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Current Comments

Is Research on Trichomoniasis Commensurate with the Prevalence of This STD?

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Last year I wrote a two-part essay on herpes simplex virus infections.[1,2] In it, I noted that although herpes has been known for over 2,000 years, it has only recently attracted the attention of medical researchers. But herpes, specifically HSV2, is just one of several sexually transmitted diseases (STDs) whose incidence has recently reached dramatic levels. This "new generation" of STDs, as they are popularly labeled, includes not only genital herpes, but also nongonococcal urethritis (an inflammation of the urethra not due to gonorrhea), pelvic inflammatory disease, candidiasis (a vaginal yeast infection), and trichomoniasis.[3,4] Although they have probably existed since antiquity, they are "new" in the sense that modern laboratory techniques to discover their prevalence, method of transmission, and health consequences have only recently been developed.[3]

By far the most widespread of the new STDs is trichomoniasis. The incidence and virulence of trichomoniasis in men is currently a matter of dispute in the scientific community. But this heretofore little-known disease, still often unreported by public health agencies,[5] is estimated to occur in over 50 percent of women with abnormal vaginal discharges,[6] or about 20 percent of the female population of the US.[7] In fact, the Centers for Disease Control estimates that there are three million new cases of trichomoniasis each year, thereby surpassing the incidence of syphilis, gonorrhea, and genital herpes combined.[4] This essay examines the etiology and epidemiology of trichomoniasis, and the controversy surrounding its diagnosis and treatment.

Trichomoniasis, a chronic disease of the urogenital tract, affects both men and women.[4] It is caused by a protozoan of the genus *Trichomonas*, a common parasite in the digestive systems of many animals. Humans may host three species of trichomonad: *Pentatrichomonas hominis*, in the intestine; *Trichomonas tenax*, in the mouth; and *Trichomonas vaginalis*, in the vagina or the male urethra.[6,8] *T. vaginalis* is the only species known to cause disease, possibly due to a toxin it produces which causes an inflammatory response.[9]

The symptomatology of trichomoniasis is somewhat difficult to characterize. Clinical manifestations of the disease in the female urogenital system differ from those presented by the male. But symptoms vary even among patients of the same sex, since different strains of *T. vaginalis* seem to have different pathogenic capabilities. Symptoms may even worsen and improve repeatedly in the same patient. Consequently, while trichomoniasis in women is usually characterized by a copious, foamy, yellowish-green discharge that may have a foul odor, as well as mild to severe vaginal itching and burning, fully 25 percent of women harboring trichomonads have no symptoms at all.[8,10]

Among women who *do* display symptoms, clinical manifestations of the disease may not be limited to vaginal dis-

charge and itching. Additional symptoms may include the following: vulvar irritation and chafing of the upper thighs and rectal area; dull lower abdominal pain; difficult or painful urination and coitus; small rash-like "strawberry" spots on the cervix and vaginal lining; and swelling of the lymph glands in and around the groin.[10] Early studies associated trichomoniasis with cervical cancer,[11] but later studies have failed to confirm such a link.[12] Yet the prevalence of trichomoniasis *is* higher in women with cervical cancer than in healthy women.[13] This may simply indicate that trichomonads find cancerous tissue a suitable invasion point.[14] But there is also the possibility that the superficial cell damage *T. vaginalis* causes leaves the urogenital tract more susceptible to carcinogens. The possibility that the protozoans *themselves* may release carcinogens does not seem to have attracted much attention.[14]

While trichomoniasis in men is most often asymptomatic, it may sometimes cause a slight urethral discharge, which may or may not be accompanied by irritation. The clinical significance of *T. vaginalis* in male urologic conditions is somewhat controversial, however. Most American investigators feel that men serve primarily as carriers, spreading symptomatic trichomoniasis among women. They have found *T. vaginalis* to be infrequently the cause of nonspecific urethritis and prostatitis (inflammation of the prostate gland). Yet the methods used to examine specimens from the male urogenital system for evidence of *T. vaginalis* may fail to detect the protozoan as much as 50 percent of the time.[13]

