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- (71) Applicant and (72) Inventor: **LAMBL, Barbara, B.** [US/US]; 26 F Sea Breeze Lane, Nahant, MA 01908 (US).
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**WO 01/97710 A1**

(54) Title: NOVEL ORGANISM ASSOCIATED WITH NONGONOCOCCAL URETHRITIS

(57) Abstract: A biologically pure culture of single-celled organism Spiky Rotating Cells (SPR).

5

## NOVEL ORGANISM ASSOCIATED WITH NONGONOCOCCAL URETHRITIS

### Background of the Invention

The most common sexually transmitted disease in men is nongonococcal urethritis (NGU). On average, 5 million new cases are reported annually in the United States alone. NGU is a syndromic diagnosis based on the finding of acute inflammation in the urethra. It has been linked to more than 10 different pathogenic species, including trichomonas, candida, herpes, and atypical bacteria. The most important pathogen, found in approximately half of cases, is *Chlamydia trachomatis*. In half of cases, however, no pathogen is identified.

Several lines of investigation have established *Chlamydia trachomatis* as the principal cause of NGU. Chlamydia has been isolated as the sole pathogen in 35-50% of cases. It is infrequently found in asymptomatic men. When present, it is usually associated with clear-cut pathology and inflammatory urethral smears. (However, it may also be harbored with minimal symptoms or signs in carriers.) Men with a history of disease have serologic evidence of specific immune response to the infection; and men with acute disease have increasing IgM serologic titers or seroconversion. Transmission of Chlamydia has been demonstrated in over 80% of female contacts of men with the infection, but only 11% of partners of negative men. Treatment with antichlamydial drugs eradicates the organism and cures the disease.

While the role of Chlamydia is well-established, the role of other pathogens is more controversial. The mycoplasmas have long been the subject of much investigation and debate. *Ureaplasma urealyticum* has been isolated in more than half of cases in some series (Tayler-Robinson, Hooton, Root,

Munday, Stefanik). However, it is just as frequently found in completely asymptomatic men. And it is isolated more often in men who are sexually active than those who are not. There are three lines of evidence that have persuaded some, though by no means all, venerologists that *Ureaplasma* must be playing a role in at least some cases of NGU: 1) evidence from partial treatment trials in which disease recurs after therapy ceases (Shepard); 2) from differential treatment trials in which disease recurs after therapy ceases (Shepard); 3) from differential treatment trials where only one of two susceptible organisms is eradicated and disease persists (Prentice); and 4) from human inoculation and reinoculation trials (Tayler-Robinson). *Mycoplasma hominis*, although pathogenic in PID and cervicitis, has not been confirmed to cause urethritis. On the other hand, another *Mycoplasma* strain, *Mycoplasma genitalium*, has been associated with 15-40% of Chlamydia-negative NGU, and only 19% of controls.

Protozoal infection as a cause of NGU has been considered rare in the developed world. Infection rates are higher in the developing world, with series from Eastern Europe, Africa, Asia and South America reporting in the range of 10-15%. However, a more recent series from Seattle casts doubt on that presumption. Using rigorous methodology including selective cultures, Krieger was able to show *Trichomonas vaginalis* in 17% of men with NGU(Krieger). Other pathogens such as the anaerobic bacteria are associated with disease in women but not in men. Finally, the viruses, Herpes simplex, Human papillomavirus, and Adenovirus, have been associated, albeit rarely, with NGU. In sum, the known pathogens account for perhaps 40-75% of all cases of NGU.

No diagnosis is determined in 21-60% of cases of NGU (Janier, Jensen, Hooton, Root, Stefanik). While for many years *Chlamydia trachomatis* infection has been reported in the range of 35-50%, more recently Stamm, and others have pointed to a declining role for this pathogen (Stamm). In a large  
5 multicenter 1990 study, only 15% of cases were associated with Chlamydia, and fully 57% were unexplained (Stamm). Interestingly, while the prevalence of Chlamydia is declining, NGU is not. Therefore, the proportion of unexplained cases of NGU may actually be increasing (Zenilman, Schmid).

