Trichomoniasis
New Ideas on an Old Disease

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SUMMARY
Trichomoniasis is probably the most widespread sexually transmitted disease of man. The causative organism, *Trichomonas vaginalis*, can normally be found on microscopic examination of vaginal exudate, although serological diagnostic techniques have recently been described. The organism has now been recognized as a pathogen, and, although infection has been associated with cervical cancer, a causative link has not been established. Despite both humoral and cellular immune responses, protective immunity has not been demonstrated in man.

Treatment schedules with metronidazole and other 5-nitro-imidazoles have been revised, many authors recommending short courses with large doses. The suspected carcinogenic properties of metronidazole have not been proved, although caution is still advised in the treatment of pregnant patients.

Recognition of trichomoniasis as a sexually transmitted disease means that treatment of sexual partners is essential to prevent reinfection.


Trichomoniasis has recently been described as the most common of the primarily sexually transmitted urogenital infections of man, estimated to affect more than 180 million people throughout the world. 

Infection rates of about 50% have been recorded in women attending gynaecology outpatient clinics in South Africa, while serological evidence has indicated that up to 31% of both men and women in Zimbabwe harbour the parasite.

It is fortunate that with such a high prevalence trichomonal infection appears to have few severe or long-term effects, the main symptom being discomfort or distress from the associated leucorrhoea, and that treatment of the infection is both simple and safe.

For such a frequently occurring condition, however, there are many widespread misconceptions regarding its aetiology, origin and treatment. In many textbooks on obstetrics and gynaecology it is given only minor reference, its venereal transmission being described merely as 'possible'.

Treatment with vinegar douches or vaginal inserts of arsenical compounds was recommended as recently as 1975, yet 4 years earlier reference had been made to 'All these things women suffered for months and sometimes years on end, only to relapse when the treatment was discontinued'.

This review is intended to counter such misconceptions and bring together up-to-date information on trichomoniasis and its treatment.

The Parasite

*Trichomonas vaginalis* was first recognized by Alfred Donné in 1836 in 'purulent fluids and secretions of genital organs from men and women'. It is now recognized as a flagellated protozoan related to but distinct from other trichomonads of man and other vertebrates. It varies considerably in shape and size, although on culture it tends to become either rounded or ovoid (10 - 20 × 7 - 10 μm). According to one report small trichomonads are associated with symptomatic infection more than large trichomonads.

Perhaps the most characteristic features of the cell are the jerky movements of viable organisms (hence their apt description as a pus cell that moves) and the oval nucleus evident in stained specimens.

Electron microscopic observations have shown the absence of mitochondria and their replacement with hydrogenosomes, and confirmed the presence of an ectoplasm layer which can form pseudopodia. Despite some claims to the contrary, a true cyst stage has not been demonstrated, although the organism may round off and reduce its flagellae. Such rounded forms can survive outside the body and their existence has led to many suggestions that venereal transmission is not the normal mode of spread.

Transmission

The spread of the parasite by sexual intercourse has been accepted as correct at all major symposia dealing with trichomoniasis. Non-venereal transmission, for example during birth, may account for the small numbers of infections recorded in infants. Many studies have shown that *T. vaginalis* organisms can survive outside the body for some time, and may remain active in urine for several days. Although culture media enhance the survival of trichomonads, organisms remain viable for several hours in tap water at low (5 - 7°C) and high (35 - 45°C) temperatures. Nevertheless, Honigberg, in a major review on *T. vaginalis*, was of the opinion that 'there is to date no undisputed evidence that bath or swimming pool water can serve as a source of infection'.

Transmission via urine on toilet seats has also been suggested, one author claiming that 80% of trichomonal infections were acquired in this way. Repeated experi-
ments by many workers, however, have failed to confirm prolonged viability of trichomonads on toilet seats.\textsuperscript{22,23} Epidemiological investigations have consistently shown high rates of infection in sexually active age groups and in populations with casual sexual relations, but virtually no infections in groups among whom sexual contact was rare, or absent.\textsuperscript{24}

**Pathogenicity**

For many years after its discovery *T. vaginalis* was regarded as a non-pathogenic commensal of the urogenital tract, or at most an opportunistic organism which would flourish when other microbes caused disease. However, there is now a vast array of literature detailing the evidence for the pathogenicity of *T. vaginalis*.\textsuperscript{25-27}

