REVIEW ARTICLE

Mycoplasmas in diseases of humans

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The roles of *Mycoplasma pneumoniae*, *M. hominis* and *Ureaplasma urealyticum* in diseases of humans are currently under investigation. *M. pneumoniae*, which causes primary atypical pneumonia, is a well established pathogen of the respiratory tract. Complications of infection by this organism are also being recognized; they include disorders of the hematopoietic, cardiovascular, central nervous, musculoskeletal, cutaneous and gastrointestinal systems. The roles of the genital mycoplasmas *M. hominis* and *U. urealyticum* are controversial but may include infections of the genitourinary tract and in pregnancy as well as diseases of the newborn, such as neonatal pneumonia and meningitis. In this review atypical pneumonia due to *M. pneumoniae* is described and the role of mycoplasmas in other diseases is discussed.

Le rôle de *Mycoplasma pneumoniae*, *M. hominis* et *Ureaplasma urealyticum* comme source de maladies chez l'humain fait présentement l'objet de recherches. *M. pneumoniae*, qui cause principalement une pneumonie atypique, est un microorganisme pathogène bien connu des voies respiratoires. Les complications d'une infection due à cet organisme sont aussi en voie d'être reconnues; elles incluent des atteintes des systèmes hématopoïétique, cardiovasculaire, nerveux central, musculosquelettique, cutané et gastrointestinal. Les rôles des mycoplasmes d'origine génitale *M. hominis* et *U. urealyticum* prêtent à controverse; ils peuvent inclure des infections des voies génitourinaires, des infections observées durant la grossesse, de même que des maladies du nouveau-né telles que pneumonie et méningite. Dans cet article de revue on décrit la pneumonie atypique due à *M. pneumoniae* et on discute le rôle des mycoplasmes dans d'autres maladies.

Mycoplasmas are the smallest known bacteria that can form recognizable colonies on cell-free media. Their minimum reproductive size, approximately 100 nm, is similar to that of the largest viruses. However, unlike viruses, mycoplasmas possess both deoxyribonucleic acid and ribonucleic acid for replication. They are pleomorphic, lacking a cell wall, but are not genetically related to the other types of bacteria with complete or partial absence of a cell wall — L-forms, spheroplasts and protoplasts. Penicillins are useless in the treatment of disease caused by these organisms, but tetracyclines are effective.[1,2]

Mycoplasmas constitute the class called Mollicutes. The only order in this class, Mycoplasmatales, is currently divided into two families: the Mycoplasmataceae, with *Mycoplasma* and *Ureaplasma* genera, which require sterols for growth, and the Acholeplasmataceae, which do not. A third family, the Spiroplasmataceae, with the genus *Spiroplasma*, is proposed for the mycoplasmas of plants and insects. The thermoplasmas, which have been isolated from acidic refuse piles, and the anaeroplasmas, which have been found in the anaerobic rumen of cows and sheep, are also considered members of the Mollicutes, but their exact taxonomic position has not yet been decided.[3]

Of the 59 species of Mycoplasmataceae described to date, 10 are found in the human body: *M. buccale*, *M. faucium*, *M. fermentans*, *M. hominis*, *M. lipophilum*, *M. orale*, *M. pneumoniae*, *M. primatum*, *M. salivarium* and *U. urealyticum*.[3] Of these, only *M. hominis*, *M. pneumoniae* and *U. urealyticum* are suspected of being pathogenic. In this paper we review, with the aid of the English literature, the known or suspected roles of these three mycoplasmas in disease of eight body systems of humans.

