JUDGE ROMAN

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

CDX DIAGNOSTICS, INC. and SHARED MEDICAL RESOURCES, LLC Plaintiffs, v. UNITED STATES ENDOSCOPY GROUP, INC. D/B/A US ENDOSCOPY And JOHN DOES 1-30 Defendants.	)	13 CV 5669 COMPLAINT AND JURY DEMAND ECF CASE

COMPLAINT

Plaintiffs, CDX DIAGNOSTICS, INC., ("CDX") and Shared Medical Resources, LLC ("SMR") (Jointly and severally known as "Plainitffs") hereby sue Defendants UNITED STATES ENDOSCOPY GROUP, INC. d/b/a US ENDOSCOPY ("US Endoscopy" or "Defendant") and John Does 1-30 (US Endoscopy and John Does 1-30 jointly and severally known as "Defendants") and alleges as follows:

THE PARTIES

1. Plaintiff CDX is a corporation of the State of Delaware having a principal place of business at 2 Executive Boulevard, Suffern, New York 10901.

2. Plaintiff SMR is a Limited Liability Company having an address of 190 Newport Center Drive Suite 100 Newport Beach, CA 92660.

3. Upon information and belief, Defendant US Endoscopy is a corporation of the State of Ohio having a place of business at 5976 Heisley Road, Mentor, Ohio

44060.

4. Upon information and belief, US Endoscopy is engaged in the business of manufacturing, offering for sale and selling endoscopy products and conducts business throughout the United States, the State of New York, and the County of Rockland and through the internet at www.usendoscopy.com.

5. Upon information and belief, Defendants JOHN DOES 1-30 are individuals, corporations, associations, or other entities that, upon information and belief, caused, participated in, or are otherwise liable for, the infringement of Plaintiffs' patents complained of herein, including but not limited to manufacturers, distributors, retail sellers, property owners, and/or individuals and entities that own and control these entities. Plaintiffs expect to amend the complaint to allege these JOHN DOES 1-30 and their capacities.

JURISDICTION AND VENUE

6. This action is a civil action arising under the patent laws of the United States.

7. The jurisdiction of this Court arises under 28 U.S.C.§§ 1331 (federal question) and §§1338(a) and (b) (patent action).

8. This Court has personal jurisdiction over Defendant US Endoscopy because Defendant US Endoscopy has established minimum contacts with the forum. Upon information and belief, US Endoscopy manufactures (directly or indirectly through third party manufacturers) endoscopy products that are and have been used, offered for sale, sold and purchased in New York which violate Plaintiffs' patent rights. Upon

information and belief, US Endoscopy through its employees and agents offers for sale and/or sells endoscopy products in New York. Finally, upon information and belief, US Endoscopy, directly or through its distribution network, places its products within the stream of commerce, which stream is directed at this district, with the knowledge and/or understanding that such products which violate Plaintiffs' patent rights will be sold in the State of New York. In addition, Defendant US Endoscopy regularly does and/or solicits business or engages in other persistent course of conduct or derive substantial revenue from goods used or consumer or services rendered in the State of New York that violate Plaintiffs' patent rights or reasonably expect or should have expected the act of violating Plaintiffs' patent rights to have consequences in New York, and US Endoscopy has derived substantial revenue from interstate commerce.

9. Venue is proper in this district under 28 U.S.C. §§ 1391 (b), (c), and/or (d) and 28 U.S.C. §§ 1400(a) and/or (b), for the reasons, *inter alia*, that Defendant US Endoscopy does business in this district and have committed acts of infringement in this district.

10. On information and belief, Defendant US Endoscopy's activities constitute purposeful activities in New York in relation to the cause of action alleged.

GENERAL ALLEGATIONS

UNITED STATES PATENTS Nos. 6,676,609, 7,004,913, and 6,258,044

11. On or about January 13, 2004, U.S. Patent No. 6,676,609 entitled RETRACTABLE BRUSH FOR USE WITH ENDOSCOPE FOR BRUSH BIOPSY ("the '609 Patent") was duly and legally issued. On or about February 28, 2006, U.S. Patent

No. 7,004,913 entitled RETRACTABLE BRUSH FOR USE WITH ENDOSCOPE FOR BRUSH BIOPSY ("the '913 Patent") was duly and legally issued. On or about July 10, 2001, U.S. Patent No. 6,258,044 entitled APPARATUS AND METHOD FOR OBTAINING TRANSEPITHELIAL SPECIMEN OF A BODY SURFACE USING NON-LACERATING TECHNIQUE ("the '044 Patent") was duly and legally issued. CDX and SMR are co-owners of the '044 Patent, and CDX is the owner of the '609 and '913 Patents. All of the above-referenced patents hereinafter shall be jointly and severally known as the "'044, '913 and '609 Patents." Attached hereto as Exhibit 1 are true and correct copies of the '044, '913 and '609 Patents asserted for this action.

12. Plaintiff CDX has the sole right to sue and recover for any and all infringements with respect to the '913 and '609 Patents, and Plaintiffs CDX and SMR have the joint right as co-owners with respect to the '044 Patent.

DEFENDANT'S ACTS OF INFRINGEMENT

13. Upon information and belief, on a date unknown to Plaintiff CDX, Defendant US Endoscopy sold a brush endoscopy product that infringed the '044 Patent throughout the United States and in this jurisdiction (hereinafter "First Infringing Product").

14. On or about March 18, 2004, Plaintiff CDX, by its attorneys, sent a letter to US Endoscopy, *inter alia*, informing US Endoscopy of Plaintiff's rights with respect to various patents, including but not limited to the '044 Patent and demanding that US Endoscopy terminate its infringing activities with respect to its First Infringing Product (hereinafter "CDX March 18, 2004 letter").

15. On or about April 19, 2004, in response to the CDX March 18, 2004

letter, US Endoscopy informed Plaintiff CDX that US Endoscopy has ceased selling and supplying the First Infringing Product, and that US Endoscopy has not and does not intend to violate any CDX patents.

16. Plaintiff CDX learned that Defendant has been offering for sale and selling new products called the Infinity Sampling Device and the Infinity Cytology Device (the "Current Infringing Products"). Such Current Infringing Products infringe the '044, '913 and '609 Patents throughout the United States and in this jurisdiction, including the '044 Patent that was asserted against the First Infringing Product. Attached hereto as Exhibit 2 are printouts from Defendant US Endoscopy's website showing its Current Infringing Products.

17. All products offered for sale, sold and currently being offered for sale by CDX are marked with its patent numbers, including those of the '044, '913 and '609 Patents.

18. Despite due notice to Defendant US Endoscopy, Defendant US Endoscopy continues to infringe the rights of Plaintiffs, and such infringement is willful.

19. As a result, this action follows.

FIRST COUNT
INFRINGEMENT OF '044 PATENT
(PLAINTIFFS CDX AND SMR)

20. Plaintiffs repeat and reallege each allegation contained in paragraphs 1 through 19 of this Complaint, as if again set forth at length.

21. Defendant US Endoscopy has infringed and is still infringing, one or more

claims of the '044 Patent, including in this district and elsewhere in the United States, by making, using, selling, and offering for sale products that embody the inventions claimed in the '044 Patent and is now infringing the '044 Patent under 35 U.S.C. 271(a).

22. Plaintiffs CDX and SMR provided notice of its patent rights as set forth in the '044 Patent in full compliance with the provisions of 35 U.S.C. 287(a).

23. Upon information and belief, Defendant US Endoscopy will continue to infringe and induce infringement of the '044 Patent unless enjoined by this court.

24. Plaintiffs have been damaged by the acts of infringements of the '044 Patent committed by Defendant US Endoscopy and will continue to be damaged by the infringements, unless the infringements by Defendant US Endoscopy are enjoined by this court.

25. Upon information and belief, Defendant US Endoscopy has had actual knowledge of the specification and issued claims of the '044 Patent, and its continuing infringement of the '044 Patent is willful and deliberate.

SECOND COUNT

INFRINGEMENT OF –'913 PATENT AND '619 PATENT

(PLAINTIFF CDX)

26. Plaintiff CDX repeats and realleges each allegation contained in paragraphs 1 through 19 of this Complaint, as if again set forth at length.

27. Defendant US Endoscopy has infringed and is still infringing, one or more claims of the '913 and '609 Patents, including in this district and elsewhere in the United States, by making, using, selling, and offering for sale products that embody the inventions claimed in the '913 and '609 Patents and is now infringing the '913 and '609

Patents under 35 U.S.C. 271(a).

28. Plaintiff CDX provided notice of its patent rights as set forth in the '913 and '609 Patents in full compliance with the provisions of 35 U.S.C. 287(a).

29. Upon information and belief, Defendant US Endoscopy will continue to infringe and induce infringement of the '913 and '609 Patents unless enjoined by this court.

30. Plaintiff CDX has been damaged by the acts of infringements of the '913 and '609 Patents committed by Defendant US Endoscopy and will continue to be damaged by the infringements, unless the infringements by Defendant US Endoscopy are enjoined by this court.

31. Upon information and belief, Defendant US Endoscopy has had actual knowledge of the specification and issued claims of the '913 and '609 Patents, and its continuing infringement of the '913 and '609 Patents is willful and deliberate.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs demand judgment against Defendant US Endoscopy as follows:

(1) for Judgment that Defendant US Endoscopy, its officers, agents, servants, employees, representatives, attorneys and all persons acting in active concert or participation with it, be found to have infringed the '044, '913 and '609 Patents;

(2) For an Order enjoining Defendant US Endoscopy, its officers, agents, servants, employees, representatives, attorneys and all persons acting in active concert or participation with it from making, using, selling, or offering for sale products, services

and/or product packaging which infringe the '044, '913 and '609 Patents;

(3) For an Order enjoining and restraining Defendant US Endoscopy, its officers, agents, servants, employees, representatives, attorneys and all persons acting in active concert or participation with it from inducing infringement of the '044, '913 and '609 Patents;

(4) That Plaintiffs be compensated for the damages caused by Defendant US Endoscopy's infringement under 35 U.S.C. §284, in an amount to be precisely determined by an accounting, but not less than a reasonable royalty plus interest;

a. That the award of damages for this exceptional case be trebled as provided by 35 U.S.C. §284;

b. That Plaintiffs be awarded its costs and attorneys fees incurred in prosecuting this action, including reasonably attorney's fees, as provided for by 35 U.S.C. §285, (plus interest); and

c. Such other and further relief as the court deems just and equitable.

(5) Ordering Defendant to turn over to the Court or to Plaintiffs or to destroy within ten (10) days from the entry of any Final Judgment or Preliminary Decree entered in this action, all property owned by Defendant which unlawfully violates the '044, '913 and '609 Patents, any infringing product literature owned by Defendant, and all other works owned by Defendant that infringe the '044, '913 and '609 Patents, including an award of costs incurred by Plaintiff sfor the destruction of said articles and product packaging.

JURY DEMAND

Plaintiffs demand a jury trial on all issues so triable.

Dated: August 13, 2013

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Exhibit 1

US006676609B1

(12) **United States Patent**
Rutenberg et al.

(10) **Patent No.: US 6,676,609 B1**
(45) **Date of Patent: *Jan. 13, 2004**

(54) **RETRACTABLE BRUSH FOR USE WITH ENDOSCOPE FOR BRUSH BIOPSY**

(75) Inventors: **Mark Rutenberg**, Suffern, NY (US); **Stephen Frist**, Suffern, NY (US)

(73) Assignee: **CDx Laboratories, Inc.**, Suffern, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/321,010**

(22) Filed: **Dec. 17, 2002**

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/849,085, filed on May 4, 2001, now Pat. No. 6,494,845.