Most European investigators, on the other hand, believe that *T. vaginalis* is a major cause of disease in men as well as women. It is thought to be responsible not only for a significant proportion of the cases of nongonococcal urethritis and prostatitis, but also some cases of balanoposthitis (inflammation of the head and foreskin of the penis), epididymitis (inflammation of the coiled structure along each testicle in which spermatozoa mature), and constriction of the urethra.[13]

The vast majority of trichomonal infections are transmitted by sexual intercourse.[8] The highest incidence of the disease is in females between the ages of 16 and 35, with the greatest rate of infection among those women who are at risk for other venereal diseases.[10] The prevalence of infection ranges from three to five percent of the asymptomatic women examined by private physicians, to 13 to 23 percent of the asymptomatic women examined in gynecological clinics. The incidence rate among prostitutes is 50 to 70 percent.[10] Male sexual partners of women afflicted with trichomoniasis have *T. vaginalis* infestations 80 percent of the time, while female partners of infected males almost always harbor the organism.[15] The difference has been attributed to the difficulty of detecting or culturing trichomonads from specimens of semen, urine, and urethral secretions, rather than to any actual absence of the protozoan in the male.

Since trichomoniasis is universally recognized as an STD, it is standard medical procedure to treat the sexual partners of patients with diagnosed infections as well as the patients themselves. However, it is generally acknowledged that in unusual circumstances, the disease may be contracted through nonvenereal means.[13] For example, infected women may transmit trichomoniasis to their infant children during childbirth.[8,13] Moreover, according to P.R. Mason, University of Zimbabwe, in a 1980 review, *T. vaginalis* has a demonstrated ability to survive outside the body for some time.[14] The protozoans can remain active in urine for several days and in tap water for several hours. (Incidentally, Mason's paper appears in the selected bibliography from the research front on the pharmacology

of metronidazole against anaerobic bacteria, culled from the 1981 *ISI/BIOMED*™, which is listed in Table 1.)

Consequently, an infection may be contracted from communal bathing water, or from contact with contaminated bath or toilet articles[8]—possibly even from contact with urine on toilet seats.[14] Indeed, a letter appearing in *Lancet* in 1953 suggested that contaminated toilet seats might be responsible for as much as 80 percent of trichomonal infections.[16] Later research has failed to confirm any prolonged viability of trichomonads on toilet seats, however,[17,18] and in a major review of *T. vaginalis* published in 1978, B.M. Honigberg noted that there had been, up to that time, no decisive evidence that bath or swimming pool water could serve as a source of trichomonal infection.[19]

A positive diagnosis of trichomoniasis in both men and women depends upon demonstrating the presence of even a single *T. vaginalis* organism in specimens obtained from the urogenital tract.[8,10] In women, the most commonly used diagnostic procedures include taking medical histories, making physical examinations, preparing microscope slides and cultures of vaginal specimens, and performing Papanicolaou (Pap) smears.[20] Unfortunately, none of these methods alone is totally reliable.

The failure of common diagnostic methods to reliably detect *T. vaginalis* can be traced to the elusive nature of the protozoan itself. Medical histories and physical examinations are of little use in diagnosing women who are asymptomatic. Even when symptoms are present, other STDs must be ruled out, and the presence of *T. vaginalis* clearly demonstrated, before a positive diagnosis may be made and treatment begun.[13] The method of mixing vaginal specimens with a saline solution and examining them under a microscope for trichomonads (the so-called "wet" mount procedure) depends for its success on the actual observation of the highly mobile protozoans with their lashing, whip-like flagella.[8] Yet *T. vaginalis* is extremely sluggish at room temperatures, and various studies indicate that wet mounts are only 60 to 70 percent accurate for women.[13] "Dry" mounting, in which specimens are prepared with various stains, fixatives, and cover slips for permanent mounting and viewing, is of even more questionable value. The preparation process necessarily kills any *T. vaginalis* organisms present in the sample, and dead trichomonads are almost indistinguishable from leukocytes.[8] Even culturing, the most sensitive diagnostic tool, will allow trichomoniasis to go undetected in ten percent or more of asymptomatic women.[8,10,20,21] And the effectiveness of the Pap smear is highly disputed.

