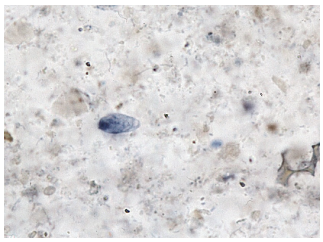

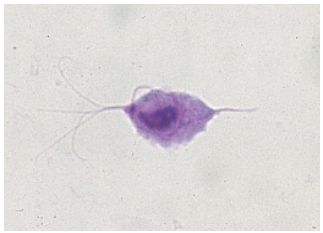

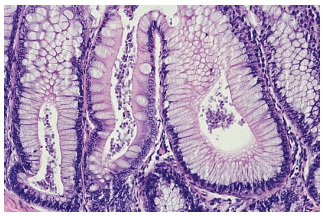

7

Trichomoniasis

Mary K. Klassen-Fischer and
Izzat S. Ali

Introduction

Definition

Trichomoniasis generally refers to infection of the genitourinary tract by the flagellate protozoon *Trichomonas vaginalis*. Trichomoniasis also applies to infection of the intestinal tract by *Trichomonas hominis* (*Pentatrichomonas hominis*) and infection of the oral cavity by *Trichomonas tenax* (*Trichomonas buccalis* and *Trichomonas elongata*). *Trichomonas hominis* and *T. tenax* will be discussed separately at the end of this chapter, since both are usually considered nonpathogenic in humans.

Unusual presentations of *T. tenax* infection have been reported in the lung,[1-3] submaxillary gland,[4] lymph node,[5] and body cavity.[6] Unusual sites of *T. vaginalis* infections have been described in the brochopulmonary tree,[2,7-10] body cavities,[11-12] esophagus,[13] and testes.[14] There appears to be substantial genomic diversity among *T. vaginalis* in the United States.[15]

General Considerations

Donné first identified *T. vaginalis* in 1836 in a vaginal discharge.[16] He believed the motile organism was the etiologic agent of vaginitis, but other investigators thought it was a commensal. In 1916 Hoehne demonstrated that eradicating *T. vaginalis* alleviated vaginitis.[17] Treatment for trichomoniasis was not widely available until the late 1950s, when Cosar and Jolou discovered that metronidazole was efficacious.[18]

Epidemiology

In 1995 the World Health Organization estimated that there were 170 million cases of trichomoniasis worldwide, making it the most common nonviral sexually transmitted disease.[19] Incidence is highest among the poor and undereducated, and in individuals who are sexually promiscuous.[1,20] Estimates of the prevalence of *T. vaginalis* vary with geographic location, methods of detection, and study settings (gynecologic clinics, sexually transmitted disease clinics, etc). Frequency rates for unselected female populations in developed countries range from 5% to 15%.[1,21-23]

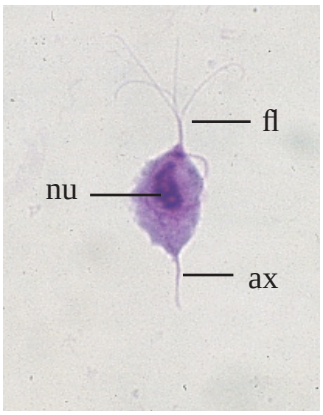

Figure 7.1
Whole mount of *Trichomonas vaginalis* trophozoite from culture. Note 4 anterior flagella (fl), nucleus (nu), and axostyle (ax). Giemsa x1030

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Frequency rates of up to 70% are reported among low socioeconomic groups and from sexually transmitted disease clinics.[1,24] Epidemiologic studies in the United States indicate that 3 to 5 million women are infected with *T. vaginalis* annually.[25] Some general frequency data follow: 5% (family planning clinics), 13% to 25% (gynecologic clinics), 7% to 35% (sexually transmitted disease clinics), 50% to 75% (female sex workers),[20,26] 4% adolescent females,[27] and 32% incarcerated females.[28]