(51) **Int. Cl.**[7] **A61B 10/00**
(52) **U.S. Cl.** **600/569**; 600/562

(58) **Field of Search** 600/569, 562, 600/570, 572; 606/161; 604/1

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,258,044 B1 * 7/2001 Lonky et al. 600/569
6,494,845 B2 * 12/2002 Rutenberg 600/569

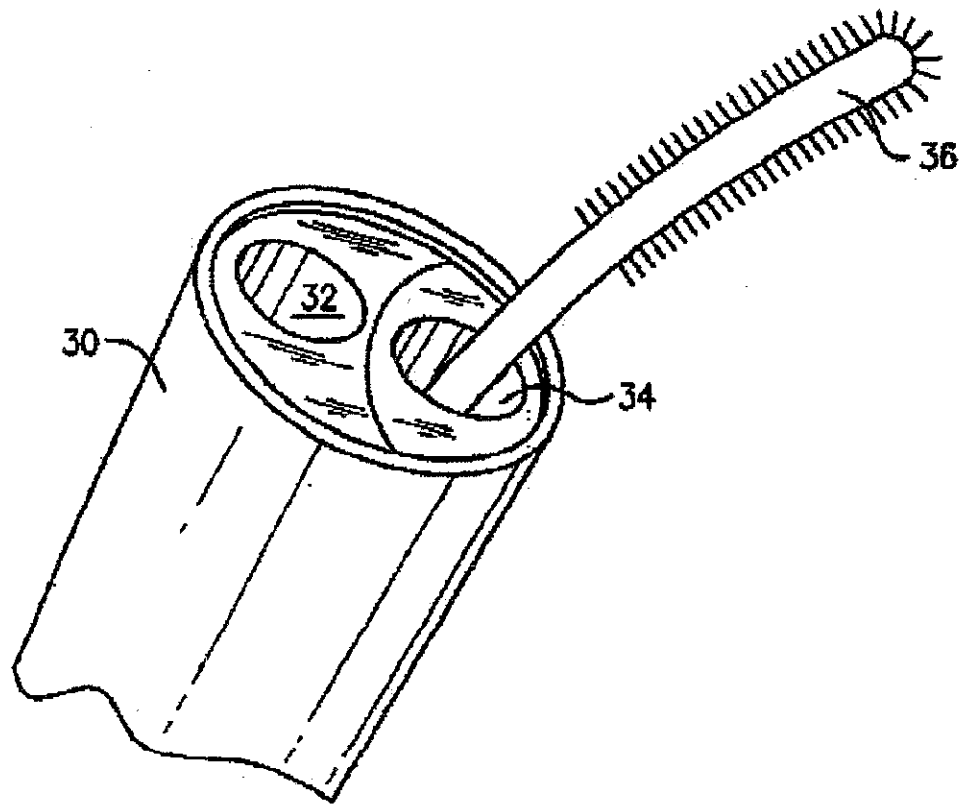
* cited by examiner

Primary Examiner—Thor Campbell
(74) *Attorney, Agent, or Firm*—Levisohn, Berger & Langsam, LLP

(57) **ABSTRACT**

A retractable brush structure is attached to a cylindrical rigid rod which in the closed position passes through a channel in an endoscope. After the brush passes through the endoscope, the brush moves against the tissue in order to remove cells from an area under examination. The brush is withdrawn from the endoscope and sample tissue is removed from said brush for examination after it is withdrawn from the endoscope.