The reasons put forth for the culture-negative case fall into four  
10 broad categories: misdiagnosis, mechanical urethral processes, immunological processes, and unrecognized pathogens. The diagnosis of urethritis can be difficult to establish because of both underdiagnosis and overdiagnosis. The sensitivity of the urethral smear is variable. It may be affected by several factors including: the duration of symptoms, the adequacy of sampling, and the  
15 pathogen involved (Arya, Bowie, Landis, Shahmanesh, Swartz, Terry). Urethritis may be overdiagnosed in some men because of the persistence of symptoms after treatment or because of hypervigilance, even in the absence of inflammation (Martin). Some chronic cases of urethritis that are unresponsive to antibiotics may be associated with mechanical urethral problems, although  
20 this is rare(Krieger). The not infrequent observation that some men continue to have evidence of inflammation after successful treatment of urethritis has led some investigators to suggest that chronic urethritis, and particularly posttreatment urethritis, may be a consequence of local immunologic processes (Krieger, Martin & Bowie, Hooton, Taylor-Robinson). This is an area of  
25 ongoing investigation. Many of these same authorities allude to the possible existence of as yet unrecognized pathogens in NGU (Stamm, Schmid, Oriel, Taylor-Robinson).

In order to prove causality in NGU, Taylor-Robinson has set out several criteria that should be met. First the putative pathogen must be isolated more frequently or be found in greater numbers in men with NGU than in asymptomatic men. Second, when an appropriate antimicrobial agent is administered, and the infection is cleared, the symptoms of the disease must also resolve. Third, there must be objective evidence of an immune response to the offending pathogen. And lastly, the putative pathogen must be transmissible and cause comparable disease in the recipient. Of all the pathogens mentioned above, only *Chlamydia trachomatis*, *Mycoplasma genitalium*, and *Trichomonas vaginalis* fulfill all the criteria for pathogenicity in NGU. Neither a convincing antibody response nor overwhelming association with disease have been demonstrated in the case of *Ureaplasma urealyticum*. One other important caveat has been put forth by Taylor-Robinson, that a putative pathogen must be shown to be associated with disease in the absence of other pathogens. Numerous prior studies have been undermined by failure to control for other potential pathogens, in particular *Chlamydia*.

The treatment of NGU is made more difficult by the frequent absence of a definitive diagnosis. Many clinicians approach it as a syndrome and direct initial therapy at the most likely pathogens, *Chlamydia* and *Ureaplasma*. Studies have borne out the effectiveness of this approach in many cases. Doxycycline, long the treatment of choice, is effective against all strains of *Chlamydia* and most strains of *Ureaplasma*, although 10% of the latter are resistant. Martin demonstrated that a single dose of Azithromycin was comparable to Doxycycline in the treatment of uncomplicated chlamydial urethritis (Martin). More recently, Stamm and colleagues demonstrated that Azithromycin was overall as effective as Doxycycline, curing 78% of cases of

NGU (Stamm). Of some concern, however, was their observation that only 47% of Ureaplasma cases responded to Azithromycin. Nevertheless, the convenience of unit dosing under direct supervision has made Azithromycin the preferred treatment in many STD clinics. Treatment failures have rarely been reported. In one series of treatment failures, Erythromycin cured 52% of men (Hooton). In a smaller series, Flagyl was used in refractory cases with good clinical efficacy (Toth).

### Summary of the Invention

10 In the course of caring for patients at the STD Clinic of the Boston Medical Center, I have observed an association between an unusual organism and NGU. Here I present my findings.

Men who presented to the STD clinic with urethral discomfort or discharge were screened for NGU. Twenty-five men with NGU were matched to 25 asymptomatic controls from the same clinic. (Asymptomatic men routinely present to the clinic for routine HIV testing or STD screening.) Cases and controls were sexually active men who were matched for age (+/- 5 years) and sexual preference (heterosexual, homosexual, bisexual).

After informed consent was obtained, men were examined and urethral samples were obtained for microbiologic testing. Three urethral swabs were obtained, for Gram's stain, direct microscopy, culture for *Neisseria gonorrhea* on Thayer-Martin media in 5% CO<sub>2</sub> enriched atmosphere, and DNA amplification using the Ligase Chain Reaction methodology (LCX) for *Chlamydia trachomatis*. NGU was defined as laboratory evidence of urethral inflammation, evidenced by  $\geq 4$  PMNs/hpf on Gram's stain. Informed consent was obtained from all participants, and this study was conducted with the approval of the Institutional Review Board of the Boston Medical Center.

Of 28 men who presented to the clinic with urethral symptoms, 25 were found to have NGU. (Three men had gonorrhea and were excluded from the study.) All men had signs of inflammation on their urethral smear, with a mean polymorphonuclear cell (PMN) count of 15 (range 4-40).