In women these protozoa are most commonly found in the vagina, but occasionally also in secretions of Skene's and Bartholin's glands.\textsuperscript{28} Reports of frequent infections of the lower urinary tract have recently been disputed;\textsuperscript{29} such infections are thought to occur in less than 12% of women harbouring vaginal trichomonads. Probably most vaginal infections are asymptomatic, but in acute cases the symptom most frequently encountered is the production of a purulent, frothy, greenish-yellow discharge sometimes causing extreme discomfort and pruritus. Enlargement of the inguinal lymph nodes and reddening of the vagina with small punctate haemorrhagic spots (the so-called 'strawberry' vagina) may be noted in many cases. The infection is also often associated with dyspareunia. Symptoms tend to vary qualitatively and quantitatively during the menstrual cycle, usually becoming worse during menstruation and pregnancy.

Histological changes in vaginal tissue in cases of trichomonal infection are not specific. Features which have been noted include increased vascularity of the squamous epithelium, small haemorrhagic foci, and inflammatory reactions such as infiltration of leucocytes, particularly polymorphonuclear cells, and coating of the epithelial surface with purulent exudate.\textsuperscript{30} *T. vaginalis* organisms are found in contact with necrotic cells only, in shallow depressions in the epithelial surface, according to electron microscopic observations. Whether contact with epithelial cells is necessary for their destruction by *T. vaginalis* is uncertain, although cell culture studies have indicated the release of cytotoxic factors by at least some strains of the parasite.\textsuperscript{31} In about one-quarter of infections abnormal cytological appearances of vaginal or cervical smears are found, evidence of nonspecific inflammation being typical.\textsuperscript{32,33}

There is no definite proof that *T. vaginalis* can cause cervical cancer. Many reports claim that the incidence of infection in patients with cervical cancer is high,\textsuperscript{34} while others deny any such association.\textsuperscript{35} Any association may be opportunistic, trichomonads finding carcinoma *in situ* a suitable place for invasion, or it may indicate that superficial damage by trichomonads renders the epithelium more susceptible to carcinogens. The possibility that *T. vaginalis* may itself release carcinogens does not appear to have been widely investigated.

An apparent increase in the incidence of symptomatic trichomoniases during pregnancy has already been men-

Some authors\textsuperscript{36} have suggested that inflammation of the vagina by *T. vaginalis* may have a deleterious effect on a fetus. There is, however, evidence that cervical mucus prevents passage of trichomonads beyond the vagina, and studies in our laboratory have shown no association between trichomonal infection and abnormal or complicated births (P. R. Mason — unpublished data).

In men, trichomonal infection is in most cases completely asymptomatic. Organisms may be found in the urethra or prostate gland, and less commonly in the epididymis. Infections are associated with urethritis and prostatitis, and there is some evidence that prolonged infection may cause sterility.\textsuperscript{37}

**Immunology**

Normal serum from a variety of mammals contains agglutinins and complement-dependent lysins against *T. vaginalis*. Whether or not these antibodies can protect against infection is a matter of debate, many workers being of the opinion that any protection would be afforded by local nonspecific or specific (IgA) factors. Anti-trichomonal IgA antibodies have been demonstrated by radio-immunoassay in the cervical mucus of 76% of infected and 42% of apparently uninfected women,\textsuperscript{38} and increased numbers of plasma cells, particularly those secreting IgM, have been demonstrated in the endocervix of patients with *T. vaginalis* infection.\textsuperscript{39} There is an apparent increase in the serum IgE concentration of patients with trichomoniases and other sexually transmitted diseases,\textsuperscript{40} although the significance of this finding is unknown. Circulating antibodies to *T. vaginalis* in infected patients have been demonstrated by complement fixation,\textsuperscript{41} agglutination,\textsuperscript{42} haemagglutination\textsuperscript{43} and indirect fluorescent antibody\textsuperscript{44} tests. It is notable that at least three and possibly four antibody classes are involved. IgA is found in cervical mucus.\textsuperscript{45} IgM-secreting plasma cells are prominent in endocervical tissues,\textsuperscript{46} IgG is more important in serum,\textsuperscript{47} while IgE levels may also be raised.\textsuperscript{48} There is no evidence, however, that any of these antibodies are protective.