A standard Pap smear is obtained by scraping cellular material from the cervix, staining it, and examining it for diseased tissue. The sensitivity of the Pap test in detecting trichomonads ranges from 60 to 80 percent.[10] A study by Michael R. Spence and colleagues, Johns Hopkins University, Baltimore, Maryland, comparing the diagnostic effectiveness of the Pap smear with culturing, wet mounts, and other procedures was published in *Sexually Transmitted Diseases* in 1980.[20] Despite the fact that trichomonads are rarely present in the cervix—except when the vagina is heavily infested[10]—and despite their own finding that the Pap smear is only 65 percent accurate in diagnosing trichomoniasis, the authors recommend the Pap test as the preferred diagnostic procedure.[20] While culturing proved to be the most sensitive technique in their study, Spence and colleagues consider it too expensive and impractical to justify its use in all clinical settings. And although they concede that wet mounts are inexpensive and easily performed, no patient in their study who had a positive wet mount failed to be identified by either culturing or the Pap smear. Moreover, the Pap smear indi-

cated *T. vaginalis* infections in four cases in which results from other diagnostic procedures were negative. The authors conclude that the Pap smear is simple and efficient, and since it is often a part of a woman's annual physical examination, it is both adequate and convenient for detecting trichomoniasis.

Yet, it is precisely the Pap smear's predilection for indicating trichomoniasis where other procedures have not, as well as its tendency to miss trichomonal infections that have not reached the cervix, that have led other investigators to recommend against relying on it. In a 1972 study of 1,199 women with vaginitis (inflammation of the vagina), use of the Pap test gave false results in 580 (48.4 percent) of the cases when it was relied upon as the criterion of evaluation.[22] A 1979 letter to the editors of the *Journal of the American Medical Association* (*JAMA*) notes that in a study of 666 women who were diagnosed as having trichomoniasis based on the results of their Pap smears, there was no evidence of *T. vaginalis* in either the wet mounts or the cultures in 246 (37 percent) of the cases.[23] The letter recommends that treatment for trichomoniasis be reserved for those whose infections are indicated by Pap smears and confirmed by other diagnostic procedures.[23]

The presence of *T. vaginalis* in the male urogenital system has historically proved even more difficult to demonstrate than in the female. Since most men infested with the protozoans are asymptomatic, a successful diagnosis depends on culturing them or microscopically observing them in specimens of urine, semen, and urethral secretions. However, as in the case of the asymptomatic female, these procedures rely heavily on there being a certain minimum number of viable organisms present in the samples. Unfortunately, whether because of spontaneous clearing of the infection, the mechanical removal of the trichomonads due to the repeated passage of urine, or simply because the urethra does not offer *T. vaginalis* as ideal an environment for reproduction as the vagina does, the organisms are often present in such low numbers that they go undetected.[24] Incidentally, it has recently been determined that the prostate gland is also an unlikely site for *T. vaginalis* to thrive in because of the concentration of zinc present in normal prostatic secretions.[25]

As of the mid-1950s there was no successful, specific treatment for trichomoniasis.[26] Nearly 150 different substances were then being used and recommended for trichomoniasis, although none were particularly effective. (Incidentally, one of these drugs was Argyrol,[26] a silver protein antiseptic which I mentioned in my recent two-part essay on its inventor, Albert C. Barnes.[27,28]) It was not until 1960 in Europe, and 1963 in the US, that an extremely effective treatment was introduced[29]—metronidazole, which is currently manufactured in the US by G.D. Searle & Company under the trade name, Flagyl.[30]

Metronidazole is a member of a group of related chemicals known as 5-nitroimidazoles, which work against anaerobic organisms—that is, organisms that thrive only in the absence of oxygen, such as *T. vaginalis*. The killing action of such drugs involves their chemical breakdown by the target organism. The resulting chemical compounds avidly bind to the target cell's DNA, causing breakage.[31] Besides metronidazole, the only member of the group available for human use in the US, the 5-nitroimidazoles also include such agents as dimetridazole and ronidazole, used to prevent infections in livestock,[32] and tinidazole and nimorazole, which are used in Europe as alternatives to metronidazole in the treatment of trichomoniasis.[15,33]