5           Routine pathogens were identified in 10/25 men with NGU: 8 Chlamydia, 1 HSV, and 1 Candida. Fifteen men with NGU had no pathogen identified by standard laboratory methods.

          Thirteen/fifteen men with no conventional pathogen were noted to have a distinctive single-celled organism in their urethral secretions. The  
10       organisms were round and motile. They were 7 $\mu$ m-8 $\mu$ m in size and had a highly refractile cell membrane, with characteristic spiky membrane projections. They moved in a peculiar rotatory fashion, translocating across the microscopic field. These organisms were present in large concentrations in urethral secretions, mean n=14/hpf (range 1-100). To my knowledge, these  
15       organisms have not previously been described, and for convenience, I have called them SPR, spiky rotating cells.

          Nine of the men with known pathogens also had coinfection with this organism. Two men with NGU had no pathogens detected.

          Among 25 asymptomatic controls, there were four genital infections  
20       diagnosed: two with Candida balanitis, one pediculosis pubis, and one secondary syphilis. None of the controls were found to have urethral inflammation. Two of the controls were found to have SPR in their urethral secretions. However, the organisms were rare in number, only 1-2 present on the entire slide.

25           In total, 22-25 men with NGU had SPR cells. Only 2 of 25 asymptomatic controls had SPR noted on examination. Men who were found to have SPR cells in urethral secretions were eighty-four times as likely to be

diagnosed with NGU as men who did not have SPR. ( $p < 0.001$ , Binomial Distribution Probability).

SPR is not present in normal healthy men. It is observed in men with nongonococcal urethritis, in whom it occurs in great numbers. I have also  
5 discovered that SPR can cause disease in other organ systems, and in fact can cause systemic disease. Infection with SPR can cause colitis, pelvic inflammatory disease (PID), adenitis (swelling of the lymph nodes), and skin eruptions. All of these infections can be treated systemically as described below.

10 Accordingly, the invention features a biologically pure culture of the single-celled organism Spiky Rotating Cells (SPR). Preferably, the culture has the biological characteristics of the SPR sample, ATCC Deposit No. \_\_\_\_\_, received at the ATCC on June 18, 2000. The SPR organisms of the culture preferably exhibits the following biological  
15 characteristics (a) spherical shape, (b) motile in an imperfect rotating manner, (c) multiple spiky membrane projections, (d) highly refractile cell membrane when viewed, e.g., by Darkfield microscopy. Preferably, further characteristics are: (e) approximately 7-8  $\mu\text{m}$  in diameter, (f) provisionally classified as a protozoan, (g) periodic colonial morphology, and (h) preferential proliferation  
20 in Diamond's Media.

The identification of the new SPR organism permits the diagnosis of an SPR infection in a human patient by the steps of: (a) obtaining a sample, e.g., a pus sample from the reproductive or other organ system, and (b) testing the sample for the presence of SPR. Where the patient is a male, the collection  
25 step preferably involves collecting a secretion from the urethra of the patient. This can be carried out using a novel collection device that includes a handle portion which is attached to means for collecting secretions from the



reproductive system of the male patient, and which also includes a pH sensor positioned adjacent to the collecting means so that it can come into contact with the sample and provide an indication of the pH of the sample, which is useful in aiding in the diagnosis of a SPR infection. Preferably, the collecting means of the instrument is adapted so that it can be inserted into the distal end of the urethra of the male patient. It may also be used for diagnosis in females, by sampling cervico vaginal secretions; and in skin or other organ infections by sampling pus.

My discovery of the novel SPR organism also provides for the treatment of SPR infections in male and female patients. The method involves first diagnosing the SPR infection, and then, upon obtaining a positive diagnosis, administering to the patient an SPR-inhibiting amount of an anti-SPR agent selected from the group consisting of itraconazole, ofloxacin, metronidazole.

By "biologically pure culture" is meant a culture of SPR in which the predominant pathogen, numerically, is SPR, present in the culture in greater proportion than occurs in naturally occurring human urethral or other secretions.

#### Brief Description of the Drawing

Fig. 1 is a plan view of a secretion sampling instrument of the invention. Fig. 2 is a plan view of the sampling instrument in operation.

Fig. 3 is a Dark field micrograph of individual SPR organisms.

Fig. 4 is a Dark field micrograph of colonial SPR organisms.

## Detailed Description

### SAMPLING

SPR occurs in a naturally contaminated environment, the human genital tract, skin and other organs. Biologically pure cultures of SPR are  
5 obtained in a process that begins with sampling, carried out as follows.