4 Claims, 5 Drawing Sheets



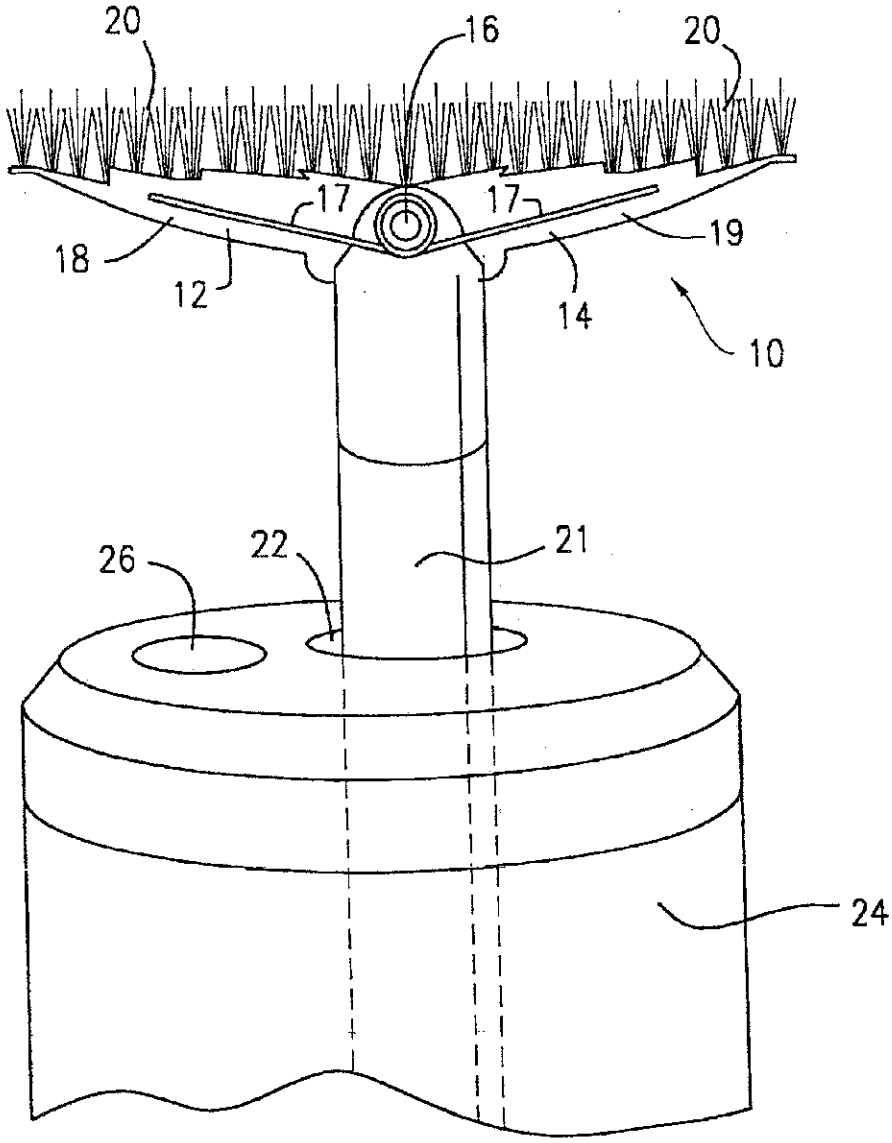


FIG. 1

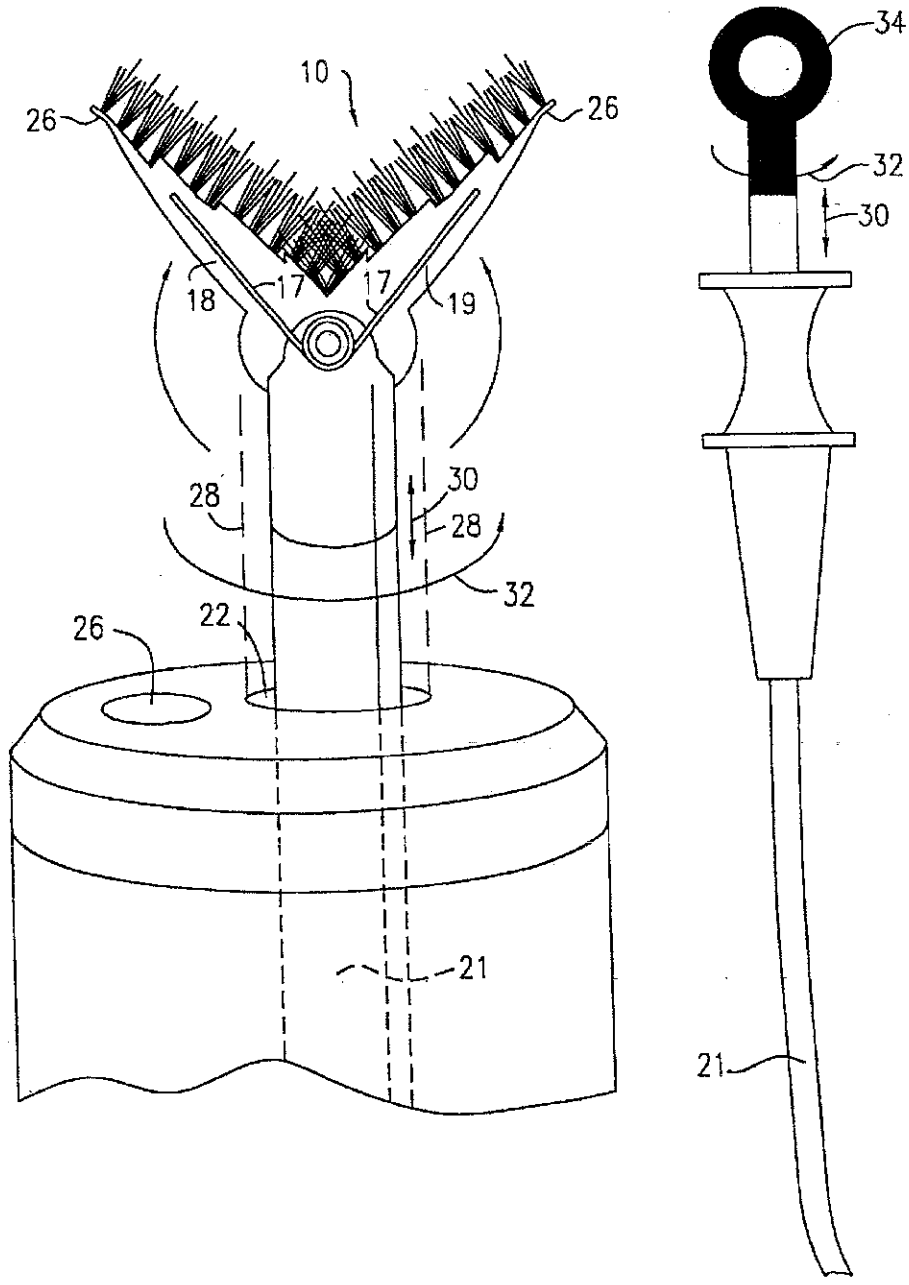


FIG. 2

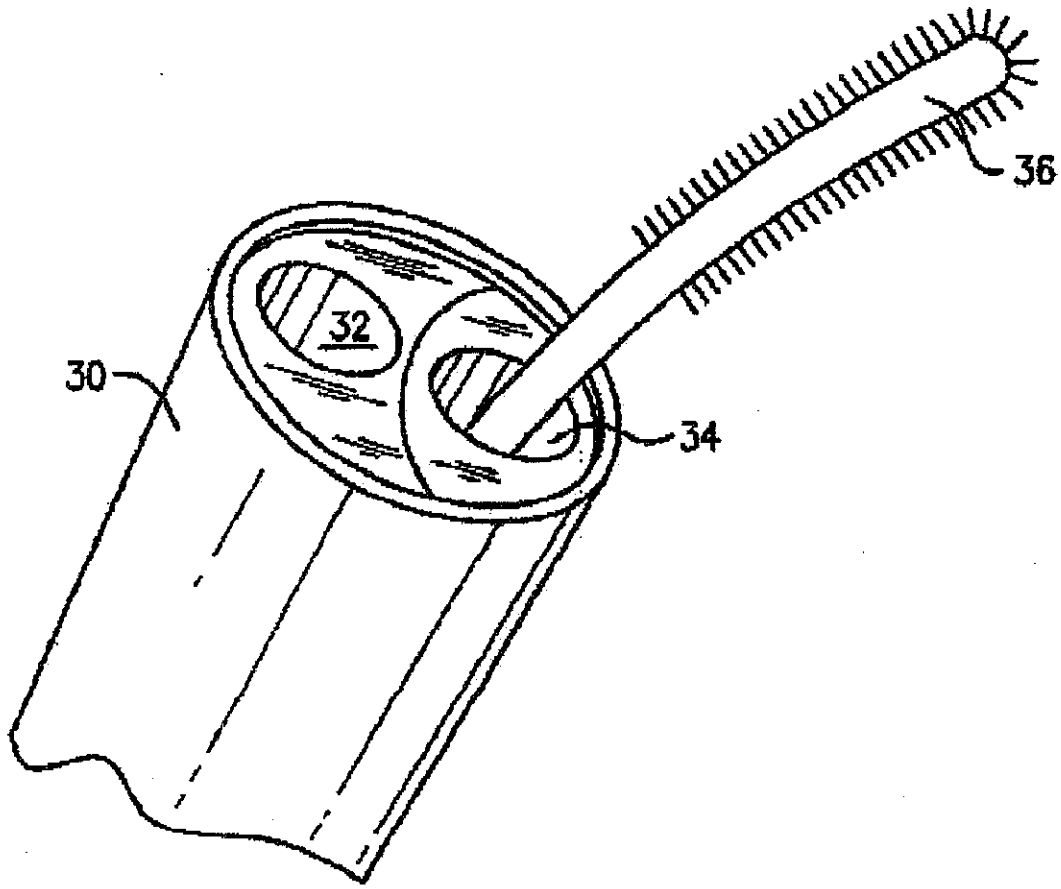


FIG. 3

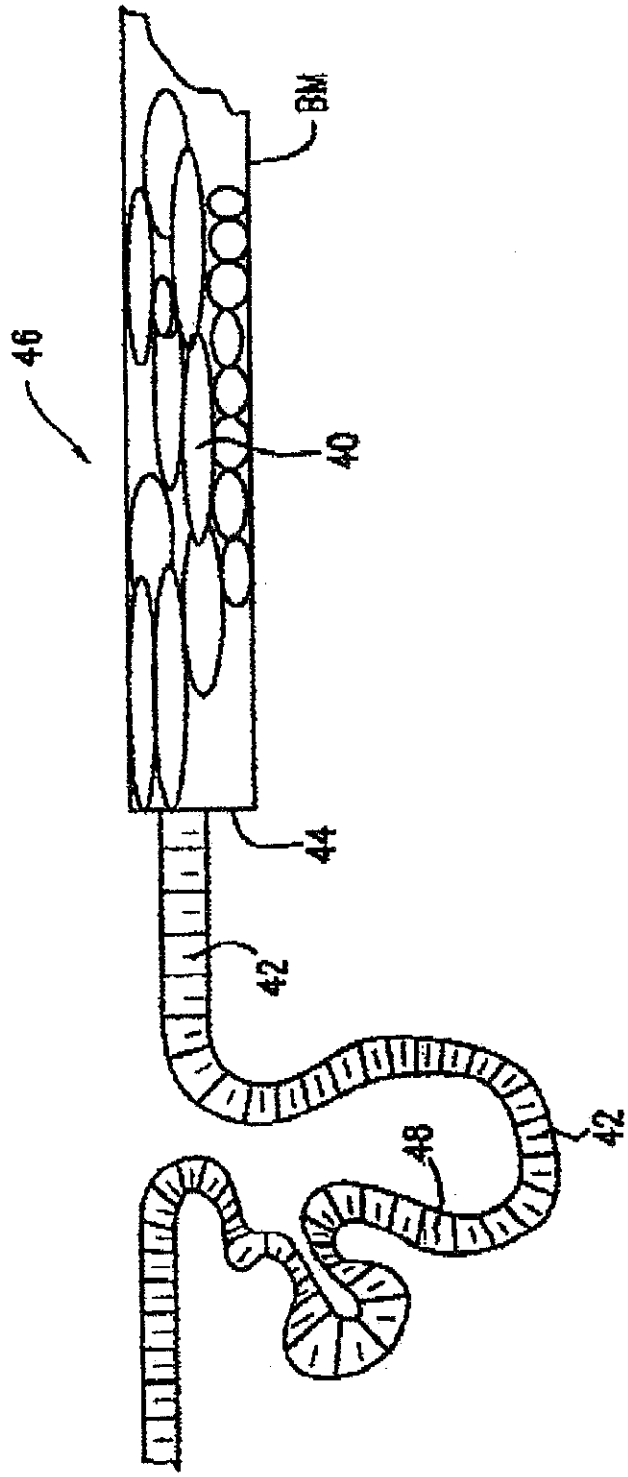


FIG. 4

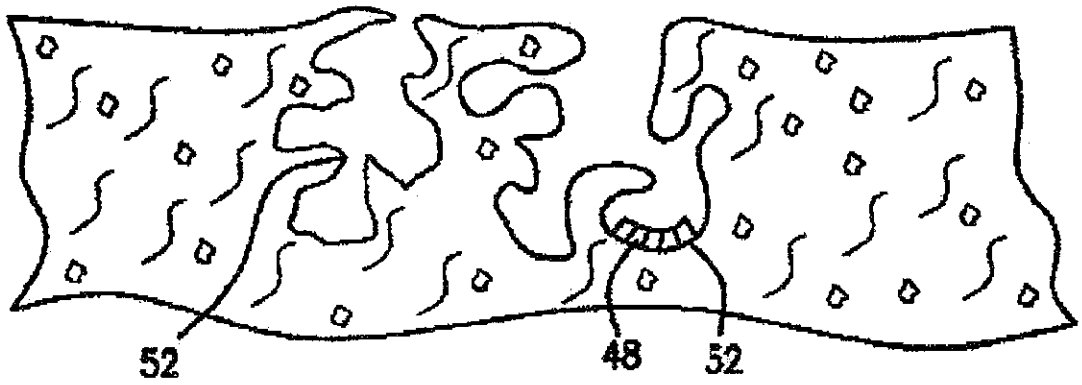


FIG. 5

RETRACTABLE BRUSH FOR USE WITH ENDOSCOPE FOR BRUSH BIOPSY

RELATED APPLICATION

This is a continuation-in-part of prior U.S. patent application Ser. No. 09/849,085, filed on May 4, 2001 which is issuing as U.S. Pat. No. 6,494,845 on Dec. 17, 2002.

FIELD OF THE INVENTION

The present invention is directed to a method and apparatus for obtaining transepithelial specimens of body surfaces using a non-lacerating technique. Specifically, the invention is directed to retractable tools such as a brush, used with endoscopes, for sampling epithelium from lesions found from the nose to the throat and in similar body tissues. The invention is also directed to an improved apparatus for non-lacerational testing of lesions that involve the epithelium of the nasopharynx, hypopharynx, pharynx, trachea, larynx, and the upper esophagus.

In metaplastic glandular epithelium as in native tissue, the invention using a brush biopsy must be certain to conduct a biopsy not merely a superficial cytology. In squamous epithelium, it is determined that the base membrane is reached and basal cells are being viewed and are included in the brush biopsy.

The transepithelial specimen sought to be examined in this C-I-P patent application is metaplastic glandular epithelium. A disaggregated specimen of the whole tissue comprises at least glandular cells plus basement membrane fragments plus elements of the lamina propria will be picked up by the brush biopsy. Such disaggregated specimen is retrieved with the brush biopsy.

BACKGROUND OF THE INVENTION

Cancers of the oral cavity and pharynx are a major cause of death from cancer in the U.S., exceeding the U.S. death rates for cervical cancer, malignant melanoma and Hodgkin's disease. According to the American Cancer Society's Department of Epidemiology and Surveillance, an estimated 30,750 new cases of oral cancer were diagnosed in the U.S. during 1997, a figure which accounts for 2% to 4% of all cancers diagnosed annually.

Cancers of the esophagus are also difficult to determine and are frequently not observable until an advanced state of the disease, often being too late for the patient to be effectively treated. In such regions of the body, it is the metaplastic glandular epithelium which needs to be examined at an early stage. Preferably, and in accordance with the teachings of this intention, such examination and cellular detection is achieved without lacerational techniques and employs a brush biopsy to pick up the desired cellular sample.

Despite advances in surgery, radiation, and chemotherapy, the mortality rate of oral cancer has not improved in the last 20 years. Ultimately, 50% of patients die from their malignancy, and 8,440 U.S. deaths were predicted for 1997. There are several reasons for the high mortality rate from oral cancer, but undoubtedly, the most significant factor is delayed diagnosis. Studies have demonstrated that the survival and cure rate increase dramatically when oral cancer is detected at an early stage. For example, the 5-year survival rate for patients with localized disease approximates 79% compared to 19% for those with distant metastases. Unfortunately, approximately two thirds of patients at time of diagnosis have advanced disease, and over 50% display evidence of spread to regional lymph nodes and distant metastases.

Delay in the diagnosis of oral and pharynx cancer is often the result of the limited diagnostic tools available in the prior art. The dentist or physician who detects such a lesion which is not clearly suggestive of a precancer or cancer clinically, and who is limited to the prior art tools and methods, is faced with a quandary. Approximately 5–10% of adult patients seen in a typical dental practice exhibit some type of oral lesion, yet only a small proportion (approximately 0.5% to 1%) are precancerous or cancerous. These oral lesions are commonly evidenced as a white or reddish patch, ulceration, plaque or nodule in the oral cavity. The overwhelming majority of these lesions are relatively harmless; however, the multitude of poorly defined lesions in the oral cavity can be confounding to the clinician. A diverse group of oral lesions may be easily confused with malignancy, and conversely, malignancy may be mistaken for a benign lesion. Benign tumors, reactive processes, traumatic lesions, oral manifestations or systemic diseases, inflammatory oral disorders, and bacterial, viral and fungal infections all display similar oral features thereby impeding establishment of an accurate clinical diagnosis.

The only reliable means currently available in the prior art to determine if a suspect oral lesion is pre-cancerous or cancerous, is to incise or excise (i.e. lacerate) the lesion surgically with either a scalpel or a laser so that a histological section of the removed tissue can be prepared for microscopic evaluation. Histology can be generally defined as the microscopic inspection or other testing of a cross section of tissue. This prior art form of oral surgical biopsy is generally performed by a surgeon, and is often inconvenient, painful, and expensive.

In many environments, endoscopes are used to examine interior parts of the body which are inaccessible to ordinary visual observation. Observation of these inner parts with an endoscope is for purposes of locating pathological areas, trying to identify them using the endoscopic visual instrument and determining how to diagnose and treat such visualized areas. Cancer in various portions of the body may be apparent to a visual observer because of certain lesions appearing at the visualized tissue in the organ or area being observed.