The prevalence of *T. vaginalis* in males has not been studied as extensively as in females.[29] Estimates vary from 4% to 20% of men with urethritis[30-33] to 20% to 40% of male sexual partners of infected females.[1,33,34] Frequency among males is less than those cited for the respective female populations.[1,28]

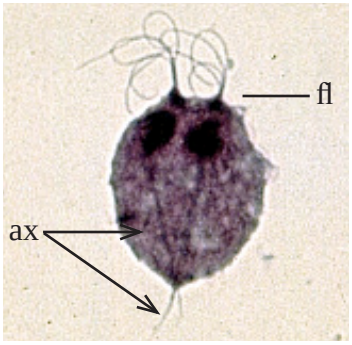


Figure 7.2
Whole mount of dividing *Trichmonas vaginalis* trophozoite from culture. Note 2 sets of anterior flagella (fl), 2 nuclei, and 2 axostyles (ax). Giemsa x1320

Infectious Agent

Morphologic Description

Strains of *T. vaginalis* vary serologically, antigenically, and morphologically. However, differences in size, growth rate, and virulence are insufficient to warrant clinical subdivision.[1,22]

Trichomonas vaginalis is the largest trichomonad infecting humans.[35] The infecting form is the trophozoite, the motile feeding stage. *Trichomonas vaginalis* typically has 4 anterior free flagella that originate in a kinetosomal complex (basal body) (Fig 7.1). A fifth flagellum extends posteriorly along the margin of the undulating membrane, and propels the organism. The fifth flagellum and undulating membrane usually do not extend beyond two thirds of the length of the cell. A parabasal body, analogous to a Golgi apparatus, is often attached by fibrils to the kinetosome of the flagella. Remaining organelles include a nucleus, axostyle (supporting structure), costa, and pelta (structural significance unknown). Hydrogesomes are located along the axostyle and costa. The cytoplasm also contains free and membrane-bound ribosomes, glycogen vacuoles, and large vacuoles.[22] Pseudopodia-like extensions are used for attachment and feeding, but not movement.[36]

By light microscopy, *T. vaginalis* is ovoid to spherical or piriform, and approximately the size of a histiocyte (7µm to 23µm by 5µm to 12µm). Flagella are retained in wet mounts (Figs 7.1 & 7.2) but lost in alcohol-fixed, Papanicolaou-stained material (Figs 7.3 and 7.4). In Papanicolaou-stained material, the organism may be hazy and poorly defined. It is gray-green, has a round or elliptical nucleus located centrally or eccentrically, and may have eosinophilic granules in the cytoplasm derived from ingested erythrocytic material (Figs 7.3 & 7.4).[37] Multinucleated forms are occasionally observed.[36,38]

Trichomonas vaginalis lacks mitochondria, derives most of its energy from glycolysis, and replicates by binary fission. Hydrogesomes generate hydrogen that combines with oxygen to form an anaerobic atmosphere.[22] Food sources include epithelial cells, yeasts, bacteria, and erythrocytes.[39-41]

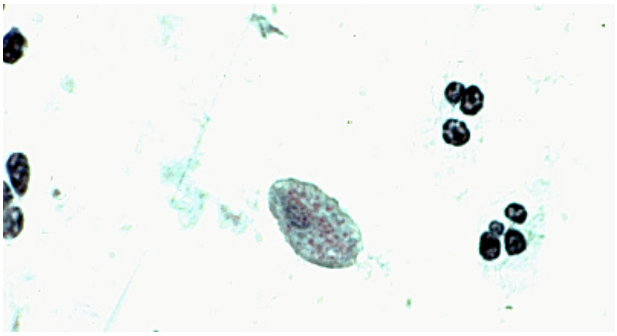


Figure 7.3
Single *Trichomonas vaginalis* trophozoite. Note eosinophilic granules and absence of flagella. Pap x1000