Metronidazole's efficiency in combating trichomoniasis is unquestioned and unsurpassed. Cure rates of 95 percent were recorded in 1977, for instance, from regimens of 200 mg given orally three times a day for seven days (or only a single 2 g dose administered orally).[34] Poor absorption of the drug in the intes-

tines or its excessive destruction by vaginal flora was blamed for the few cases in which infections persisted despite several courses of treatment,[34] although there have been some recent reports of drug resistant strains of *T. vaginalis*.[31,35-38] Metronidazole is also effective in treating diseases caused by other species of protozoans, such as amebiasis (infection by the amoeba *Entamoeba histolytica*), and giardiasis (infection by a protozoan of the genus *Giardia*, causing diarrhea). In addition, it greatly reduces the risk of infection by anaerobic organisms after such procedures as colonic surgery.[35]

Yet, while metronidazole's known side effects of nausea, headache, dry mouth, and metallic taste were relatively mild and self-limiting, disturbing reports of possible carcinogenic (cancer-causing), mutagenic (mutation-causing), and teratogenic (birth defect-causing) effects began to come to the attention of practitioners.[29] Just prior to its release in the US, for instance, the *Medical Letter on Drugs and Therapeutics* warned that metronidazole had "an unusual range of toxic effects for an agent to be used clinically in a non-life-threatening disease."[39] The effects at high dosage levels included neurological disorders, testicular damage, and disturbance in sperm formation in the male, and heightened susceptibility to candidiasis in the female. The report concludes that metronidazole should be administered with caution in women, and not at all in pregnant or lactating women, or in men (unless the female partner becomes reinfected).[39]

In a 1974 letter to the commissioner of the US Food and Drug Administration (FDA), the Health Research Group in Washington, DC—founded by Ralph Nader—urged that the FDA take "prompt action" to forbid use of metronidazole for the treatment of trichomoniasis, because the drug caused cancer, gene mutations, and birth defects.[40] A 1975 report in the *Medical Letter*,[40] commenting on the Health Research Group's charges, notes a 1972 study in which mice fed metronidazole throughout their entire lives suffered an increased incidence of lung cancer, as well as a variety of other malignant tumors not found in control animals.[41] Female rats also showed an increased incidence of various tumors, particularly mammary neoplasms.

In addition, the *Medical Letter* reports a study in which the mutation rate of certain strains of bacteria (*Salmonella typhimurium*) increased due to doses of metronidazole,[32] and another in which the *urine* of patients taking 750 mg of the drug per day caused genetic changes in the bacteria.[42] In fact, one of the products resulting from the body's assimilation of the drug that was found in the urine of these patients was discovered to be far more mutagenic than the drug itself.

The *Medical Letter* concludes that metronidazole is carcinogenic in rodents, mutagenic in bacteria, and potentially dangerous for humans. It also repeats its earlier warning that the drug should be avoided during pregnancy, and adds that it should not be used in the treatment of trichomoniasis if the infection can be rendered asymptomatic by any other means.[40]

The evidence declaring metronidazole unsafe has not gone unchallenged, however. According to a 1979 study, the increase in the number of cancers among women treated with metronidazole is not enough to be statistically significant.[43]

In response to the petition by the Health Research Group asking the FDA to withdraw its approval of metronidazole, Alexander M. Schmidt, then-commissioner of the FDA, stated that a substance which is carcinogenic (or is suspected of being carcinogenic) in laboratory test animals is not necessarily so in humans.[44] Moreover, it has been found that an increase in the incidence of tumors in mice can be explained by a number of environmental factors that have nothing to do with the suspected

carcinogen.[45] Many laboratory animals are never exercised, kept one to a cage, and allowed no sexual activity. These conditions seem to result in severe hormonal imbalances—which, in turn, are a likely cause of the observed high incidence of mammary, pituitary, adrenal, and other tumors. In addition, the proportion of carbohydrate to protein to fat in the animals' diets influences the number of tumors appearing in a given population. Even the amount of total calories consumed has a significant effect on tumorigenicity. Indeed, in many instances, the standard laboratory feed of test animals *itself* contained significant amounts of such potent carcinogens as aflatoxin, 3,4-benzopyrene, and dimethylnitrosamine.[45]