Respiratory system

In the respiratory system the most common mycoplasma of clinical significance is *M. pneumoniae* (Eaton's agent), which is responsible for various respiratory syndromes,

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Reproduced on the cover of this issue of the Journal is a Carl Zeiss Nomarski interference contrast photomicrograph of colonies of *Mycoplasma hominis* isolated on agar; the final magnification is ×385. The photomicrography was performed by Mr. F. Stefani of Dalhousie University's photographic unit.

including primary atypical pneumonia.[4] Other less common mycoplasmas found in this system are *M. buccale*, *M. faucium*, *M. fermentans*, *M. lipophilum*, *M. orale* and *M. salivarium*, which are generally believed to be commensals.[3,5] *M. hominis* and *U. urealyticum* have also been found in the respiratory system in association with neonatal pneumonia following exposure in utero or during birth.[6,7]

Epidemiologic aspects

M. pneumoniae is responsible for epidemics of respiratory illness every 2 to 6 years[8,9] and may account for 10% to 50% of diagnosed cases of pneumonia.[9-11] The peak occurrence of these illnesses is in early fall and winter, although *M. pneumoniae* is endemic throughout the year and may be the most common cause of respiratory illnesses in summer.[9] Children from 5 to 19 years of age are most often affected; those less than 5 years of age rarely have severe symptoms.[8,12-14] Pneumonia occurs in 3% to 10% of those known to be infected, most frequently in persons between 10 and 30 years of age.[9] Since the illness is often mild and only the more severe cases come to medical attention, the incidence of *M. pneumoniae* infection is probably underestimated. The incubation period is 2 to 3 weeks[15] and, although the carrier state may last up to 5 months, the organism appears to be spread by coughing during the 2 to 3 weeks of the acute stage of the illness.[4] Close contact is needed for transmission, so the illness is more frequent among members of a family, military recruits, schoolchildren and other "closed" populations.[9]

Pathophysiologic findings

Although primary atypical pneumonia is usually mild, fatal cases have been reported; pathological examination has shown congested lungs with numerous small grey nodules, hyperemic respiratory mucosa, a mononuclear alveolar exudate and interstitial infiltration with plasma cells.[16,17] In one proven case of infection due to *M. pneumoniae*, the walls of the bronchioles were thickened by edema and infiltration by macrophages, lymphocytes and plasma cells.[17] In another case these features were accompanied by severe bronchiectasis, with ulceration and fibrosis of the bronchial walls.[18]

In mycoplasmal pneumonia various immunologic abnormalities may occur: autoantibody formation to lung, smooth muscle, lymphocytes and other tissues;[9] decreased tracheobronchial clearance of inhaled foreign particles;[19] and diminished reactivity to tuberculin in a sensitized individual.[20] Because severe symptoms are rare despite evidence of exposure in children less than 5 years of age, pneumonia is thought to result from hypersensitivity due to repeated exposure.[13]

Signs and symptoms

The illness begins with headache, fevers, chills, malaise and anorexia. A sore throat follows; the accompanying cough is dry at first, but after a week mucoid sputum is produced.[4] Earache occurs in about 30% of cases, but otitis externa, otitis media and bullous myringitis are rare.[9] Rhonchi, rales and wheezing are common,[10] as is substernal soreness, while pleurisy and hemoptysis are unusual.[21]

Radiologic features

Generally the physical findings are much less striking than the roentgenographic findings, which, however, are not diagnostic of mycoplasmal pneumonia. In 90% of cases the lower lobe of one of the lungs shows a patchy or reticular interstitial infiltrate extending from hilum to periphery. A mixed interstitial and acinar pattern is sometimes seen. Involvement of the upper or middle lobe, bilateral involvement, hilar adenopathy and lobar consolidation rarely occur.[9,11,22]

Pleural effusions are seen occasionally;[23] they are sterile serous or serosanguineous proteinaceous exudates with a specific gravity of 1.015 to 1.028.[9]

Laboratory diagnosis

The diagnosis of pneumonia due to *M. pneumoniae* is based upon recovery of the organism from throat swabs, nasopharyngeal aspirations, sputum or other samples from the respiratory system or diagnostic rises in antibody titres, or both, along with the clinical and radiologic features.

M. pneumoniae is difficult to isolate and may take up to 3 weeks to grow. Therefore, isolation is usually attempted only for research purposes or in very special circumstances.