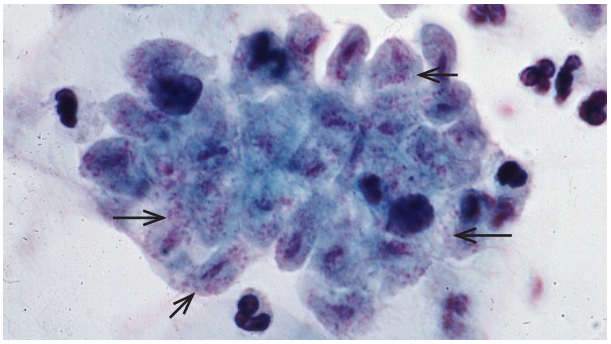


Figure 7.4
Aggregate of multiple *Trichomonas vaginalis* organisms. Note eosinophilic granules (arrows) and absence of flagella. Pap x1000

Transmission

Trichomoniasis is transmitted sexually, although nonsexual transmission is theoretically possible.[42] Newborns are sometimes infected during delivery through the birth canal.[7,10,43] The incubation period is 4 to 28 days in 50% of infected females.[22] Transmission rate is high: 85% of females having sexual contact with infected males and approximately 80% of males having a single sexual exposure to an infected female.[20,33]

Clinical Features and Pathogenesis

Severity of infection depends upon the virulence of the organism, parasite burden, host environment, and host response. *Trichomonas vaginalis* can survive at any vaginal pH, but develops fully at pH 6 to 7. Severity increases during the late secretory phase of the menstrual cycle, during menstruation, and during pregnancy.[44] The exact mechanism of host tissue destruction is not known, but it appears that *T. vaginalis* damages tissue by direct contact and by cytotoxicity.[45,46] Proteins found on *T. vaginalis* but not on *T. tenax* may be key to the pathogenicity and virulence of *T. vaginalis*.[47] Neutrophils are the predominant host response and inhibit deep invasion into host tissue.[48,49] The efficacy of host response in female patients is unknown, but repeated infections do not confer protective immunity.[20]

In females, the organism resides most frequently in the vagina, Skene's glands, and urethra. Cervical mucus acts as a barrier to *T. vaginalis* and inhibits infection beyond the cervix.[1,36,50,51] No evidence links *T. vaginalis* to pelvic inflammatory disease, spontaneous abortion, or sterility, nor is there convincing evidence that *T. vaginalis* causes squamous intraepithelial lesions or cervical carcinoma.[52-57]

Trichomonas vaginalis infection in females ranges from asymptomatic (10% to 50%) to severely symptomatic.[58,59] Approximately one third of asymptomatic females become symptomatic within 6 months. Green, foamy vaginal discharge is the most common presentation in symptomatic women.[20,60] Other symptoms include pruritus, red and edematous vulva and vagina, "strawberry" cervix, vaginal bleeding, dyspareunia, and enlarged and tender lymph nodes. Lymphadenopathy is rare.[22] A yellow-green, malodorous vaginal discharge is usually associated with accompanying bacterial infection. In addition to vaginitis and bartholinitis, the lower urinary tract may be infected, resulting in dysuria, urinary frequency, cystitis, urethritis, and infection of Skene's glands.[61] Vaginal trichomoniasis may be associated with bacterial vaginosis, candidiasis, gonorrhea, and syphilis.[46,62,63] Concurrent infections with herpes simplex virus and human papillomavirus are also noted. Respiratory or pharyngeal infections may occasionally be seen. [2,7-10]

In males, the organism resides in the urethra and prostate. Most males infected with *T. vaginalis* are asymptomatic.[46] Reported symptoms include urethral discharge and, less commonly, dysuria, pruritus, prostatitis, orchitis, and epididymitis.[14,31] In a study of trichomoniasis in males, 59% of patients experienced spontaneous regression within 2 weeks; 41% had infections that persisted for 2 weeks or longer. In patients with spontaneous regression of *T. vaginalis*, symptoms were minimal or not apparent, the organism was not evident in large numbers, and the interval between last exposure and detection was relatively long. The reverse was true for male patients with persistent infection.[33]

