicated mycoplasma being associated with (A) or causing (C) the conditions shown in the left-hand column. ++++, overwhelming; +++, good; ++, moderate; +, small; −, nil; NE, not examined; ?, not certain.

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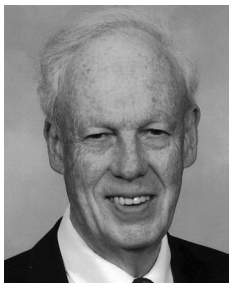

David Taylor-Robinson, M.D., F.R.C.P., F.R.C.Path., qualified in Medicine in 1954. Subsequently, he studied the virological relation between chickenpox and herpes zoster. Next, during National Army Service, he studied polioviruses, after which virological work continued at the Common Cold Research Unit (CCRU) in Salisbury, United Kingdom. From 1963 to 1965, while at the NIH, Washington, DC, he became interested in mycoplasmas. This interest, mainly on genital microbes, continued upon returning to the CCRU. A move in 1970 to the Clinical Research Centre in Harrow, United Kingdom, saw the development of a Division for Sexually Transmitted Diseases (STDs) and collaboration with the STD Department at St. Mary's Hospital and Medical School, London, United Kingdom, at which Dr. Taylor-Robinson was appointed Professor of Genitourinary Microbiology and Medicine. From 1970 to 1996, the etiology, pathogenesis, and treatment of various STDs (NGU, BV, and PID, etc.) were investigated. Since retirement in 1996, Dr. Taylor-Robinson has maintained interest in these topics, especially the role of *M. genitalium* in disease.

Jørgen Skov Jensen, M.D., Ph.D., D.Med. Sci., graduated as an M.D. from the University of Copenhagen, Copenhagen, Denmark, in 1986 and worked as a clinician in different hospitals until he was employed at the Mycoplasma Laboratory, Statens Serum Institut (SSI), in 1987. He is now working as a consultant physician at the SSI, heading the Sexually Transmitted Infections Research and Development group. In 1993 he defended his Ph.D. thesis, "Direct detection of *Mycoplasma pneumoniae* in clinical samples. An acute phase diagnostic test," and in 2005 he defended his D.Med.Sci. dissertation, "*Mycoplasma genitalium* infections. Diagnosis, clinical aspects, and pathogenesis." In 1993 he published one of the first clinical studies linking *M. genitalium* to male urethritis and has been actively investigating this infection, including clinical, diagnostic, and treatment aspects. Dr. Jensen has published more than 100 papers in international peer-reviewed journals as well as four book chapters on human mycoplasma infections.