Antibody titres can be determined by several methods: complement fixation, metabolic inhibition, mycoplasmacidal complement-dependent antibody, radioimmunoprecipitation, counterimmunoelectrophoresis and indirect hemagglutination.[9]

A nonspecific diagnostic aid is the presence of cold agglutinins, IgM antibodies that are found in 33% to 75% of cases.[9] These agglutinins also appear in infectious mononucleosis, rubella, influenza and adenovirus infections, as well as in a number of noninfectious conditions, such as some of the hemolytic anemias, blood dyscrasias, liver diseases, certain allergic conditions and peripheral vascular disorders.[9,24] They are likely to occur with pneumonia and have been thought to reflect its severity. However, they are less common in children.[15]

Blood counts and levels are usually normal; however, there may be an increase in the neutrophil count, with a shift to less mature cells, and the erythrocyte sedimentation rate is often raised.[11,15]

Treatment

Therapy with erythromycin or tetracycline relieves the symptoms but does not eliminate the organism, thereby leaving the immune response intact.[4,15] However, tetracycline is not recommended for children or pregnant women. Left untreated, the acute illness usually resolves within 2 to 3 weeks. With antibiotic therapy the symptoms disappear or are markedly reduced within 3 to 4 days and the radiologic abnormalities and cough are gone within 2 weeks.[4] The response to therapy differentiates atypical pneumonia caused by *M. pneumoniae* from that caused by viruses.

Complications

M. pneumoniae, along with the respiratory viruses, has been associated with exacerbations of bron-

chial asthma[25] and with chronic bronchitis.[26] The symptoms are more severe in children with some hemoglobinopathies,[27] and immunodeficiency may alter the symptoms drastically.[28] Recently the organism was associated with Legionnaires' disease in one patient.[29] Infection with *M. pneumoniae* does not usually predispose to secondary infection by more pathogenic organisms.[9] However, a possible respiratory complication may be the Swyer–James syndrome — residual hyperlucent areas of the lung.[30]

Complications of *M. pneumoniae* infection have also involved the hematopoietic, cardiovascular, central nervous, musculoskeletal, cutaneous and gastrointestinal systems.[31]

Hematopoietic system

The production of cold agglutinins by *M. pneumoniae* is responsible, along with infection by this organism, for a number of fairly rare hematologic complications, such as hemolytic anemia, acrocyanosis and thrombocytopenia.[9,31] Disseminated intravascular coagulation has been reported; in two instances it led to acute renal failure and in one symmetric peripheral gangrene.[32-34] Treatment includes administration of heparin and prednisone along with erythromycin or tetracycline and transfusion of warmed erythrocytes or type i erythrocytes from adults.[9]

Cardiovascular system

M. pneumoniae infection has been serologically associated with pericarditis, myopericarditis, myocarditis, hemopericardium, complete heart block, congestive heart failure and death.[9,34-36] The organism has also been isolated from pericardial fluid.[37]

Cardiovascular problems occur in either the acute or the recovery phase of *M. pneumoniae* infection. Consequently, two separate mechanisms of damage may be at work. Heart disease in the acute phase may be due to the toxic effects of the organism and can be treated with antimicrobial drugs. In the recovery phase the damage may be due to immunologic mechanisms.[36] Residual effects are rare.

M. pneumoniae infection should be considered when heart failure occurs during or after an upper respiratory tract infection.[36]

Central nervous system

M. pneumoniae infection has also been associated with neurologic syndromes, such as psychosis in the elderly, meningitis, meningoencephalitis, transverse myelitis, hemiplegia, ascending paralysis, cranial nerve palsy, brain stem encephalitis and poliomyelitis-like illness. The organism is identified either by isolation at the time of the neurologic illness or by a diagnostic rise in antibody titres.[9,38-40] A respiratory illness may or may not occur before the onset of neurologic symptoms.

The frequency of neurologic complications has not been accurately determined. Furthermore, the pathogenesis of the association between *M. pneumoniae* and neurologic symptoms is not clear, but it is most likely due to an immunologic mechanism. *M. pneumoniae* is rarely isolated from the cerebrospinal fluid and produces no distinctive symptoms. The diagnosis is based primarily on a rise in antibody titres. Although antimicrobial therapy is not effective, patients usually recover completely.