Since the majority of oral abnormalities detected clinically prove benign when tested microscopically, and given the limitations of biopsy, including cost, inconvenience, pain and potential for complications, relatively few oral lesions are subjected to biopsy. It is primarily for this reason that only oral lesions with clinical features strongly suggestive of cancer or precancer are referred for biopsy as described in the prior art. As a result, many patients with ominous, but visually less suggestive lesions are allowed to progress to advanced oral cancer, with their condition undiagnosed and untreated.

The oral epithelium is substantially identical to the epithelium of the nasopharynx, hypopharynx, pharynx, trachea, larynx, and the upper esophagus. As a result, otolaryngology currently suffers from the effects of the same diagnostic dilemma which affects dentistry, i.e. the inability to clinically distinguish between common benign-appearing lesions and identically appearing pre-cancerous and early cancerous lesions. Thus, the only two cancers in the U.S. which have not improved in mortality in the last thirty years are oral cancer and laryngeal cancer.

Common, benign-appearing nose and throat lesions are usually noticed by the otolaryngologist during a routine, office examination of the throat which is typically conducted using a flexible nasopharyngoscope. This thin optical tube is

easily threaded from the patent's nose into the throat and requires only a local anesthetic sprayed into the nose. This routine office procedure is performed by the average otolaryngologist many times each day.

The diagnostic dilemma for the otolaryngologist that is posed by the identical appearance of benign and pre-cancerous lesions is actually more acute than it is for the dentist. Although invasive and therefore avoided, a scalpel biopsy of the oral cavity is typically performed as an office procedure. Only local anesthetic is required, and bleeding from a scalpel biopsy of the oral cavity does not pose any aspiration danger. In contrast, a scalpel biopsy in many areas of the throat cannot be performed as an office procedure. This is because a scalpel biopsy in many areas of the throat may result in potentially dangerous aspiration of blood if the procedure is not performed under general anesthesia.

Referral of the patient for an operating room procedure requiring general anesthesia is both expensive and intrusive, and may expose the patient to other risks such as anesthesia and infection risk. The otolaryngologist is therefore hesitant to scalpel biopsy most benign-appearing throat lesions although they may represent the most treatable stage of a pre-cancer or cancer.

In many body sites, but not the oral cavity, a technique known as cytology is commonly utilized as an alternative to performing a lacerating biopsy and histological evaluation. In these body sites, pre-cancerous and cancerous cells or cell clusters tend to spontaneously exfoliate, or "slough off" from the surface of the epithelium. These cells or cell clusters are then collected and examined under the microscope for evidence of disease.

Since prior-art cytology is directed towards the microscopic examination of spontaneously exfoliated cells, obtaining the cellular sample is generally a simple, non-invasive, and painless procedure. Exfoliated or shed cells can often be obtained directly from the body fluid which is contiguous with the epithelium. Urine can thus be examined for evidence of bladder cancer, and sputum for lung cancer. Alternatively, exfoliated or shed cells may be obtained by gently scraping or brushing the surface of a mucus membrane epithelium to remove the surrounding mucus using a spatula or soft brush. This is the basis for the well known procedure known as the Pap smear used to detect early stage cervical cancer.

Because of the ease by which a cellular sample can be obtained from these body sites, prior-art cytology is typically utilized to screen asymptomatic populations for the presence of early stage disease. In the cervical Pap smear, for example, the entire surface area of the cervical regions where cancer generally occurs is gently scraped or brushed to collect and test the mucus from those regions. Abrasion of the underlying cervical epithelium is undesired, as it can cause bleeding and discomfort to the patient. This procedure is thus typically performed when no particular part of the cervix appears diseased, and when no suspect lesion is visible.

The design of prior art cytology sampling instruments reflects their use to sweep up cells which were spontaneously exfoliated and present on the superficial epithelial surface. Since prior-art cytology brushes need only to gently remove surface material, they are designed of various soft materials which can collect the cervical mucous with minimal abrasion to the underlying epithelium. These cytology sampling instruments therefore either have soft bristles, soft flexible fimbriated or fringed ends, or even, as in the case of the cotton swab or spatula, no bristles at all.

Examples of prior art cytological sampling tools include the wooden, metal or plastic spatula. According to the traditional method of Pap smear sampling, the spatula is placed onto the surface of the cervix and lightly depressed or scraped across the surface of the cervix to pick up exfoliated cells.

Further examples of prior art cytological sampling tools include the Cytobrush®; a device which uses soft and tapered bristles to sample shed cells from the cervical canal. U.S. Pat. No. 4,759,376, which allegedly covers this product, likewise describes a conical tapered soft bristle brush (a mascara brush shape) which is placed into the cervical canal and rotated for endocervical sampling. U.S. Pat. No. 4,759,376 teaches that the bristles "are to be relatively soft such as that of a soft toothbrush to more readily bend and avoid damaging the tissues." By way of further example, physicians have long used the common swab, commercially known as the Q-Tip®, to perform endocervical sampling.

Other prior art cytological sampling tools designed to obtain a cytological sample from the cervix may combine both endocervical and exocervical sampling regions into one device. These devices swab the surface of mucous-covered tissue by soft brushing the mucous layer of the endocervix and exocervix at the same time, thereby collecting the cells contained in the mucous layer tissue of those surfaces. These devices include the Unimar®-Cervex Brush™, a brush that has a contoured flat comb-like head with a single layer of flexible plastic bristles (similar to a flat paint brush having only one row of bristles) in which the center bristles are longer than the bristles on the ends. According to the method of use for the device, the center bristles are inserted into the cervical canal until the lateral bristles bend against the exocervix. The device is then removed and the cells are swabbed across a microscope slide similar to painting with a paintbrush.

Similarly, the Bayne Pap Brush™, which Medical Dynamics, Inc. represents is covered by U.S. Pat. No. 4,762,133, contains a center arm, made of soft DuPont bristles, running horizontal to the cervical canal and a second arm of soft bristles at ninety degrees to the first arm, creating an L-shape. The center arm is placed within the cervical canal and then rotated. Upon rotation, the soft bristles of the second arm automatically sweep the surface of the exocervix in a circular motion thereby sampling the exocervix along with the endocervix.

Although cytology has been adopted for use in several other body sites, it has not been found useful to test questionable lesions of the oral areas. This is in large part due to the fact that the prior art devices and methods used to obtain a cellular sample for cytology are unsatisfactory when used to sample lesions of the oral and nasal areas and areas containing similar epithelia. Unlike the uterine cervix, questionable lesions of the oral cavity and similar epithelia may be typically coated with multiple layers of keratinized cells. This "keratin layer" forms a relatively hard "skin-like" coating over the surface of the lesion and may thus hide the abnormal cells lying underneath it and prevent their exfoliation from the surface.

As noted above, the design of prior art cytology sampling instruments reflect their use in tissues where spontaneously exfoliated abnormal cells are commonly present on the surface of an area of epithelium that harbors disease. These cytology sampling instruments therefore either have soft bristles, soft flexible fimbriated ends, or even no bristles at all. Since prior-art cytology brushes only need to gently

remove surface material, they are designed of various soft materials which can collect the cervical mucous with minimal abrasion to the underlying epithelium.

While abnormal cells can spontaneously exfoliate to the epithelial surface and be gently removed by prior art instruments in the uterine cervix and other similar tissues, in many oral cavity lesions the abnormal cells never reach the surface because they are blocked by the keratin layer. This limitation is a major cause of the high false negative rate of prior art cytological testing to detect lesions of the oral cavity. That is, a large proportion of oral lesions found to be positive using lacerating biopsy and histology are found to be negative using cytology. In one major study, this false negative rate was found to be as high as 30%.

It is largely due to this lack of correlation between histology and prior art oral cytology that there is currently no significant use of oral cytology in the United States or elsewhere to test questionable oral lesions. Since it is well known that dangerous, truly cancerous oral lesions may commonly be reported as "negative" using prior art cytologic sampling techniques, prior art cytologic techniques offer little as a reliable diagnostic alternative to the lacerating biopsy and histology.

In addition to investigation of squamous epithelium above, diseases such as GERD and other lower gastrointestinal tract areas is required in which glandular epithelium exists. A further use of this brush biopsy invention is to reach the lower gastrointestinal tract and generate a sufficient cell sample for appropriate computer diagnosis as taught by the parent application of this continuation-in-part patent application.

A keratinized layer exists in the upper portion of the esophageal tract, and there is a rough boundary between the keratinized layer and the glandular epithelium in that tract. Glandular epithelium exists in areas deep within the body which is not subject to the external environmental, as is squamous epithelium which is the tissue found on the skin, the mouth, etc. which is in regular contact with the outside environment. The structure of glandular epithelium is, thus, different from the squamous epithelical three layer structure previously identified in connection with the parent application of which this is a continuation in part.

SUMMARY OF THE INVENTION

An object of the present invention to provide an apparatus and method for sampling epithelial cells from the anatomy without the pain or injury of lacerational biopsies.

Another object of this invention is to provide a brush biopsy device conveniently used with endoscopes so as to effectively sample tissue in a questionable area without needing a lacerational technique.

A further object of the present invention to provide an apparatus for sampling epithelial tissue in the nasopharynx, hypopharynx, pharynx, trachea, larynx, and the upper esophagus.

Still another object of this invention includes utilizing such a brush technique for use with endoscopic examination in any area in which sampling of questionable tissue through non-lacerational techniques provide an enhanced medical procedure as contrasted with current lacerational techniques employed.

It is a further object of the present invention to provide a non-lacerating apparatus which may readily sample cells from all levels of a surface epithelial lesion, including the basal, intermediate and superficial layers of the lesion.

It is a further object of the present invention to provide a nonlacerational apparatus which will pick up a disaggregated specimen of the whole tissue of metaplastic glandular epithelium, the whole tissue being defined as glandular cells plus basement membrane fragments plus elements of the submucosa.

Other objects and advantages and features this invention will become more apparent from the following description.

In accordance with the present invention, an apparatus is provided for sampling all types of epithelium, particularly squamous epithelium, from lesions found in the nasopharynx, hypopharynx, pharynx, trachea, larynx, and the upper esophagus. Further, in accordance with the invention, an improved method is provided for testing questionable lesions found in the epithelium of the nasopharynx, hypopharynx, pharynx, trachea, larynx, and the upper esophagus and other body tissues. The method invented involves exerting sufficient pressure in the lesion area with a surface or edge capable of dislodging cells in and under a keratinized layer.

For purposes of this patent application, the prior art scalpel procedure is defined as lacerational, whereas the novel invention herein is non-lacerational and therefore minimally invasive. To the extent that an abrasive brush has characteristics that may cause minor discomfort and or bleeding, there is substantial difference between the prior art scalpel trauma and the minimal trauma associated with the present invention.

The above and other objects are accomplished by providing a channel in the longitude interior of an endoscope through which a retractable brush may pass. The brush is formed so as to be closed as it passes through the endoscope and is opened after passing through the endoscope when in the appropriate location. The brush is capable of being rotated and moved against the tissue so as to remove suspect tissue, and the brush is then closed and withdrawn from the endoscope. The tissue collected by the brush is then ultimately examined for potential cancerous or pre-cancerous conditions in accordance with well known cell examination techniques.