First, the region to be sampled, e.g., the urethra, the surface of the skin, or the cervix, is sterilized, e.g., with isopropyl alcohol, and allowed to air dry. Next, a sample is collected from the region of interest. Referring to Fig. 1, if the sample is to be obtained from the male urethra a sampling instrument is  
10 employed. The instrument consists of a handle portion 10 with gripping region 11; the handle extends to the collecting means 12, which in this embodiment is a streaking loop commonly used to plate microorganisms. Adjacent to loop 12 is a region 14 that has been rendered a pH sensor, e.g., by wrapping the region with pH indicator tape. Referring to Fig. 2, the sampling instrument of Fig. 1 is  
15 inserted approximately 1-2cm into the distal end of the male urethra and then withdrawn, bringing with it a secretion sample from the urethra, in such a way that some of the sample contacts the pH sensor 14 of the instrument.

After the sample has contacted the pH sensor, the pH of the secretion is determined as a step in the diagnosis of SPR. SPR infection, particularly  
20 where it is heavy infection, raises the pH of the secretions, which normally is in the range of 4.5-5. A pH greater than about 6.0 is indicative of an SPR infection, and a heavy infection can cause the pH reading to be as high as 7.5.

These foregoing steps are repeated a sufficient number of times to result in the collection of 0.5-1 microliter of secretion.

## IDENTIFICATION

In the next step, identification of SPR, the collected secretion is diluted in 1-2 drops of normal saline. The diluted sample is then covered with a cover slip and examined immediately by microscopy. The organism is  
5 identified by observing the morphologic characteristics of SPR summarized above, and is best carried out by using a Darkfield microscope. Preferably, there are sufficient organisms so that they can be observed at various stages in the life cycle of the organism. As is discussed above, in its solitary living stage, each SPR is a motile, spherical organism, most probably a protozoan, with a  
10 diameter of 7  $\mu$ m-8  $\mu$ m. It has a highly refractile membrane with characteristic spikes, and moves in a peculiar rotary manner across the microscope field. The organism may also be observed under conventional light microscopy and appears as a pale yellowish green sphere.

The organisms also exhibit a characteristic colonial clustering  
15 morphology in which many organisms come together to form large colonies.

## CULTURE

The SPR organism can be selectively cultured in modified Diamond's Medium (LS Diamond, J. Parasit, (43):488-90 (1957)).

In order to prevent overgrowth of contaminating microorganisms, the  
20 Diamond's Medium is modified as follows. To 100 ml of medium are added 500 mg cycloheximide and 40 mg of chloramphenicol. The pH of the medium is adjusted to 6.8-7.0, and sterilized by autoclaving for ten minutes at 15 pounds of pressure.

The SPR organisms are inoculated, using the collecting instrument of  
25 Fig. 1, into the modified Diamond's Medium; 2-3  $\mu$ l sample are inoculated into 3 ml medium. The inoculated medium is stoppered loosely and incubated at

36°C in a 5% CO<sub>2</sub> enhanced atmosphere for 3-4 days. These conditions selectively bring about the proliferation of the SPR organism compared to other contaminating organisms.

5 The presence of SPR organisms is confirmed by gently decanting the top two-2.5 ml of fluid from the culture tube, and then aspirating the sediment from the tube using a sterile needle and syringe. A drop of sediment is then placed on a slide under a cover slip and examined for the characteristic morphologic traits of the SPR organism, as described above.

### PURIFICATION

10 The SPR organism is cultured in the medium described above for 96-120 hours, after which time the top 2-2.5 ml of fluid is gently decanted from the culture tube. Using a sterile needle and syringe, the sediment is aspirated and examined for SPR. The SPR is then inoculated into a fresh tube of selective, modified Diamond's Medium, and these steps are repeated as often as  
15 necessary to obtain a biologically pure culture. The purity of the culture is confirmed by inoculating the culture into a brain-heart infusion and thioglycollate broth, and then testing for the absence of contaminating microorganisms.

### TREATMENT

20 I have found that several commercially available drugs are effective in treating infection with SPR. One such drug is itraconazole, sold under the trade name Sporanox®, available from Jansen Pharmaceuticals. The patient ingests one 200 mg tablet per day for three-four weeks.

Another drug that can be used to treat SPR infection is metronidazole, sold under the trade name Flagyl®. The patient takes 500 mg twice per day for six weeks.

Yet another drug that is effective in treating SPR infection is  
5 ofloxacin, sold under the trade name Floxin®. The patient takes 400 mg twice per day for two weeks.