M. hominis was reported as the causative agent isolated from the cerebrospinal fluid in cases of neonatal meningitis[41,42] and from a brain abscess in one case.[43] Therefore it should be considered in cases of neonatal meningitis if the results of Gram-staining are negative, no growth occurs on conventional culture media and there is a history of possible genital tract infection in the mother.[41,42]

Musculoskeletal system

M. pneumoniae infection is often accompanied by nonspecific arthralgias or myalgias during the acute phase. Occasionally it leads to migratory polyarthropathy affecting middle-sized joints, in which combinations of joint swelling, morning stiffness, "gelling" with stiffness after inactivity and considerable functional disability may occur. Symptoms may last up to a year but will eventually disappear.[44,45]

M. hominis has been isolated from the synovial fluid of an inflamed hip joint in a patient with septic arthritis following childbirth. The condition was believed to have been caused by septicemia after delivery and was cured by the administration of tetracycline.[46] In view of this case *M. hominis* should be considered in patients with postpartum arthritis whose condition does not respond to penicillin.

U. urealyticum was isolated from the synovial fluid of an acutely inflamed joint in a patient with hypogammaglobulinemia; treatment with tetracycline was successful.[47]

Cutaneous system

A wide variety of nondistinctive rashes frequently occur with or after infection by *M. pneumoniae*. These have been described as "discrete or confluent, pruritic or nonpruritic erythematous macular, maculopapular, urticarial, vesicular, bullous, or petechial lesions. Some of these rashes are scaling, scarlatiniform, pityriasis rosea-like, Henoch-Schönlein purpura or erythema nodosa."[9] Reports of the Stevens–Johnson syndrome (severe erythema multiforme) associated with *M. pneumoniae* infection have been numerous.[14,48]

The exact mechanism by which the rashes are produced is unknown, but they may be due to increased sensitivity to antibiotics. The rash usually lasts for 7 to 10 days.[9]

Gastrointestinal system

During the acute phase of infection by *M. pneumoniae* prolonged anorexia, nausea, vomiting and diarrhea occur in 12% to 44% of patients.[9] *M. pneumoniae* infection, as demonstrated by a diagnostic rise in antibody titres, has been documented in patients with acute pancreatitis,[49] but the exact nature of the relationship is obscure.

Genitourinary system

M. hominis (Figs. 1A and 1B)

and *U. urealyticum* (Fig. 2) are the genital mycoplasmas of clinical importance for humans. *M. fermentans*, the other genital mycoplasma, is rarely found and has not yet been associated with any pathologic condition.[1]

About one third of healthy infants are colonized at birth with *U. urealyticum*, presumably acquired during passage though the birth canal. *M. hominis* is much less common. Rates of isolation of both mycoplasmas decrease during the first year of life and are extremely low before puberty. Recolonization is associated with sexual activity and increases with the number of partners.[50-53] In a study of healthy women McCormack and colleagues[51] isolated mycoplasmas from the genital tract of 37% of the subjects who had had one sexual partner but 75% of those who had had more than three partners. Similar isolation rates have been found for healthy men.[52]

M. hominis and *U. urealyticum* have been associated with a number of diseases of the genitourinary system, problems in pregnancy and diseases of the newborn.

Thomsen[54] isolated *M. hominis* from the bladder urine significantly more often in patients with chronic pyelonephritis than in those without. The possible causal relation between the organism and this condition was demonstrated by both the isolation of the mycoplasma and diagnostic rises of antibody titres in acute exacerbations of the disease.

U. urealyticum splits urea and may play a role similar to that of *Proteus mirabilis* in the formation of bladder stones. No cases in humans have been documented, although *U. urealyticum* has been shown experimentally to cause such stones in rats.[55]

The role of *M. hominis* and *U. urealyticum* in nongonococcal urethritis is controversial. Mycoplasmas have been isolated from men with and without this condition, although some investigators have reported a higher isolation rate, particularly for *U. urealyticum*, in those with the condition.[1] Others have reported similar rates.[56] In some instances *U. urealyticum*