Pathologic Features

The appearance of *T. vaginalis* in conventional Papanicolaou (Pap) smears varies widely. In nearly a quarter of cases of trichomoniasis, the organism appears without accompanying background and cellular changes.[55] Background milieu and cytologic features may be minimal or marked. The smear background can be clean or "dirty," with relatively uniform proteinaceous debris (Fig 7.5). Inflammatory response may be mild or intense, with numerous neutrophils and few lymphocytes, plasma cells, and histiocytes. Leukocytes may appear singly or in aggregates (sometimes called cannonballs) around epithelial cells (Fig 7.6). Inflammation may cause a spread maturation index, resulting in an increased number of parabasal cells or superficial cells. The increased number of superficial cells, apparently caused by increased epithelial vascularity,[55] can produce a greater number of eosinophils than would normally be expected on a well-stained Pap smear.

Squamous epithelial cells often exhibit inflammatory changes such as slight cellular hypertrophy, slight nuclear enlargement, hyperchromasia, and binucleation (Fig 7.7). Perinuclear halos are often prominent (Fig 7.8). Pyknosis and karyorrhexis, degenerative changes associated with inflammation, may also be noted. These changes affect squamous epithelial cells more often than endocervical cells. Endocervical cells, however, can exhibit slight nuclear and nucleolar enlargement and hyperchromasia (Fig 7.9). Bac-

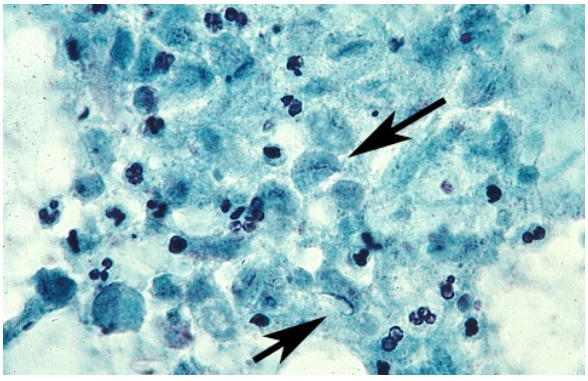


Figure 7.5
Numerous trichomonads (arrows) amid proteinaceous debris ("dirty" smear background) sometimes seen in vaginal trichomoniasis. Debris is usually more uniform than in tumor diathesis. Pap x630

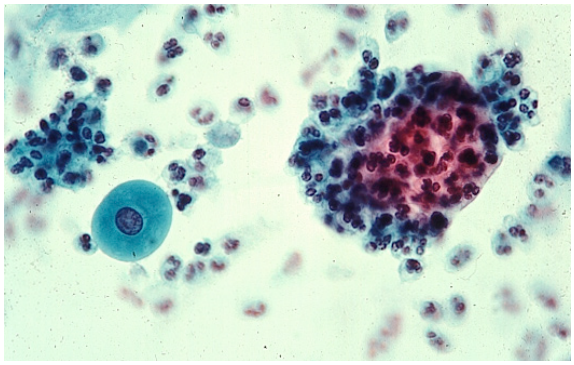


Figure 7.6
Acute inflammatory cells aggregating around epithelial cell at right (cannonball appearance). Structures represent nonspecific inflammatory response, but are often associated with trichomoniasis. Pap x630

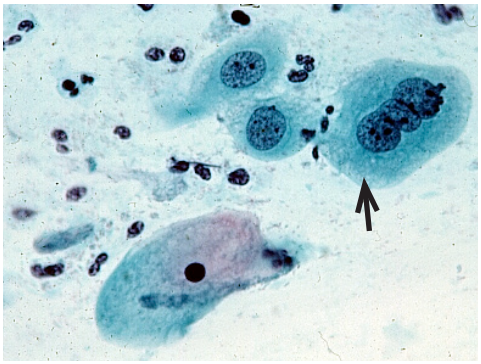


Figure 7.7
Cellular hypertrophy, slight nuclear enlargement, hyperchromatism, and bi- or multinucleation in epithelial cells (arrow). Nuclear enlargement is generally within limits of inflammatory cell changes (less than 3 times the size of intermediate cell nucleus). Pap x630