Focal sampling of questionable lesions of the nose and throat areas and of similar epithelia is provided using a stiff-bristled brush. By rubbing harder than normal cytological sampling and using a stiff device which penetrates epithelium, one can reach to the basement membrane without lacerating. As opposed to the prior art, use of the device allows cell sampling which can readily and consistently produce a trans-epithelial cytologic sample. That is, by utilizing the invention disclosed herein, cells can readily and consistently be obtained from all levels of the epithelium (basal, intermediate and superficial) of a suspect lesion, thus overcoming the limitation in the prior art of abnormal epithelial cells being inaccessible to cytology for a variety of reasons, including because they are covered by a keratin layer. The resulting cellular sample functionally approximates the cellular sample of a lacerating biopsy device but is obtained with the ease of a stiff brush sweeping and without discomfort to the patient. The subject invention therefore makes practical the routine testing of questionable lesions of the nasopharynx, hypopharynx, pharynx, trachea, larynx, and the upper esophagus, thus allowing early detection and treatment of cancer and pre-cancer of those areas.

While the preferred embodiment has been described with respect to a brush, the present invention generally describes a method and apparatus for obtaining transepithelial specimens of a body surface. The invention relates to a non-

lacerational method and apparatus to obtain such a specimen. The reason one seeks to obtain a transepithelial sample is because suspect cells appear at the superficial layer of the epithelium originate at the basal layer within the tissue. With respect to the nasopharynx, hypopharynx, pharynx, trachea, larynx, and the upper esophagus, basal cells originate in the general area of the basement membrane separating the epithelial tissue from the tissue below the membrane known as the submucosa. In determining whether or not a patient has a precancerous or cancerous condition, it is important to reach down to the basement membrane and slightly therebelow because metastases may be suspected depending on the cellular architecture existing at just below or at the basement membrane through to the superficial layer.

The structure of the brush and bristles including the stiffness thereof as well as the shape of the bristle tips contribute to the effectiveness of the brushing or scrubbing action in retrieving cells from the transepithelial layers. The shape of the bristle tips is determined by the bristle cutting process. The bristle tips, preferably, have scraping edges. The tips of the brush and the brush itself may be considered as an assemblage of penetrating edges.

Although the preferred embodiment of the parent application, when filed, was to a hinged brush, a new preferred embodiment has been achieved. This new preferred embodiment is shown in FIG. **3**, and will be described in the detailed description of this application. More importantly, the new preferred embodiment resembles, at least in appearance, a conventional endoscope with a brush carried therein, but is different from all prior art because of the stiffness of the bristles of the brush enabling a disaggregated specimen of the whole tissue to be achieved with nonlacerational brushing techniques.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a partial perspective and sectional view illustrating the retractable brush in an open position after passing through the endoscope;

FIG. **2** is an exploded partial perspective and sectional view showing the handle manipulating the brush and illustrating the retractable brush folding together as it is drawn into the endoscope;

FIG. **3** is a partial perspective and sectional view of a preferred embodiment of this invention in which a non-hinged brush is employed;

FIG. **4** is a figure of the esophagus showing a general boundary area between squamous epithelium and metaplastic glandular epithelium; and

FIG. **5** illustrates the metaplastic glandular epithelium being investigated.

DETAILED DESCRIPTION

The prior art has used brushes with endoscopes to sample the examined area by moving the bristles of the brush across the suspect tissue area. Such brushes are similar to those described above which remove cells from the superficial layer, and the bristles do not penetrate below such layer because there is no direct force applied pushing tips of the bristles into the tissue being examined. Further, the prior art brushes merely rub against the surface and the brush area is very limited. The present retractable brush opens to a large size, the bristles thereof directly bear on said tissue transversely thereto and are urged further into said tissue by direct pressure. The brush is then rotated to sample a large area while concurrently reaching through the basement membrane to the basal cell layer.

FIG. **1** is a partial perspective and sectional view of an embodiment of this invention comprising a brush **10** formed of two separate brush sections **12** and **14** hingedly connected together as at **16** and outwardly biased by a spring **17** connected to rigid backbones **18** and **19** to which are attached bristles **20**. The bristles **20** could be of different structures as in order to be more adapted to the environment in which the brushes will be employed. A cylindrical rigid rod **21** passes through a channel **22** in an endoscope **24** having a viewing lens or window **26** shown at the distal end of the endoscope. Endoscopes are commonly provided with channels through the instrument, such as **22** through which medical instruments pass in order to perform certain medical procedures which are employed in conjunction with the observational aspects of the endoscope **24**.

FIG. **2** is similar to FIG. **1** but shows the brush sections **18** and **19** being urged together against the pressure of spring **17** as the brush biopsy device of this invention is withdrawn in the endoscope as shown in dotted lines **28**. Of course, it is understood that FIG. **2** also shows how the brush **10** opens when it is inserted through channel **22** and spring **17** forces the brush sections **12** and **14** to open fully. The area to be sampled is maximized by employing the retractable brush structure which can be narrow when closed to pass through the endoscope but open fully when in position to sample the suspected tissue.

The spring **17** applies a constant biasing force to the brush sections **12** and **14**. In an equivalent structure, the force opening and closing the brush need not be continuous and need only be applied to open and close the brush sections **12** and **14** when they are in the proper position. The rigid rod **21** can be used for this purpose with conventional mechanical or hydraulic linkage. Before the brush is inserted in the patient, it is in a closed position with a distal front tip **26**. The closed brush passes through channel **22**, and the brush sections **18** and **19** are opened after they pass through the endoscope into the examining area. The rigid rod **21** permits direct transverse pressure by the brush bristles against the tissue being examined and enables the brush to be rotated in order to remove cells from the epithelium tissue being examined, arrows **30** and **32** indicating the reciprocating and rotational movement at handle **34** which is transmitted to brush **10** by rod **21**. Handle **34** is located at the proximal end. The rigid construction for backbone **17** and **18** assures a direct transfer of force from the user to the brush bristles **20** in order to effectively operate the brush. The retractable bristles in conjunction with the rigid rod allows a rotating or drilling action to be employed as desired.

As understood from the above, the bristles of the brush can penetrate through the basement membrane of the tissue under examination and reach into the basal cell layer so as to ensure that cells from all three layers are sampled. When the retractable brush closes either before or as it is withdrawn into the endoscope, the brush bristles also close retaining the sample cells. After the device is removed from the endoscope the brush again opens permitting the bristles to be wiped across a suitable carrier for later analysis of the cells deposited on the carrier.

The brush **10** is illustrative of a tissue removing structure, and other tissue removing structures may be employed. The size of the brush can be varied; the number and structure of bristles can be varied; the retractable brush structure can be varied so that more than one pair of bristles may be employed, all of which would be available to one of ordinary skill in the art seeking to utilize the present non-lacerational cell sampling technique in conjunction with an endoscope. In essence, the retractable front end brush allowing non-

lacerational removal of tissue from a desired area by manipulation of a rigid rod passing through a channel in an endoscope provides enhanced benefits to patients who may have suspected lesions without having to perform lacerational biopsies on such patients.

FIG. **3** is a view of a preferred embodiment of this invention showing a conventional endoscope having a channel through which a brush may pass.

Although the brush illustrated in FIG. **3** may appear similar to cytological brushes, it is different from cytological brushes in the stiffness of the bristles, enabling a deeper removal of cells from merely the superficial cytological layer. In the prior art, the bristle strength of the brush merely is to brush the exfoliated top surface cells for examination, while in the present invention, the brush is stiff enough to reach in through the basement membrane whether for squamous or glandular epithelium, in order to be certain that the brush biopsy of the invention conducts a biopsy, not merely a superficial cytology. Endoscope **30** has a channel **32** for carrying suitable endoscopic instruments and a channel **34** through which the brush **36** biopsy of this invention is carried. The stiffness of the bristles permits reaching beyond the basement membrane, whether in squamous or glandular epithelium. Reference to reaching beyond squamous epithelium is the subject of parent application, U.S. Pat. No. 6,494,845. Described below is the glandular epithelium structure in order to further understand the biopsy aspects of this invention.

FIG. **4** shows adjacent squamous **40** and metaplastic glandular epithelium tissue **42** at the junction **44** of the glandular epithelium **42** and the normal squamous epithelium **40** in the esophagus **56**. The invention is seeking metaplastic glandular epithelium cells as part of a complete transepithelial biopsy of that area. The glandular epithelium includes columnar cells **48**.

The actual depth of the squamous epithelium **40** is perhaps 350 microns. The depth of the metaplastic glandular epithelium **42** which must be reached in order to do a complete biopsy is approximately 1000 microns. The brush bristle size penetration thus is at least 1000 microns, or approximately 3/32nds of an inch.

Referring now to FIG. **5**, a focus of a sample of glandular epithelium in FIG. **4** is shown. There is a basement membrane **52**, and columnar cells **48**. In order to be certain that a complete brush biopsy is performed, the pathologist or the computer will recognize that the brush biopsy has picked up a disaggregated specimen of the whole tissue, and the whole tissue is defined to be at least glandular cells plus basement membrane fragments plus elements of the submucosa. The submucosa exists below the basement membrane **52**. If all elements are in the brush biopsy, the brush biopsy of this invention is the equivalent of a lacerational biopsy which becomes substantially failsafe for medical diagnosis.

Other supplementary evidence of completeness of the biopsy of this glandular portion of the tissue is the fact that, in addition to the cellular disaggregated specimen, there are frequently microbiopsies which show all of the elements and their normal architecture present in this specimen as a function of the tissue itself.

Having described this invention with regard to specific embodiments, it is to be understood that the description is not meant as a limitation since further modifications and variations may be apparent or may suggest themselves to those skilled in the art. It is intended that the present application cover all such modifications and variations as fall within the scope of the appended claims.

What is claimed is:

1. An apparatus to be used in conjunction with an endoscope to examine tissue cells located within epithelium tissue having a surface, said apparatus comprising a channel extending the length of the endoscope; said apparatus comprising a rod passing through said channel having a distal and a proximal end; a retractable non-lacerational brush attached to the distal end of the rod, said brush being movable to bear against the tissue being examined and being controlled by said rod to remove tissue from a tissue area being examined, said brushing apparatus comprising bristles which exert sufficient pressure to conduct a biopsy to dislodge cells and pick up a specimen of the tissue area located below the surface of said epithelium tissue.

2. An apparatus as setforth in claim **1**, wherein said brush bristles are at least 1000 microns in length.

3. An apparatus as set forth in claim **1**, wherein said epithelium tissue comprises metaplastic glandular epithelium tissue.

4. An apparatus as set forth in claim **3**, wherein said specimen of the tissue area comprises a disaggregated specimen of the whole tissue, said whole tissue being defined of at least glandular cells, plus basement membrane fragments, plus elements of the submucosa in the area being examined.

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US007004913B1

(12) **United States Patent**
Rutenberg et al.

(10) **Patent No.: US 7,004,913 B1**
(45) **Date of Patent: Feb. 28, 2006**

(54) **RETRACTABLE BRUSH FOR USE WITH ENDOSCOPE FOR BRUSH BIOPSY**

(75) Inventors: **Mark Rutenberg**, Suffern, NY (US); **Stephen Frist**, Suffern, NY (US)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/756,696**

(22) Filed: **Jan. 12, 2004**

Related U.S. Application Data

(63) Continuation of application No. 10/321,010, filed on Dec. 17, 2002, now Pat. No. 6,676,609, which is a continuation-in-part of application No. 09/849,085, filed on May 4, 2001, now Pat. No. 6,494,845.