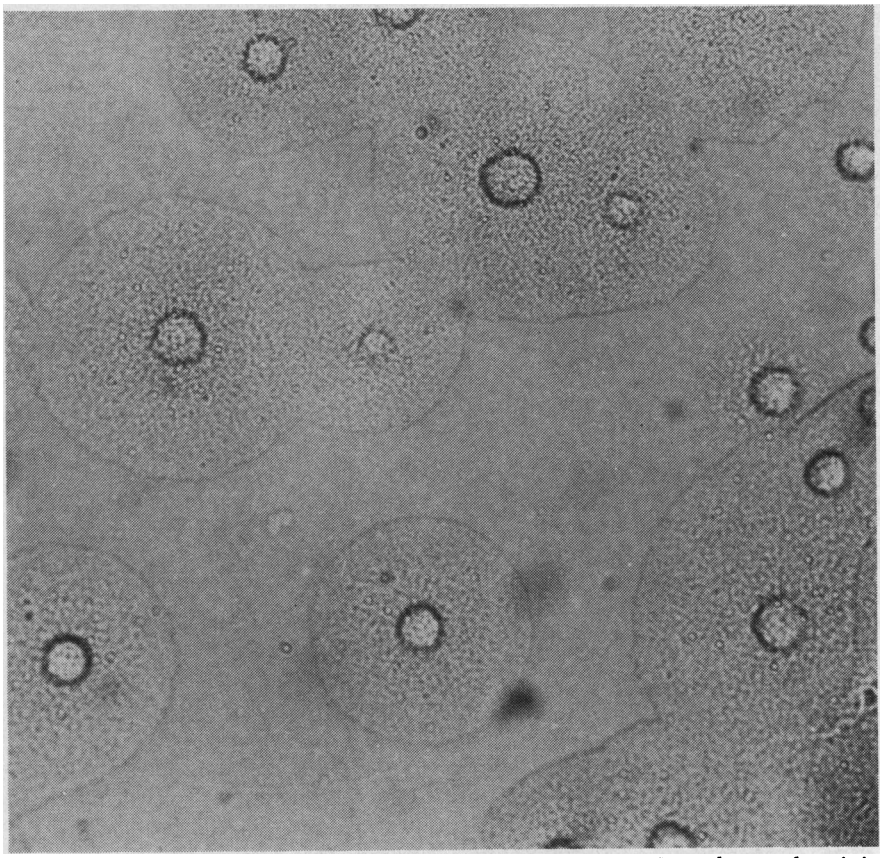

FIG. 1A—Bright-field photomicrograph of colonies of *Mycoplasma hominis* isolated from female genital tract (×275).