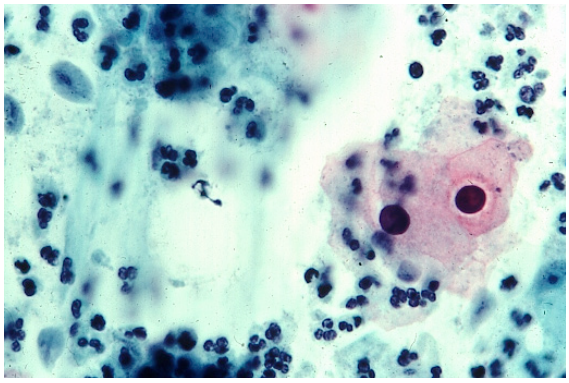
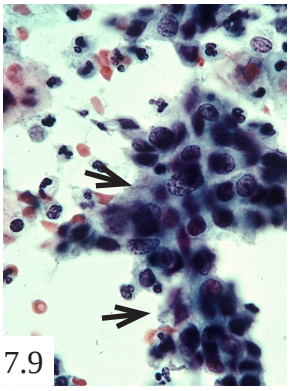


Figure 7.8
Slightly enlarged, hyperchromatic nuclei and perinuclear halo associated with vaginal trichomoniasis. Pap x630



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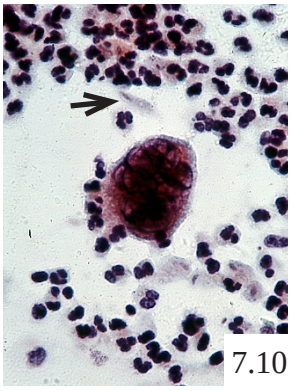

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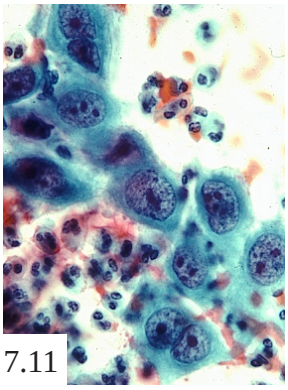

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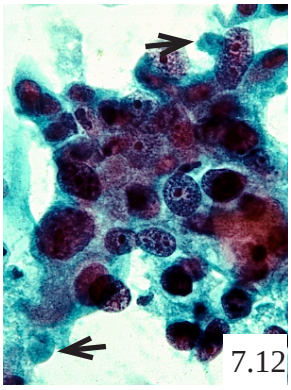

7.12

Figure 7.9
Slight nuclear enlargement and hyperchromatism of endocervical cells due to *Trichomonas vaginalis* infection (arrows). Nucleoli may be more prominent than usual. Pap x630

Figure 7.10
Concurrent herpes simplex virus inclusion (center) and trichomonads (arrow). Pap x630

Figure 7.11
Atypical repair is differentiated from squamous cell carcinoma (see Figure 7.12) by single layer of cells exhibiting well-defined borders. Pap x630

Figure 7.12
Squamous cell carcinoma showing characteristic syncytial grouping of cells with loss of polarity (also present in layer of atypical reparative cells) and pronounced nuclear crowding. Note trichomonads (arrows). Pap x630

teria (including *Leptothrix)*, fungi, herpes simplex virus, and human papillomavirus may be evident along with *T. vaginalis* (Fig 7.10). In the vast majority of cases, the cellular changes associated with *T. vaginalis* infection are readily distinguishable from squamous intraepithelial lesions or carcinoma. However, 2 factors should be noted. First, increased cellular maturation in postmenopausal women may simulate increased estrogen levels, requiring a meticulous search for the organism. Second, reparative processes due to epithelial destruction are sometimes cytologically evident on Pap smears. Typical repair is easily identified; atypical repair is more difficult to differentiate from epidermoid or endocervical carcinoma (Figs 7.11 & 7.12). A "dirty" slide background, increased cellular maturation or eosinophilia, aggregates of inflammatory cells, and perinuclear halos all suggest a trichomonal infection.