It has been known for many years that partial protection against laboratory-induced infection in mice can be afforded by prior injection with living, heat-killed or formalinized flagellates. The protection appears to be cell-mediated and associated with delayed hypersensitivity reactions.\textsuperscript{49} Similar delayed-type reactions occur in infected women.\textsuperscript{50} Experiments in our laboratory have shown that polymorphonuclear cells are attracted *in vitro* to *T. vaginalis*, apparently by a high molecular weight heat-labile compound secreted by live organisms.\textsuperscript{51} Current investigations indicate that polymorphonuclear cells may kill *T. vaginalis* *in vitro* in the presence of homologous serum (P. R. Mason — unpublished data); therefore the apparent inability of the cells to affect *in vivo* protection deserves investigation. Macrophages in cell cultures are known to phagocytose trichomonads, although pathogenic strains of the parasite survive within these cells.\textsuperscript{52}

**Diagnosis**

Despite the demonstration of circulating antitrichomonal antibodies in patients harbouring the parasite, the
diagnosis of infection, in most laboratories, is still dependent on microscopic demonstration of organisms in fresh saline smears, culture or stained preparations.38 Of many culture media described we have found Diamond’s medium the best, with cultures kept under hydrogen or carbon dioxide. For the staining of specimens received in the laboratory, Giemsa is recommended if the specimen is fresh. If delay in processing the specimen is envisaged the use of fixative-coated slides and acridine orange stain has been shown to be more effective. Although Papanicolaou staining may demonstrate parasites, it gives a large number of apparently false-positive results.

**Treatment**

Although recognized as a disease in 1916, it was only with the introduction of the 5-nitro-imidazoles nearly half a century later that treatment of trichomoniasis veered away from “perpetual local treatment, douches, paintings, insufflations, and insertions of pessaries” to effective specific chemotherapy.

Metronidazole, first introduced in France, is now probably the drug of choice in the treatment of trichomoniasis in Europe, although perhaps not, owing to the US Food and Drugs Administration restrictions, in the USA. It rapidly eliminates parasites from the urogenital tract in both men and women, and has few side-effects, the most common but least noted being its ‘Antabuse’-like effect when taken with alcohol. Doubts about the use of metronidazole stem from its transmission to the fetal circulation, its known carcinogenicity in mice, and its mutagenicity with bacteria. Reports that microsomal fractions from mammalian liver enhanced the mutagenicity of metronidazole have increased doubts on the advisability of using 5-nitro-imidazoles for what is far from a life-threatening infection. It should, however, be noted that there is no evidence that metronidazole is mutagenic in a fetus or in adults at recommended dose levels, and that mutagenicity in bacteria is thought to result from metabolites of metronidazole, not from the drug itself. Recent tests have indicated that these metabolites may in fact be produced by intestinal microorganisms rather than by the patient, and that co-treatment with antimicrobial agents inhibits their production.

There is now much evidence from trials in many countries showing that single-dose treatment with 1–2 g metronidazole has considerable (>90%) success with few side-effects. In addition, newer 5-nitro-imidazoles such as tinidazole, nimorazole and ornidazole appear to be as effective as metronidazole, if not more so, and have fewer side-effects.

In view of the fact that *T. vaginalis* infection does not harm fetal development, while 5-nitro-imidazoles may, the decision whether or not to treat infections in women during early pregnancy with systemic trichomonacides should depend on the severity of symptoms.

**Conclusions**

Trichomoniasis is a widespread disease; although not significant in terms of morbidity and mortality, it is a frequently encountered, distressing condition which can be quickly, effectively and safely cured. Control of the spread of the disease will depend on the reliability of diagnosis, particularly in men, in whom most cases are asymptomatic, and on the recognition that the transmission is sexual in the vast majority of cases.

The recent introduction of serological tests for trichomonal infection may go a long way towards providing a more reliable diagnosis, and these tests need to be fully evaluated. The use of single-dose regimens with 5-nitro-imidazoles means that infections can be rapidly and reliably treated. But perhaps most important of all is the recognition by all associated with the medical profession that trichomoniasis is a sexually transmitted disease, in which treatment of both sexual partners is necessary if control is to be effective.

**REFERENCES**

48. English summary available from Dr P. R. Mason, Dept of Medical Microbiology, University of Zimbabwe, PO Box MP 167, Mount Pleasant, Salisbury, Zimbabwe.

References 25–27 are abstracted in English in *Biological Abstracts*, vol. 49, 1968, Nos 66647, 66657 and 66644 respectively.