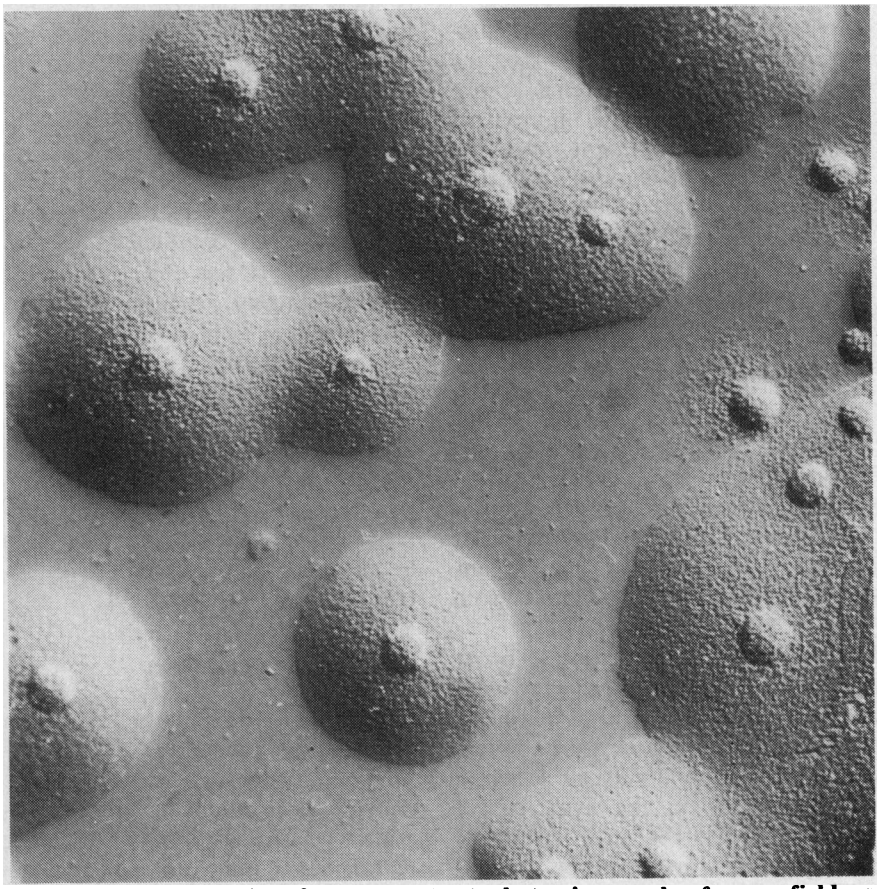

FIG. 1B—Nomarski interference contrast photomicrograph of same field as in Fig. 1A (×275).

has been the only organism isolated from patients with nongonococcal urethritis.[57]

Mycoplasmas have also been isolated from women with various diseases of the female reproductive tract. They were isolated from an abscess of Bartholin's gland, but it was not established that they had caused the abscess.[58] In vaginitis the presence of *M. hominis* may depend on that of *Trichomonas vaginalis*.[59,60] For example, antibiotics used to eliminate *T. vaginalis* have also eliminated *M. hominis*, but the reverse has not occurred.[59] Infection by *T. vaginalis* may provide optimum conditions for the growth of *M. hominis*; however, *M. hominis* is also found alone. Both genital mycoplasmas have been isolated from inflamed fallopian tubes and from tubo-ovarian and pelvic abscesses, but only *M. hominis* appears to have instigated these infections.[1,61] Vaginal discharge, however, cannot be attributed to *M. hominis*.[59] *M. pneumoniae* was isolated from a tubo-ovarian abscess in one patient who had had pneumonia 2 weeks earlier; the mycoplasma was thought to have spread via the bloodstream.[62] The exact role of these organisms in diseases of the female reproductive tract is not clear and needs controlled studies.