Histologically, *T. vaginalis* elicits a somewhat generalized inflammatory response in approximately two thirds of infected patients.[55,64] As described by Koss, blood vessels within papillae are often distended, especially in postmenopausal women.[55] Elongation of the papillae is variable,

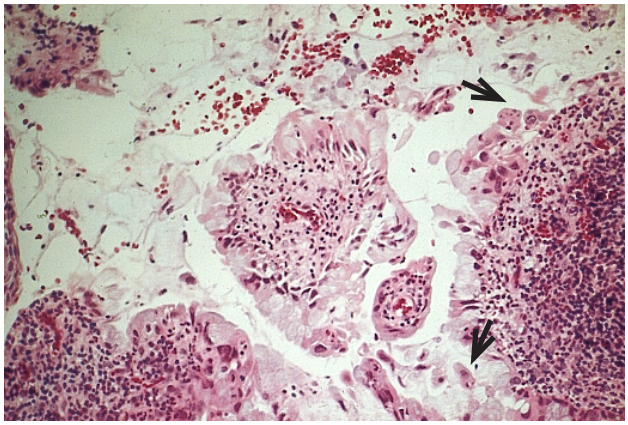

Figure 7.13
Histologic section from patient with trichomoniasis (arrows) and nonspecific cervicitis. x300

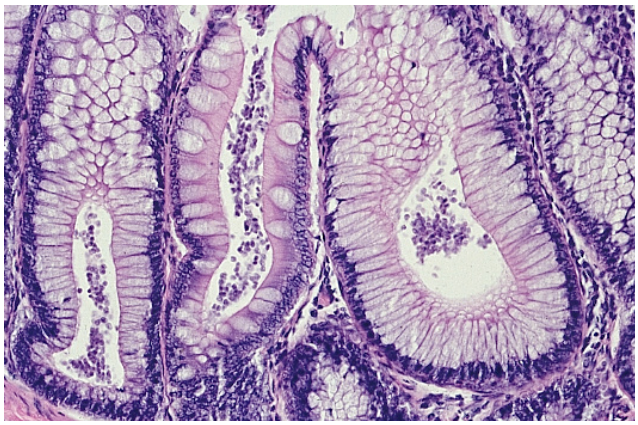

Figure 7.14
Trichomonads fill intestinal crypts of monkey. x160

sometimes producing stasis, margination and migration of neutrophils, and papillitis. The strawberry appearance of the cervix is caused by vascular distention and hemorrhage. Edema of the squamous epithelium is accompanied by separation of the epithelial cells. Perinuclear halos, correlative in cytologic material, are characteristically observed in all layers of the epithelium. In nontrichomonal cervicitis, perinuclear halos are less frequently observed and are present only in the basal layer. Layers of squamous epithelium exfoliate, exhibit cytologic features previously described, and become more vulnerable to infection. Necrosis and ulceration can occur, and purulent material may coat the eroded surface. Mild or marked basal-cell hyperactivity is occasionally seen and is exclusive to trichomonal cervicitis. Squamous metaplasia is frequently observed. Because the organism is noninvasive, underlying connective tissue stroma is usually unaffected (Fig 7.13).[65] Trichomonads are rarely observed in tissue sections; Figures 7.14 and 7.15 show trichomonads in the intestinal lumen of an infected monkey.