(51) **Int. Cl.**
A61B 10/00 (2006.01)

(52) **U.S. Cl.** **600/569**; 600/562

(58) **Field of Classification Search** 600/569, 600/562, 570, 572; 606/161; 604/1
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,494,845 B1 * 12/2002 Rutenberg 600/569
6,676,609 B1 * 1/2004 Rutenberg et al. 600/569

* cited by examiner

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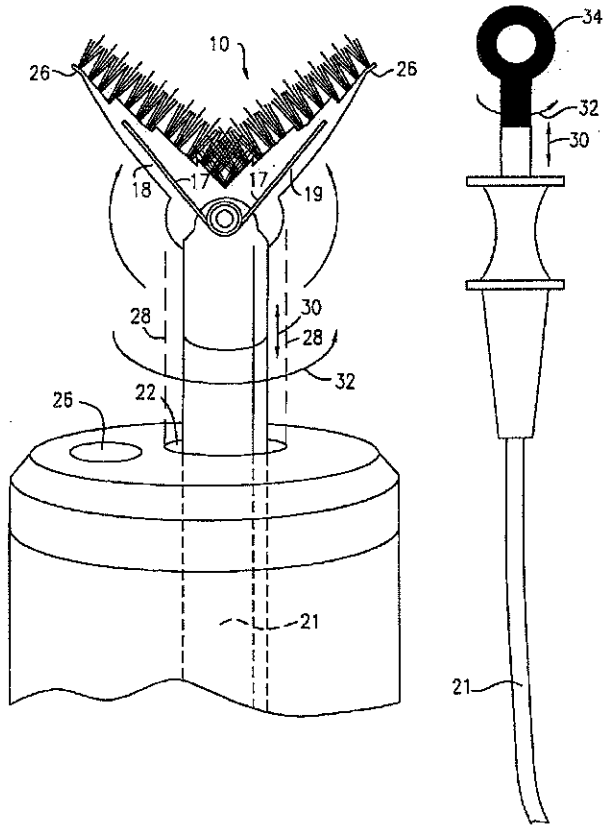
(74) *Attorney, Agent, or Firm*—Levisohn, Berger & Langsam, LLP

(57) **ABSTRACT**

A retractable brush structure is attached to a cylindrical rigid rod which in the closed position passes through a channel in an endoscope. After the brush passes through the endoscope, the brush moves against the tissue in order to remove cells from an area under examination. The brush is withdrawn from the endoscope and sample tissue is removed from said brush for examination after it is withdrawn from the endoscope.