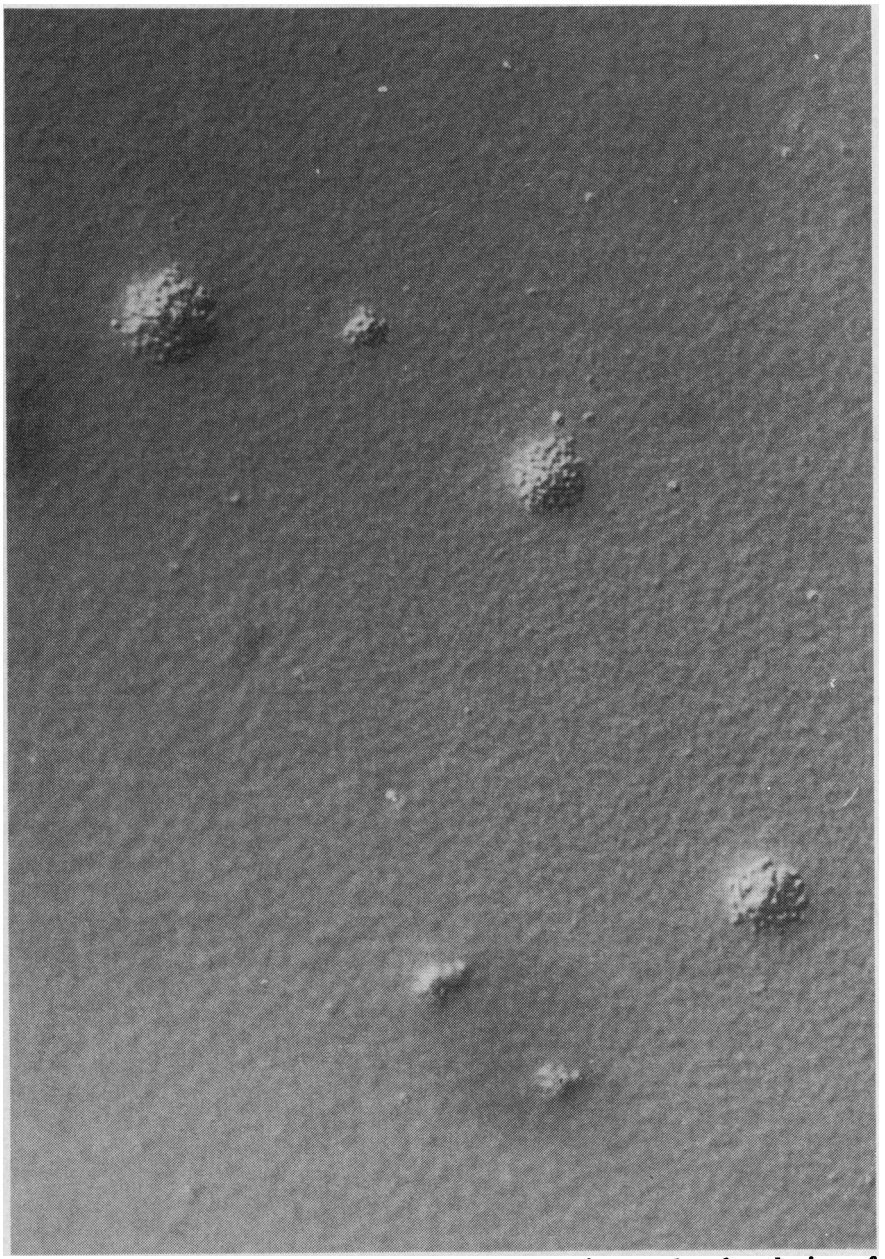

FIG. 2—Nomarski interference contrast photomicrograph of colonies of *Ureaplasma urealyticum* isolated from female genital tract (×350).

Opinions about the role of mycoplasmas, particularly *U. urealyticum*, in primary infertility differ markedly. Some studies have shown a significantly higher rate of isolation of *U. urealyticum* from infertile than from fertile couples,[63] while other studies have not.[60,64] Colonies of T-mycoplasmas (T for tiny) have been seen attached to sperm;[65] this has led to the belief that the organism prevents fertilization by interfering with sperm function. Alternatively, pelvic inflammatory disease due to these organisms may account for the problem.[1,61] Conception rates of 29% to 84% have been reported in couples treated with tetracycline to eliminate *U. urealyticum*,[66,67] but these studies were not controlled. The only controlled study reported[68] showed that the increase in the rate of conception with tetracycline treatment was not significantly greater than the increase with placebo treatment.

M. hominis and *U. urealyticum* have been isolated from mother, fetus or placenta in numerous cases of spontaneous abortion;[6,69-72] however, a causal relation has not been proved. In view of the number of healthy pregnant women who carry genital mycoplasmas and deliver healthy infants at term, and the potential hazard of tetracycline to both mother and fetus, treatment during pregnancy to eliminate mycoplasmas and prevent abortion is not advisable. Treatment before conception will not necessarily eliminate genital mycoplasmas for the duration of the pregnancy.

The isolation of genital mycoplasmas from women and their infants has been related to a lower mean birth weight,[53,71,73,74] prematurity,[74] prolonged rupture (for more than 24 hours) of the placental membranes[50,74,75] and inflammation of the placenta.[6,7,74,76] Finally, genital mycoplasmas have been associated with a low-grade postpartum fever of short duration that does not usually result in significant disability.[75]

Conclusion

As more physicians become aware of mycoplasmas as a possible cause of numerous conditions more information concerning their role will become available. All the mycoplasmas are susceptible to tetracycline, and *M. pneumoniae* and *U. urealyticum* are also susceptible to erythromycin. Therefore recognition and treatment to eliminate these organisms will, in most instances, significantly shorten the course of the illness and decrease the accompanying disability. At the moment the greatest problem is a lack of clinical suspicion.

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