### DEPOSIT

A biologically pure culture, as defined herein, of SPR was deposited with the American Type Culture Collection, 10801 University Boulevard,  
10 Manassas, VA 20110-2209 on June 18, 2000, and given ATCC accession number \_\_\_\_\_.

This deposit was made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder ("Budapest  
15 Treaty"). This assures maintenance of viable cultures for 30 years from the date of the deposit. The organisms will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between myself and ATCC, which assures permanent and unrestricted availability of the cultures to the public upon issuance of the pertinent U.S. patent or upon laying open to the  
20 public of any U.S. or foreign patent application, whichever comes first, and assures availability of the cultures to one determined by the U.S. Commissioner of Patent and Trademarks to be entitled thereto according to 35 U.S.C. §122 and the Commissioner's rules pursuant thereto (including 37 C.F.R. §1.12 with particular reference to 886 OG 638).

25 In respect of those designations in which a European patent is sought, a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the

date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample. (Rule 28(4) EPC)

The assignee of the present application has agreed that if the cultures  
5 on deposit should die or be lost or destroyed when cultivated under suitable conditions, they will be promptly replaced on notification with a viable specimen of the same culture. Availability of the deposited strain is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent  
10 laws.

#### Other Embodiments

Other embodiments are within the following claims. For example, in diagnostic tests for SPR, rather than identifying the organism microscopically, it can be identified using other known methods. One such class of methods,  
15 immunological identification, employs antibodies specific for SPR, in any of the many conventional immunoassay formats, e.g., ELISA tests using, e.g., enzymes such as horseradish peroxidase. The SPR-specific antibody used in such an assay can be polyclonal or monoclonal, and can be produced using conventional methods, e.g., challenging a rabbit or mouse with the SPR  
20 organism and then obtaining the antibody using conventional techniques.

Other diagnostic tests for SPR can be nucleic acid based. One class of such tests employs DNA probes that specifically hybridize to unique regions of the genome or ribosomal RNA of the SPR organism. Alternatively, the diagnostic assay can employ RNA/DNA amplification, e.g., PCR/TMA or Q-  
25 beta replicase amplification, using primers unique to the SPR genome.

What is claimed is:

1. A biologically pure culture of the single-celled organism Spiky Rotating Cells (SPR).

2. The biologically pure culture of Spiky Rotating Cells of claim 1, having the biological characteristics of the single-celled Spiky Rotating Cells of  
5 A.T.C.C. Deposit No. \_\_\_\_\_.

3. The culture of claim 1, wherein said SPR exhibit the following biological characteristics:

- a. spherical shape,
- b. motile in an imperfect rotating manner,
- 10 c. multiple spiky membrane projections, and
- d. refractile cell membrane.

4. The culture of claim 3, wherein said SPR further exhibit the following biological characteristics:

- e. approximately 7-8  $\mu$ m in diameter,
- 15 f. classified as a protozoan,
- g. periodic colonial morphology, and
- h. proliferation in Diamond's Media.

5. A method of diagnosing an SPR infection in a human patient, said method comprising the steps of:

- 20 a. obtaining a sample from said patient, and
- b. testing said sample for the presence of SPR.

6. The method of claim 5, wherein said patient is a male, and wherein step a) comprises collecting a secretion from the urethra of said male patient.

7. The method of claim 6, wherein said secretion is collected with an instrument that includes a pH indicator positioned to contact said secretion.

8. The method of claim 7, wherein said instrument includes a loop sized and shaped for insertion into the distal end of the urethra for secretion collection.

9. The method of claim 8, wherein, following step a), said sample is mixed with saline to form a diluted sample, and wherein, following said mixing, said diluted sample is examined by microscopy.

10. The method of claim 5, wherein said patient is a female, and wherein step a) comprises collecting a cervico vaginal secretion from said female patient.

11. The method of claim 10, wherein said secretion is collected with an instrument that includes a pH indicator positioned to contact said secretion.

12. The method of claim 5, wherein said patient has a skin eruption or lymph node abscess, and wherein step a) comprises collecting a secretion from said eruption or abscess.



13. The method of claim 12, wherein said secretion is collected with an instrument that includes a pH indicator positioned to contact said secretion.

14. An instrument for collecting male urethral secretions, said instrument comprising:

- 5           a) a handle portion,
- b) attached to said handle portion, a means for collecting secretions from the reproductive system of a male patient, and
- c) a pH sensor positioned adjacent the collecting means to come into contact with said sample.