3 Claims, 5 Drawing Sheets



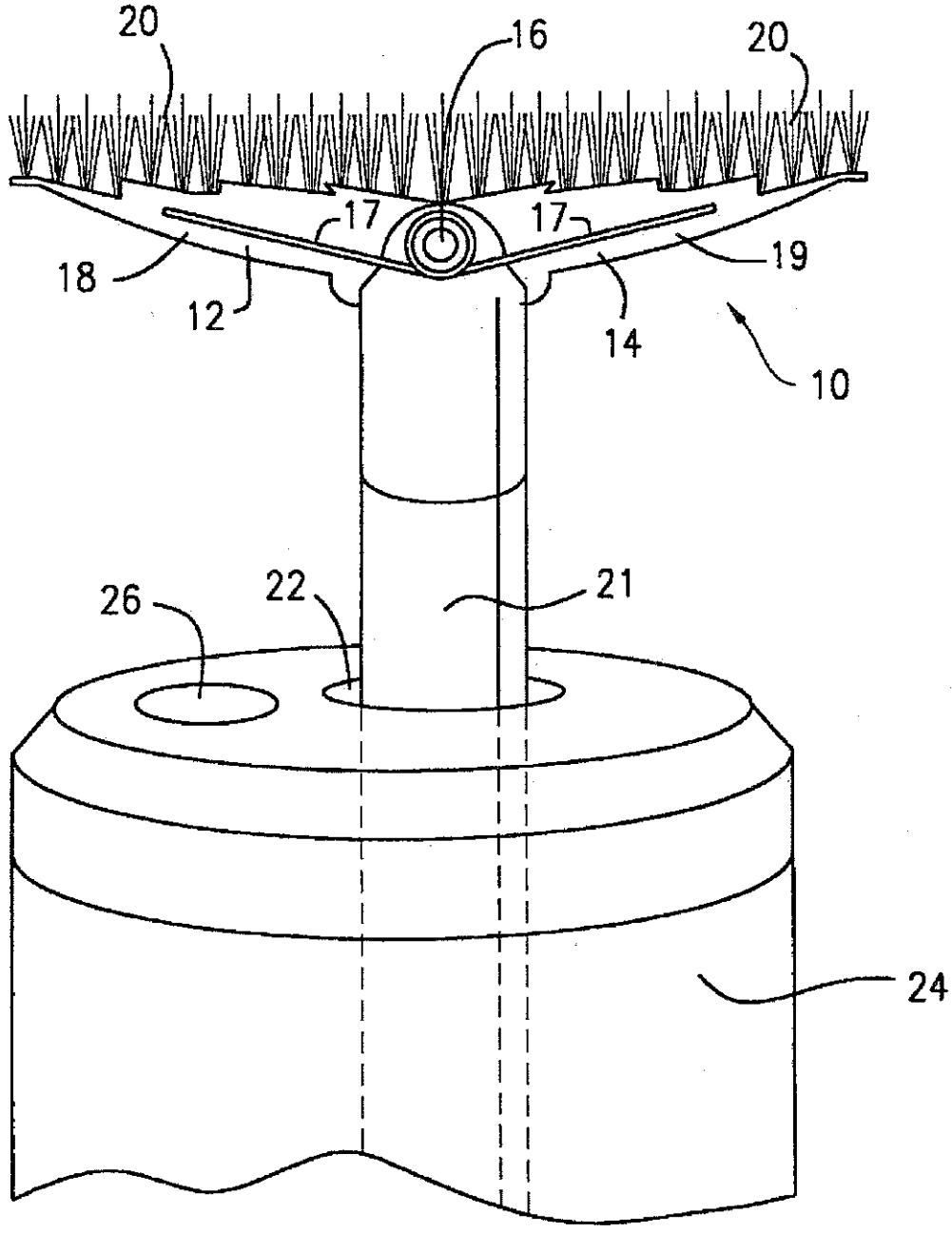


FIG. 1

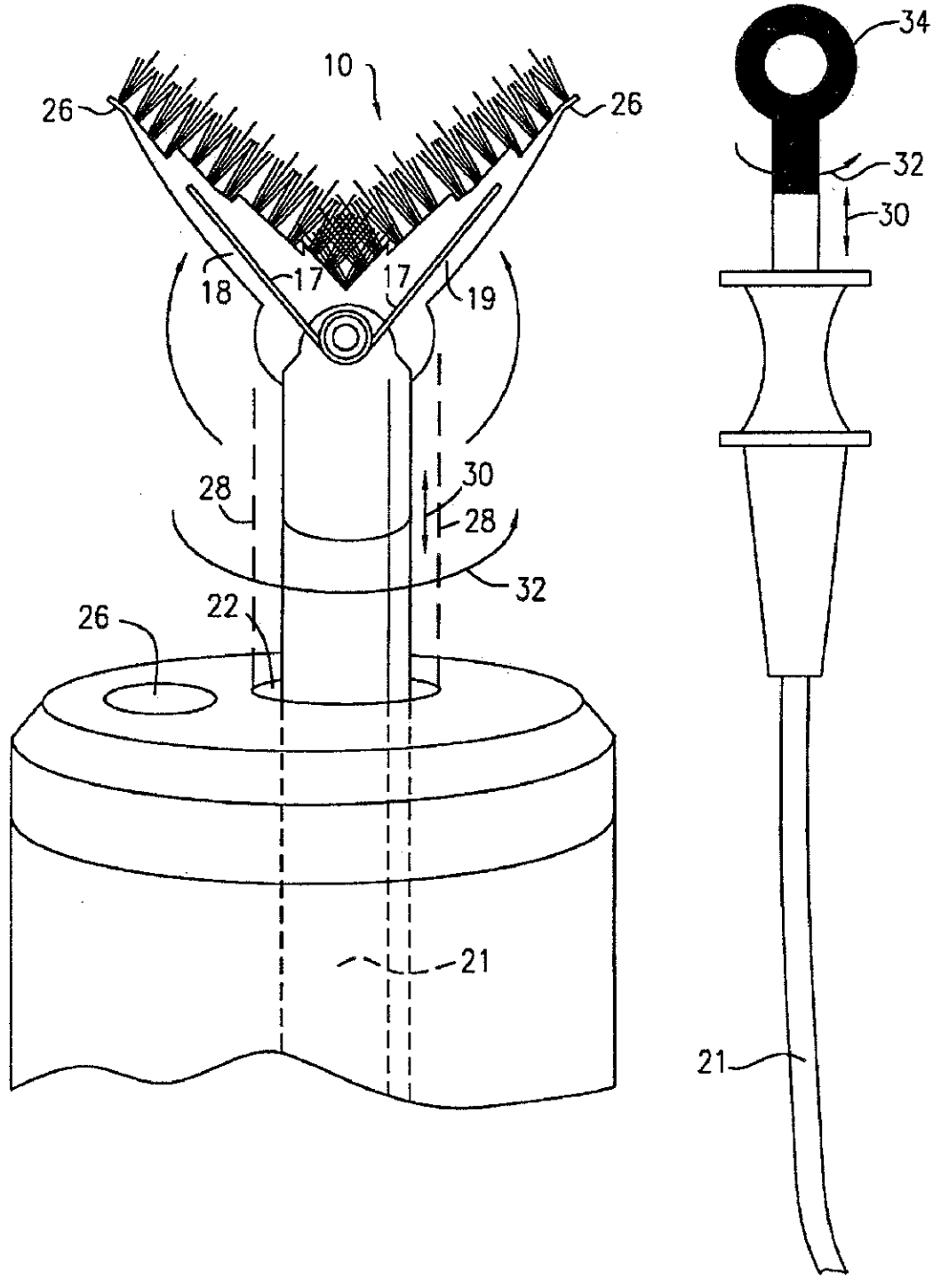


FIG. 2

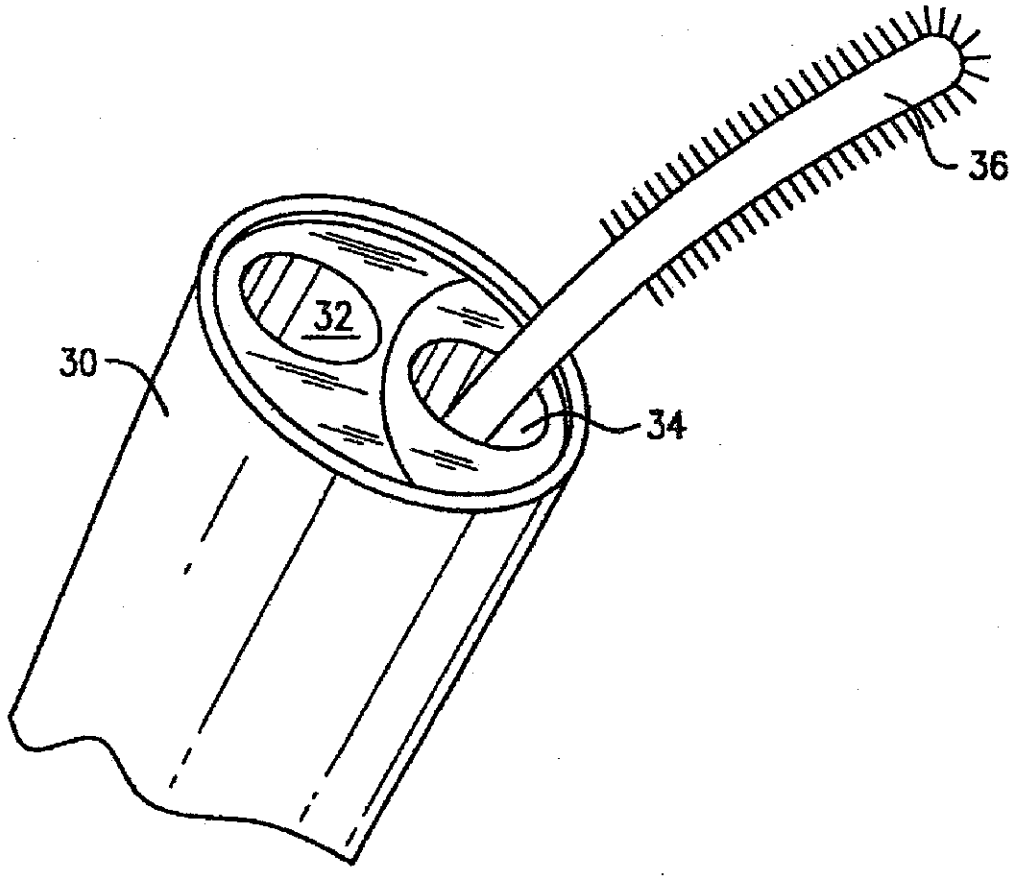


FIG. 3

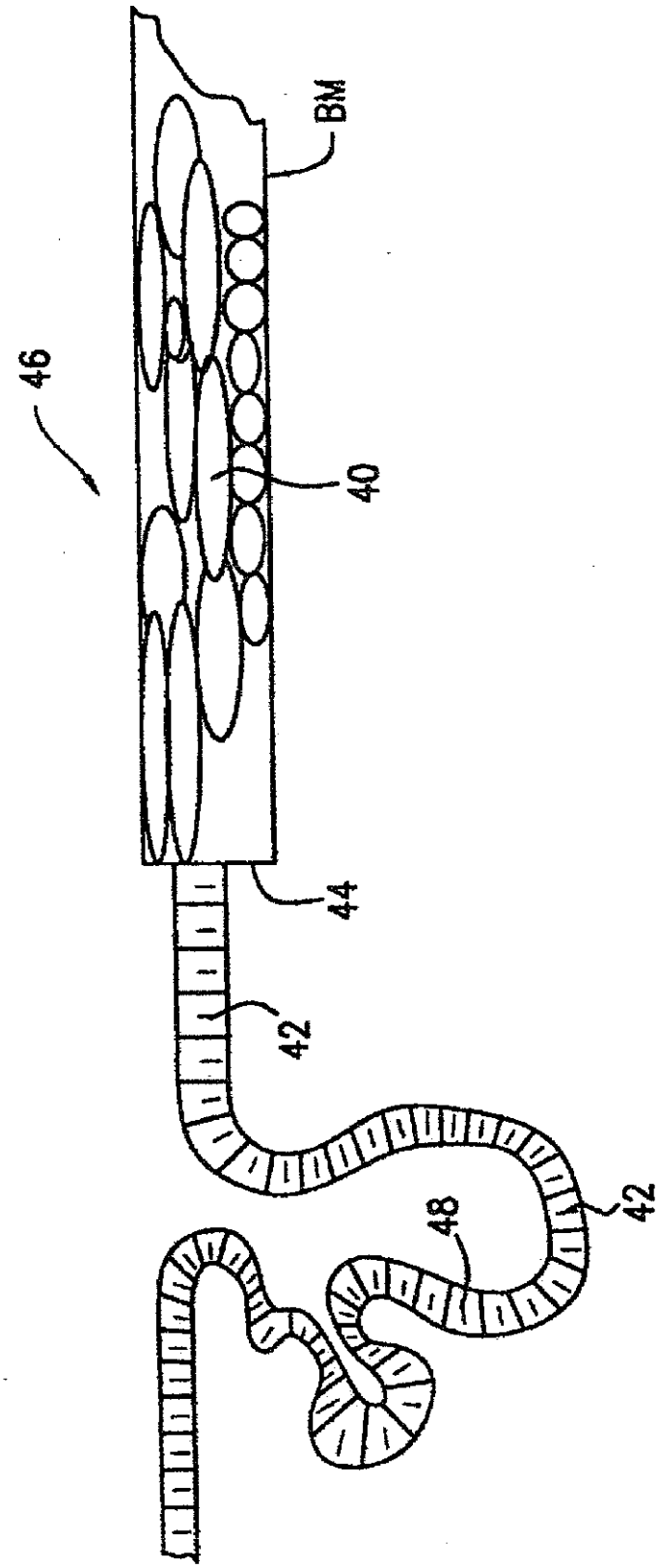


FIG. 4

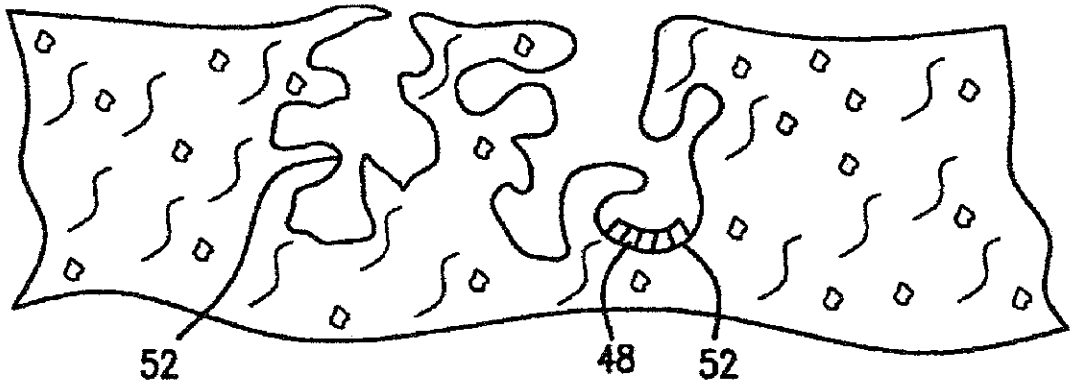


FIG. 5

RETRACTABLE BRUSH FOR USE WITH ENDOSCOPE FOR BRUSH BIOPSY

RELATED APPLICATION

This is a continuation of U.S. patent application Ser. No. 10/321,010, filed Dec. 17, 2002, which is to issue on Jan. 13, 2004 as U.S. Pat. No. 6,676,609, which was a continuation-in-part of prior U.S. patent application Ser. No. 09/849,085 filed May 4, 2001, which issued as U.S. Pat. No. 6,494,845 on Dec. 17, 2002, each of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention is directed to a method and apparatus for obtaining transepithelial specimens of body surfaces using a non-lacerating technique. Specifically, the invention is directed to retractable tools such as a brush, used with endoscopes, for sampling epithelium from lesions found from the nose to the throat and in similar body tissues. The invention is also directed to an improved apparatus for non-lacerational testing of lesions that involve the epithelium of the nasopharynx, hypopharynx, pharynx, trachea, larynx, and the upper esophagus.

In metaplastic glandular epithelium as in native tissue, the invention using a brush biopsy must be certain to conduct a biopsy not merely a superficial cytology. In squamous epithelium, it is determined that the base membrane is reached and basal cells are being viewed and are included in the brush biopsy.

The transepithelial specimen sought to be examined in this C-I-P patent application is metaplastic glandular epithelium. A disaggregated specimen of the whole tissue comprises at least glandular cells plus basement membrane fragments plus elements of the lamina propria will be picked up by the brush biopsy. Such disaggregated specimen is retrieved with the brush biopsy.

BACKGROUND OF THE INVENTION

Cancers of the oral cavity and pharynx are a major cause of death from cancer in the U.S., exceeding the U.S. death rates for cervical cancer, malignant melanoma and Hodgkin's disease. According to the American Cancer Society's Department of Epidemiology and Surveillance, an estimated 30,750 new cases of oral cancer were diagnosed in the U.S. during 1997, a figure which accounts for 2% to 4% of all cancers diagnosed annually.

Cancers of the esophagus are also difficult to determine and are frequently not observable until an advanced state of the disease, often being too late for the patient to be effectively treated. In such regions of the body, it is the metaplastic glandular epithelium which needs to be examined at an early stage. Preferably, and in accordance with the teachings of this intention, such examination and cellular detection is achieved without lacerational techniques and employs a brush biopsy to pick up the desired cellular sample.

Despite advances in surgery, radiation, and chemotherapy, the mortality rate of oral cancer has not improved in the last 20 years. Ultimately, 50% of patients die from their malignancy, and 8,440 U.S. deaths were predicted for 1997. There are several reasons for the high mortality rate from oral cancer, but undoubtedly, the most significant factor is delayed diagnosis. Studies have demonstrated that the survival and cure rate increase dramatically when oral cancer is

detected at an early stage. For example, the 5-year survival rate for patients with localized disease approximates 79% compared to 19% for those with distant metastases. Unfortunately, approximately two thirds of patients at time of diagnosis have advanced disease, and over 50% display evidence of spread to regional lymph nodes and distant metastases.

Delay in the diagnosis of oral and pharynx cancer is often the result of the limited diagnostic tools available in the prior art. The dentist or physician who detects such a lesion which is not clearly suggestive of a precancer or cancer clinically, and who is limited to the prior art tools and methods, is faced with a quandary. Approximately 5–10% of adult patients seen in a typical dental practice exhibit some type of oral lesion, yet only a small proportion (approximately 0.5% to 1%) are precancerous or cancerous. These oral lesions are commonly evidenced as a white or reddish patch, ulceration, plaque or nodule in the oral cavity. The overwhelming majority of these lesions are relatively harmless; however, the multitude of poorly defined lesions in the oral cavity can be confounding to the clinician. A diverse group of oral lesions may be easily confused with malignancy, and conversely, malignancy may be mistaken for a benign lesion. Benign tumors, reactive processes, traumatic lesions, oral manifestations or systemic diseases, inflammatory oral disorders, and bacterial, viral and fungal infections all display similar oral features thereby impeding establishment of an accurate clinical diagnosis.

The only reliable means currently available in the prior art to determine if a suspect oral lesion is pre-cancerous or cancerous, is to incise or excise (i.e. lacerate) the lesion surgically with either a scalpel or a laser so that a histological section of the removed tissue can be prepared for microscopic evaluation. Histology can be generally defined as the microscopic inspection or other testing of a cross section of tissue. This prior art form of oral surgical biopsy is generally performed by a surgeon, and is often inconvenient, painful, and expensive.

In many environments, endoscopes are used to examine interior parts of the body which are inaccessible to ordinary visual observation. Observation of these inner parts with an endoscope is for purposes of locating pathological areas, trying to identify them using the endoscopic visual instrument and determining how to diagnose and treat such visualized areas. Cancer in various portions of the body may be apparent to a visual observer because of certain lesions appearing at the visualized tissue in the organ or area being observed.

Since the majority of oral abnormalities detected clinically prove benign when tested microscopically, and given the limitations of biopsy, including cost, inconvenience, pain and potential for complications, relatively few oral lesions are subjected to biopsy. It is primarily for this reason that only oral lesions with clinical features strongly suggestive of cancer or precancer are referred for biopsy as described in the prior art. As a result, many patients with ominous, but visually less suggestive lesions are allowed to progress to advanced oral cancer, with their condition undiagnosed and untreated.