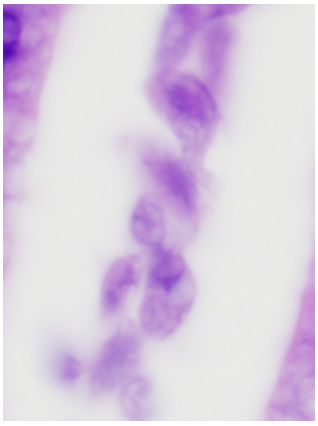

Figure 7.15
Trichomonads averaging 8 by 5 µm in intestine of monkey. x800

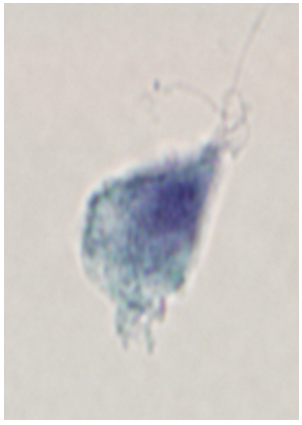

Figure 7.16
Thin Prep® smear of *Trichomonas vaginalis* using liquid-based cytology. Note flagella, nucleus, and clean background compared to Figure 7.3. Pap original magnification x1000.

Diagnosis

Identification of trichomoniasis depends on finding an intact *T. vaginalis* in preparations of wet mount smears of vaginal (Figs 7.16 & 7.17) , cervical, or urethral secretions. Numerous studies have compared the sensitivity and specificity of various diagnostic techniques.[66-73] Culture, antibody-related, and molecular biologic methods can provide up to 95% sensitivity in vaginal specimens.[67] Though not the most sensitive, wet mounts and Pap smears are used in clinical settings because they are cost-effective and easy to collect and evaluate.[74] Wet mounts are most often used to detect *T. vaginalis* in symptomatic patients; Pap smears are useful for asymptomatic patients.[1,66,75] It is important to avoid fecal contamination of specimens because of the possibility of *T. hominis* in stool. FDA-cleared tests for trichomoniasis in women include OSOM® Trichomonas Rapid Test (Genzyme Diagnostics, Cambridge, Massachusetts), an immunochromatographic capillary flow dipstick technology, and the Affirm™ VP III (Becton Dickenson, San Jose, California), a nucleic acid probe test that detects *T. vaginalis*, *Gardnerella vaginalis,* and *Candida albicans*. Each of these tests, which are performed on vaginal secretions, have a sensitivity of >83% and a specificity of >97%. Both tests are considered point-of-care diagnostics. The results of the OSOM Trichomonas Rapid Test are available in approximately 10 minutes, whereas results of the Affirm VP III are available within 45 minutes. Although these tests tend to be more sensitive than those requiring vaginal wet preparation, false positives might occur, espe-

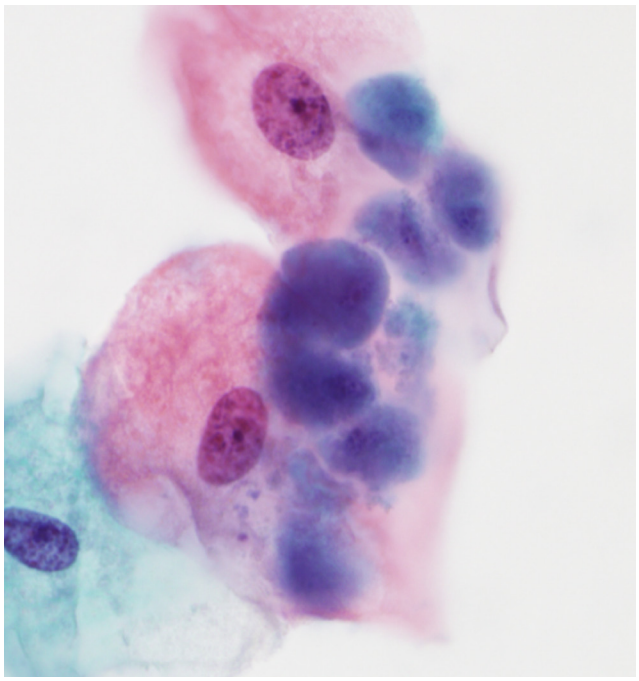

Figure 7.17
Thin Prep® smear of *Trichomonas vaginalis.* Note aggregate of multiple organisms attached to vaginal cells. Compare to Figure 7.4. Pap original magnification x1000.