10           15. The instrument of claim 14, wherein said collecting means is adapted for insertion into the distal end of the urethra of a male patient.

16. An instrument for collecting cervico vaginal secretions, said instrument comprising:

- a) a handle portion,
- 15           b) attached to said handle portion, a means for collecting cervico vaginal secretions from a female patient, and
- c) a pH sensor positioned adjacent the collecting means to come into contact with said sample.

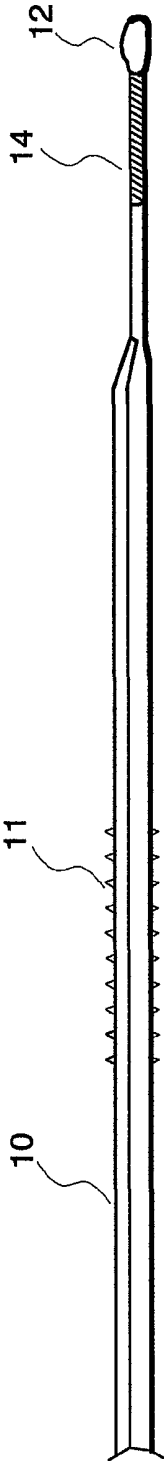
17. A method of treating an SPR infection in a patient, said method comprising:

a) diagnosing said SPR infection, and

5 b) upon obtaining a positive diagnosis in step a), administering to said patient an SPR-inhibiting amount of an anti-SPR agent selected from the group consisting of intraconazole, ofloxacin, and metronidazole.

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FIG. 1



2/4

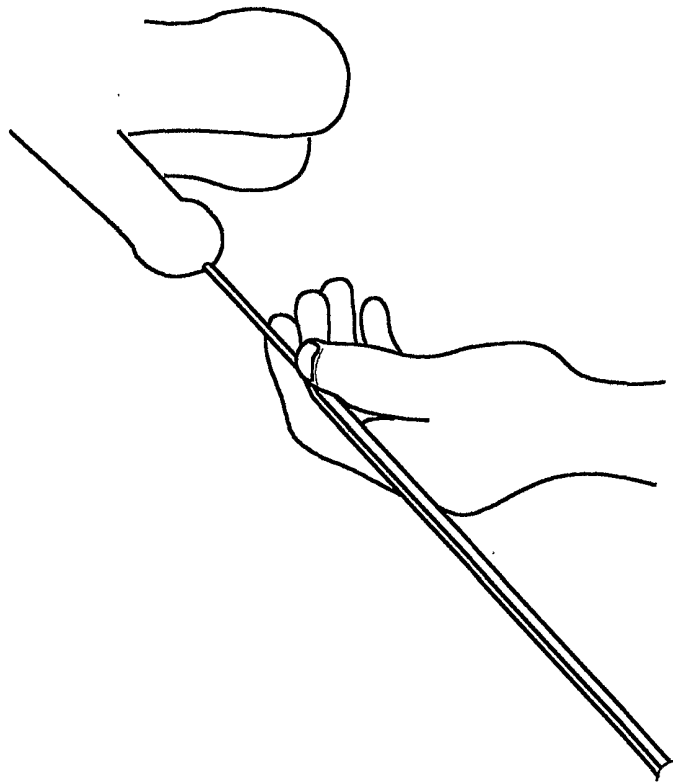
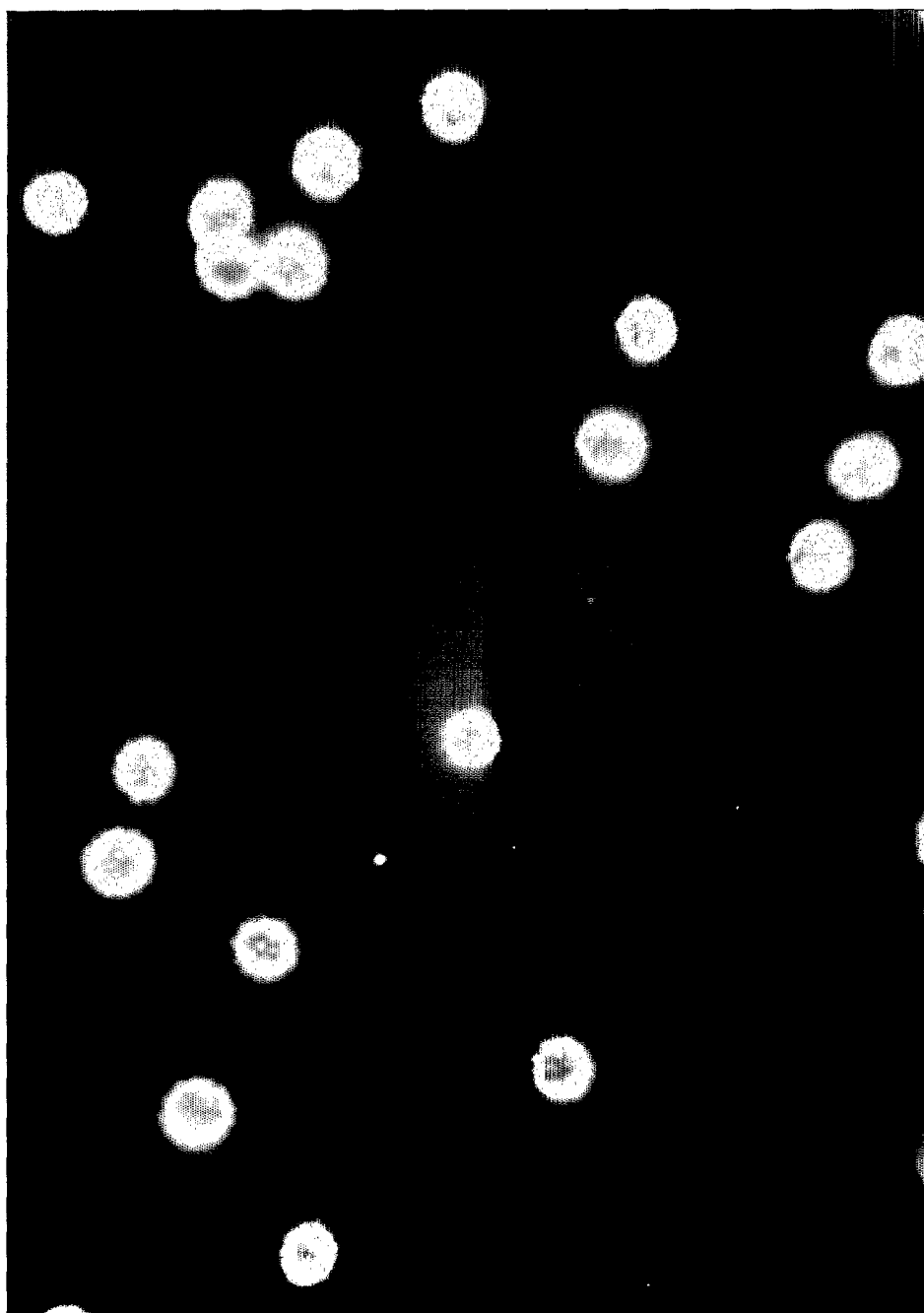