Concerning the drug's possible mutagenicity, chromosomal analysis of patients taking 200 mg of metronidazole three times a day for seven days showed no increase in the expected number of chromosomal aberrations.[46] Moreover, it has been found that the levels of mutagens associated with the body's metabolism of metronidazole can be reduced from seven- to over ninefold by the concurrent administration of erythromycin, an antibiotic, with an antioxidant—with *no* reduction in metronidazole's anti-trichomonal effectiveness.[47,48] And while there is still marked reluctance to prescribe the drug to pregnant and lactating women, since it diffuses freely across the placenta and is excreted in breast milk, there has been no recorded case of damage to either the fetus or the suckling child that can be blamed directly on metronidazole.[34]

With the evidence concerning the safety of metronidazole inconclusive, perhaps caution in its use is called for. There is no question that its effect on *T. vaginalis* is spectacularly lethal. The issue centers on whether or not the use of metronidazole, over which so many unresolved questions hover, can be justified against a disease whose main effect seems to be one of discomfort. Virtually no study indicates an increased incidence of cancer in humans previously exposed to the drug; yet most studies of this type have been conducted on relatively small numbers of patients, who were followed up for periods of time that may well prove to have been too short to observe metronidazole's suspected carcinogenic effects.[35] The evidence in human beings so far, therefore, is adequate to exclude only gross increases in cancer incidence due to exposure to metronidazole. On the other hand, trichomoniasis may not be as harmless as has historically been supposed, since it has been recently thought to be linked in some way with cancer of the cervix.[13] Patients may be faced with the paradox of risking cancer from taking metronidazole to avoid the risk of cancer from trichomoniasis.

In the US, several research projects on trichomoniasis are currently under way. The National Institutes of Health (NIH) is sponsoring a study at Rockefeller University, New York City. The study is attempting to describe the cytology of *T. vaginalis* and explain the effects metronidazole has on the protozoan's metabolism. At Johns Hopkins University School of Medicine, another NIH-sponsored study is investigating the mutagenic effects in patients being treated with metronidazole. The Mayo Clinic, Rochester, Minnesota, is studying the risk of developing cancer in women who have been exposed to metronidazole. At the NIH itself, a study on the structure, division, virulence factors, and endogenous viruses of *T. vaginalis* and other pathogenic protozoa is under way. Finally, a major collaborative research project on *T. vaginalis* has been initiated by the University of Massachusetts and Johns Hopkins University, under the sponsorship of the NIH. Although there are no research fronts in *ISI/BIOMED* on either *Trichomonas vaginalis* or on trichomoniasis, a selected bibliography from the two research fronts on metronidazole can be found in Tables 1 and 2.

Despite the projects mentioned above, however, the lack of a research front on both the disease and the dis-

Table 1: Selected bibliography of the research front on the pharmacology of metronidazole against anaerobic bacteria, contained in *ISI/BIOMED*™ 1981.

Dobiáš L. Mutagenicity testing of the antiparasitic drug entizol (Polfa) in the detection system of *Salmonella typhimurium* mutants. *Mutat. Res.* 77:117-26, 1980.

Ford W D A, MacKellar A & Richardson C I L. Pre- and postoperative rectal metronidazole for the prevention of wound infection in childhood appendicitis. *J. Pediat. Surg.* 15:160-3, 1980.

Goldman P. Metronidazole: proven benefits and potential risks. *Johns Hopkins Med. J.* 147:1-9, 1980.

Guilhou J J & Meynadier J. Letter to editor. (Rosacea, metronidazole and pregnancy.) *Brit. J. Dermatol.* 103:585, 1980.

Ingham H R, Hall C J, Sission P R, Tharagonnet D & Selkon J B. The activity of metronidazole against facultatively anaerobic bacteria. *J. Antimicrob. Chemother.* 6:343-7, 1980.

Klein J R. Update: adolescent gynecology. *Pediat. Clin. N. Amer.* 27(1):141-52, 1980.

Mahood J S & Willson R L. Failure to induce sister chromatid exchanges (SCE) with metronidazole. *Toxicol. Lett.* 8:359-61, 1981.

Mason P R. Trichomoniasis: new ideas on an old disease. *S. Afr. Med. J.* 58:857-9, 1980.

Meyer E A & Radulescu S. Giardia and giardiasis. *Advan. Parasitol.* 17:1-47, 1979.

Perez-Reyes E, Kalyanaraman B & Mason R P. The reductive metabolism of metronidazole and ronidazole by aerobic liver microsomes. *Mol. Pharmacol.* 17:239-44, 1980.