cially in populations with a low prevalence of disease.[60]

Treatment

The standard treatment for *T. vaginalis* infection is oral administration of metronidazole (Flagyl®), tinidazole, or ornidazole. Of these drugs, only metronidazole and tinidazoe are approved for use in the United States. Metronidazole is administered either by a single 2g oral dose or by a 500 mg oral dose 2 times/day for 7 days. Cure rates for both regimens are essentially the same and are optimized when both sexual partners are treated simultaneously.[60,76] Tinidazole is given 2g orally in a single dose.[60] If treatment failure occurs with metronidazole 2g single dose, and reinfection is excluded, the patient can be treated with metronidazole 500 mg orally twice daily for 7 days. For patients failing this regimen, treatment with tinidazole or metronidazole at 2g orally for 5 days should be considered.[60] In a small percentage of treated patients, metronidazole produces side effects such as nausea, vomiting, diarrhea, darkening of the urine, generalized skin reactions, and an unpleasant or metallic taste.[1,77] Short-term side effects usually peak 72 to 96 hours after administration of the drug.[78] Adverse neurologic reactions have been reported with long-term therapy.

Vaginal trichomoniasis has been associated with adverse pregnancy outcomes, particularly premature rupture of membranes, preterm delivery, and low birth weight. However, metronidazole treatment has not been shown to reduce perinatal morbidity. Although some trials suggest the possibility of increased prematurity or low birth weight after metronidazole treatment, limitations of the studies prevent definitive conclusions regarding risks for treatment.[60] Metronidazole crosses the placenta during pregnancy. Taking metronidazole during the second and third trimesters of pregnancy is controversial because of the drug's carcinogenicity in laboratory animals.[79] Opinions vary as to the drug's safety for nursing mothers. Infected neonates should be treated only if they are symptomatic; dosages of 10 to 30 mg/kg body weight daily for 5 to 8 days have proven curative. Older children with *T. vaginalis* infection should be treated with 15 mg/kg body weight in 3 oral doses daily for 7 to 10 days.[78] There is no conclusive evidence that standard metronidazole regimens are carcinogenic in humans.[78,80,81]

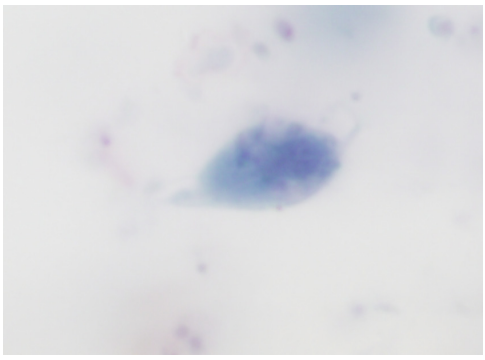

Figure 7.18
Fecal smear of intestinal *Trichomonas hominis.* Pap original magnification x1000.

Trichomonas hominis and *Trichomonas tenax*

Trophozoites of the intestinal commensal *T. hominis* are ovoid and 6 to 14 µm by 4 to 7 µm (Fig 7.18). *Trichomonas hominis* has 5 anterior free flagella and is distinguished from *T. vaginalis* by a sixth flagellum that extends beyond the undulating membrane and the cell. It is prevalent in tropical climates, is present in children more than adults, and is transmitted via contaminated food.[1] *Trichomonas tenax,* a commensal of the oral cavity, has 4 anterior flagella, is smaller than *T. hominis*, and is distributed worldwide. It is most commonly found in older adults and is transmitted by kissing.

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