FIG. 2

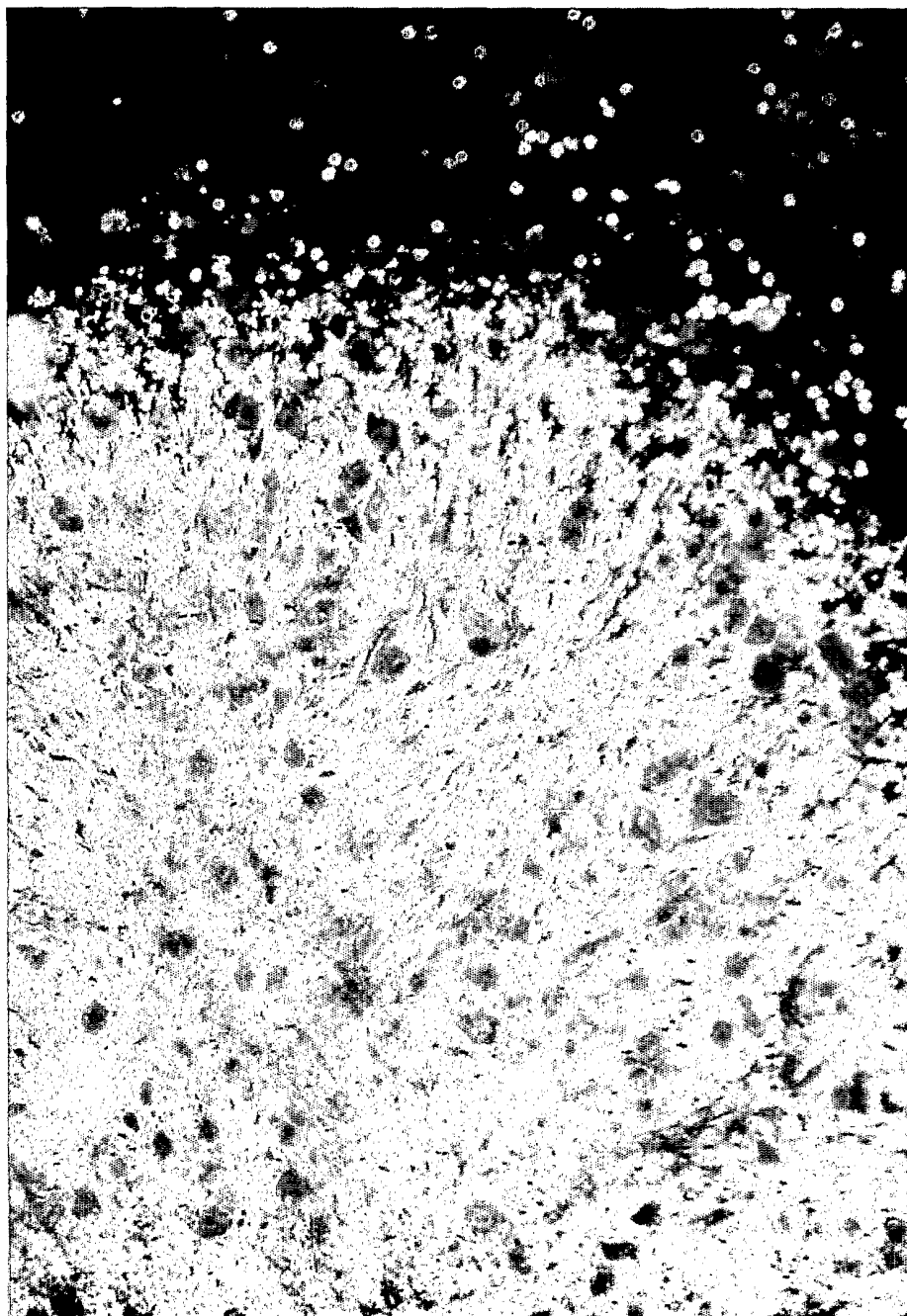
3/4

FIG. 3



4/4

FIG. 4



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/16842

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61C 19/04; A61B 5/00

US CL : 433/72; 128/634

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 433/72; 128/634

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST, DIALOG, MEDLINE,

search terms: protozoa, instrument, urethritis, exudate, pH, microscop\$

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SURESH, K. et al, In vitro encystment and experimental infections of Blastocystis hominis, Parasitology Research, 1993, Vol. 79, No. 6, pages 466-460, see pages 456 and 458, and entire document.	1
X	ABOU EL SEOUD, S. et al, Study of Trichomoniasis among Egyptian Male Patients, Journal of Egyptian Society of Parasitology, April 1998, Vol. 28, No. 1, pages 263-270, see abstract, introduction, results, discussion and subjects and methods sections.	1-6, 10, 12
X	BIRTHISTLE, K. et al, Microsporidia: a new sexually transmissible cause of urethritis, Genitourinary Medicine, 1996, Vol. 72, No. 6, page 445, see entire document.	17

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	"T" Later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"G" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

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14 JULY 2001

Date of mailing of the international search report

30 OCT 2001

 Name and mailing address of the ISA/US  
 Commissioner of Patents and Trademarks  
 Box PCT  
 Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

GINNY PORTNER

Telephone No. (703) 308-0196

# INTERNATIONAL SEARCH REPORT

ational application No.  
PCT/US01/16842

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,928,165 A (CAILLOUETTE) 27 July 1999, see abstract, figures, col. 1, lines 18-32, col. 6, lines 31-39, col. 6, lines 54-60, and all claims.	5, 10-11, 14-16
X	US 5,474,997 A (GRAY et al) 12 December 1995, see all claims, col. 11-12.	17
Y	US 5,704,353 A (KALB et al) 06 January 1998, see title, figures 5 and 6, col. 5, lines 48-50, col. 6, lines 56-67 and col. 7, lin 1-3, and claim 3.	7-8
Y	US 5,776,694 A (SHEINESS et al), 07 July 1998, see col. 3, lines 13-19 and col. 2, lines 21-28.	9
X	US 5,725,373 A (YEH) 10 March 1998, see title, col. 1, lines 58-62, and claims.	5,12-13