Salamanca-Gómez F, Castañeda G, Farfán J, Santillán M C, Muñoz O & Armendares S. Chromosome study on bone marrow cells of patients treated with metronidazole. *Arch. Invest. Med.* 11(Suppl. 1):325-8, 1980.

Schwartz L E, Geard C R & Miller R C. An investigation in vitro of the chromosomal effects of misonidazole. *Int. J. Radiat. Oncol. Biol. Phys.* 6:915-21, 1980.

Seligman S A & Willis A T. Infection with non-sporing anaerobes in obstetrics and gynaecology. *Brit. J. Obstet. Gynaecol.* 87:846-55, 1980.

Voogd C E. On the mutagenicity of nitroimidazoles. *Mutat. Res.* 86:243-77, 1981.

Table 2: Selected bibliography of the research front on the mutagenic action of metronidazole, contained in *ISI/BIOMED*™ 1981.

Fox A. Light-microscopy of membranoproliferative glomerulonephritis Type-II (MPGN with homologous extraglomerular lesions). *Amer. J. Clin. Pathol.* 76:644-51, 1981.

Kim Y & Michael A F. Idiopathic membranoproliferative glomerulonephritis. *Annu. Rev. Med.* 31:273-88, 1980.

Lévy M, Sich M & Habib R. Complement and nephritic activity in membranoproliferative glomerulonephritis. *Arch. Fr. Pediat.* 36(Suppl.):64-74, 1979.

Mazzucco G, di Belgiojoso G B, Confalonieri R, Coppo R & Monga G. Glomerulonephritis with dense deposits: a variant of membranoproliferative glomerulonephritis or a separate morphological entity? *Virchows Arch. A Path. Anat. His.* 387:17-29, 1980.

McLean R H, Siegel N J & Kashgarian M. Activation of the classic complement pathway in patients with the C3 nephritic factor. *Nephron* 25:57-64, 1980.

Mezzano S, Olavarria F & Caorsi I. Membranoproliferative glomerulonephritis. *Rev. Med. Chile* 108:10-9, 1980.

Nyberg M, Pettersson E, Tallqvist G & Pasternack A. Survival in idiopathic glomerulonephritis. *Acta Pathol. Microbiol. Scand. A* 88:319-25, 1980.

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ease-causing organism is significant, indicating a lack of basic research in these areas. It is true that trichomoniasis is not a life-threatening disease. Perhaps justifiably, it attracts only a small fraction of the kind of research funds and attention that are routinely devoted to such major causes of death as cancer and heart disease. But it is also true that trichomoniasis is a significant cause of human discomfort and misery. The disease's most disagreeable symptoms strike only women, leading one to wonder whether a possible sexist bias on the part of the scientific and medical establishments could account for the lack of interest. If trichomoniasis were a disease that primarily struck men, would there be significantly more money and research invested in it?

One clinician who thinks so is Spence. He notes, "The literature is

replete with references to [trichomoniasis] as a 'minor' venereal disease. It doesn't cause death, it doesn't cause sterility, therefore it's not important."[37] Moreover, Spence notes that federal funds channeled to Johns Hopkins last year for the study of nongonococcal urethritis, an STD affecting only men, amounted to significantly more than the sum received for research on trichomoniasis.

But C.F.T. Mattern, NIH, although admitting that some clinicians may be sexist, doubts that institutional sexism is rampant in attitudes toward trichomoniasis. He points out that, contrary to what one would expect from a supposedly sexist medical establishment, very little attention is being devoted to benign prostatic hypertrophy, a condition afflicting only men. Moreover, he says, physicians treat *any* STD in women seriously, since such diseases carry with them a variety of serious—and often multiple—risks to patients, partners, and the unborn child.[36]

Both workers agreed, however, that much work remains to be done on trichomoniasis. Spence would like to see more work done on the pathogenesis of the infection,[37] and Mattern thinks an experimental model for studying that pathogenesis would be of great help.[36] He also suggests that the mechanism by which various strains of *T. vaginalis* develop resistance to metronidazole needs to be investigated. But whatever the specific area of research, it is almost certain that the field could benefit from a more sensitive and compassionate attitude toward the discomfort and suffering of others.

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