The oral epithelium is substantially identical to the epithelium of the nasopharynx, hypopharynx, pharynx, trachea, larynx, and the upper esophagus. As a result, otolaryngology currently suffers from the effects of the same diagnostic dilemma which affects dentistry, i.e. the inability to clinically distinguish between common benign-appearing lesions and identically appearing pre-cancerous and early cancerous

lesions. Thus, the only two cancers in the U.S. which have not improved in mortality in the last thirty years are oral cancer and laryngeal cancer.

Common, benign-appearing nose and throat lesions are usually noticed by the otolaryngologist during a routine, office examination of the throat which is typically conducted using a flexible nasopharyngoscope. This thin optical tube is easily threaded from the patent's nose into the throat and requires only a local anesthetic sprayed into the nose. This routine office procedure is performed by the average otolaryngologist many times each day.

The diagnostic dilemma for the otolaryngologist that is posed by the identical appearance of benign and pre-cancerous lesions is actually more acute than it is for the dentist. Although invasive and therefore avoided, a scalpel biopsy of the oral cavity is typically performed as an office procedure. Only local anesthetic is required, and bleeding from a scalpel biopsy of the oral cavity does not pose any aspiration danger. In contrast, a scalpel biopsy in many areas of the throat cannot be performed as an office procedure. This is because a scalpel biopsy in many areas of the throat may result in potentially dangerous aspiration of blood if the procedure is not performed under general anesthesia.

Referral of the patient for an operating room procedure requiring general anesthesia is both expensive and intrusive, and may expose the patient to other risks such as anesthesia and infection risk. The otolaryngologist is therefore hesitant to scalpel biopsy most benign-appearing throat lesions although they may represent the most treatable stage of a pre-cancer or cancer.

In many body sites, but not the oral cavity, a technique known as cytology is commonly utilized as an alternative to performing a lacerating biopsy and histological evaluation. In these body sites, pre-cancerous and cancerous cells or cell clusters tend to spontaneously exfoliate, or "slough off" from the surface of the epithelium. These cells or cell clusters are then collected and examined under the microscope for evidence of disease.

Since prior-art cytology is directed towards the microscopic examination of spontaneously exfoliated cells, obtaining the cellular sample is generally a simple, non-invasive, and painless procedure. Exfoliated or shed cells can often be obtained directly from the body fluid which is contiguous with the epithelium. Urine can thus be examined for evidence of bladder cancer, and sputum for lung cancer. Alternatively, exfoliated or shed cells may be obtained by gently scraping or brushing the surface of a mucus membrane epithelium to remove the surrounding mucus using a spatula or soft brush. This is the basis for the well known procedure known as the Pap smear used to detect early stage cervical cancer.

Because of the ease by which a cellular sample can be obtained from these body sites, prior-art cytology is typically utilized to screen asymptomatic populations for the presence of early stage disease. In the cervical Pap smear, for example, the entire surface area of the cervical regions where cancer generally occurs is gently scraped or brushed to collect and test the mucus from those regions. Abrasion of the underlying cervical epithelium is undesired, as it can cause bleeding and discomfort to the patient. This procedure is thus typically performed when no particular part of the cervix appears diseased, and when no suspect lesion is visible.

The design of prior art cytology sampling instruments reflects their use to sweep up cells which were spontaneously exfoliated and present on the superficial epithelial surface. Since prior-art cytology brushes need only to gently remove surface material, they are designed of various soft materials which can collect the cervical mucous with minimal abrasion to the underlying epithelium. These cytology sampling instruments therefore either have soft bristles, soft flexible fimbriated or fringed ends, or even, as in the case of the cotton swab or spatula, no bristles at all.

Examples of prior art cytological sampling tools include the wooden, metal or plastic spatula. According to the traditional method of Pap smear sampling, the spatula is placed onto the surface of the cervix and lightly depressed or scraped across the surface of the cervix to pick up exfoliated cells.

Further examples of prior art cytological sampling tools include the Cytobrush®; a device which uses soft and tapered bristles to sample shed cells from the cervical canal. U.S. Pat. No. 4,759,376, which allegedly covers this product, likewise describes a conical tapered soft bristle brush (a mascara brush shape) which is placed into the cervical canal and rotated for endocervical sampling. U.S. Pat. No. 4,759,376 teaches that the bristles "are to be relatively soft such as that of a soft toothbrush to more readily bend and avoid damaging the tissues." By way of further example, physicians have long used the common swab, commercially known as the Q-Tip®, to perform endocervical sampling.

Other prior art cytological sampling tools designed to obtain a cytological sample from the cervix may combine both endocervical and exocervical sampling regions into one device. These devices swab the surface of mucous-covered tissue by soft brushing the mucous layer of the endocervix and exocervix at the same time, thereby collecting the cells contained in the mucous layer tissue of those surfaces. These devices include the Unimar®-Cervex Brush™, a brush that has a contoured flat comb-like head with a single layer of flexible plastic bristles (similar to a flat paint brush having only one row of bristles) in which the center bristles are longer than the bristles on the ends. According to the method of use for the device, the center bristles are inserted into the cervical canal until the lateral bristles bend against the exocervix. The device is then removed and the cells are swabbed across a microscope slide similar to painting with a paintbrush.

Similarly, the Bayne Pap Brush™, which Medical Dynamics, Inc. represents is covered by U.S. Pat. No. 4,762,133, contains a center arm, made of soft DuPont bristles, running horizontal to the cervical canal and a second arm of soft bristles at ninety degrees to the first arm, creating an L-shape. The center arm is placed within the cervical canal and then rotated. Upon rotation, the soft bristles of the second arm automatically sweep the surface of the exocervix in a circular motion thereby sampling the exocervix along with the endocervix.

Although cytology has been adopted for use in several other body sites, it has not been found useful to test questionable lesions of the oral areas. This is in large part due to the fact that the prior art devices and methods used to obtain a cellular sample for cytology are unsatisfactory when used to sample lesions of the oral and nasal areas and areas containing similar epithelia. Unlike the uterine cervix, questionable lesions of the oral cavity and similar epithelia may be typically coated with multiple layers of keratinized cells. This "keratin layer" forms a relatively hard "skin-like" coating over the surface of the lesion and may thus hide the abnormal cells lying underneath it and prevent their exfoliation from the surface.

As noted above, the design of prior art cytology sampling instruments reflect their use in tissues where spontaneously exfoliated abnormal cells are commonly present on the

surface of an area of epithelium that harbors disease. These cytology sampling instruments therefore either have soft bristles, soft flexible fimbriated ends, or even no bristles at all. Since prior-art cytology brushes only need to gently remove surface material, they are designed of various soft materials which can collect the cervical mucous with minimal abrasion to the underlying epithelium.

While abnormal cells can spontaneously exfoliate to the epithelial surface and be gently removed by prior art instruments in the uterine cervix and other similar tissues, in many oral cavity lesions the abnormal cells never reach the surface because they are blocked by the keratin layer. This limitation is a major cause of the high false negative rate of prior art cytological testing to detect lesions of the oral cavity. That is, a large proportion of oral lesions found to be positive using lacerating biopsy and histology are found to be negative using cytology. In one major study, this false negative rate was found to be as high as 30%.

It is largely due to this lack of correlation between histology and prior art oral cytology that there is currently no significant use of oral cytology in the United States or elsewhere to test questionable oral lesions. Since it is well known that dangerous, truly cancerous oral lesions may commonly be reported as "negative" using prior art cytologic sampling techniques, prior art cytologic techniques offer little as a reliable diagnostic alternative to the lacerating biopsy and histology.

In addition to investigation of squamous epithelium above, diseases such as GERD and other lower gastrointestinal tract areas is required in which glandular epithelium exists. A further use of this brush biopsy invention is to reach the lower gastrointestinal tract and generate a sufficient cell sample for appropriate computer diagnosis as taught by the parent application of this continuation-in-part patent application.

A keratinized layer exists in the upper portion of the esophageal tract, and there is a rough boundary between the keratinized layer and the glandular epithelium in that tract. Glandular epithelium exists in areas deep within the body which is not subject to the external environmental, as is squamous epithelium which is the tissue found on the skin, the mouth, etc. which is in regular contact with the outside environment. The structure of glandular epithelium is, thus, different from the squamous epithelical three layer structure previously identified in connection with the parent application of which this is a continuation in part.

SUMMARY OF THE INVENTION

An object of the present invention to provide an apparatus and method for sampling epithelial cells from the anatomy without the pain or injury of lacerational biopsies.

Another object of this invention is to provide a brush biopsy device conveniently used with endoscopes so as to effectively sample tissue in a questionable area without needing a lacerational technique.

A further object of the present invention to provide an apparatus for sampling epithelial tissue in the nasopharynx, hypopharynx, pharynx, trachea, larynx, and the upper esophagus.

Still another object of this invention includes utilizing such a brush technique for use with endoscopic examination in any area in which sampling of questionable tissue through non-lacerational techniques provide an enhanced medical procedure as contrasted with current lacerational techniques employed.

It is a further object of the present invention to provide a non-lacerating apparatus which may readily sample cells from all levels of a surface epithelial lesion, including the basal, intermediate and superficial layers of the lesion.

It is a further object of the present invention to provide a nonlacerational apparatus which will pick up a disaggregated specimen of the whole tissue of metaplastic glandular epithelium, the whole tissue being defined as glandular cells plus basement membrane fragments plus elements of the submucosa.

Other objects and advantages and features this invention will become more apparent from the following description.

In accordance with the present invention, an apparatus is provided for sampling all types of epithelium, particularly squamous epithelium, from lesions found in the nasopharynx, hypopharynx, pharynx, trachea, larynx, and the upper esophagus. Further, in accordance with the invention, an improved method is provided for testing questionable lesions found in the epithelium of the nasopharynx, hypopharynx, pharynx, trachea, larynx, and the upper esophagus and other body tissues. The method invented involves exerting sufficient pressure in the lesion area with a surface or edge capable of dislodging cells in and under a keratinized layer.

For purposes of this patent application, the prior art scalpel procedure is defined as lacerational, whereas the novel invention herein is non-lacerational and therefore minimally invasive. To the extent that an abrasive brush has characteristics that may cause minor discomfort and/or bleeding, there is substantial difference between the prior art scalpel trauma and the minimal trauma associated with the present invention.

The above and other objects are accomplished by providing a channel in the longitude interior of an endoscope through which a retractable brush may pass. The brush is formed so as to be closed as it passes through the endoscope and is opened after passing through the endoscope when in the appropriate location. The brush is capable of being rotated and moved against the tissue so as to remove suspect tissue, and the brush is then closed and withdrawn from the endoscope. The tissue collected by the brush is then ultimately examined for potential cancerous or pre-cancerous conditions in accordance with well known cell examination techniques.

Focal sampling of questionable lesions of the nose and throat areas and of similar epithelia is provided using a stiff-bristled brush. By rubbing harder than normal cytological sampling and using a stiff device which penetrates epithelium, one can reach to the basement membrane without lacerating. As opposed to the prior art, use of the device allows cell sampling which can readily and consistently produce a trans-epithelial_cytologic sample. That is, by utilizing the invention disclosed herein, cells can readily and consistently be obtained from all levels of the epithelium (basal, intermediate and superficial) of a suspect lesion, thus overcoming the limitation in the prior art of abnormal epithelial cells being inaccessible to cytology for a variety of reasons, including because they are covered by a keratin layer. The resulting cellular sample functionally approximates the cellular sample of a lacerating biopsy device but is obtained with the ease of a stiff brush sweeping and without discomfort to the patient. The subject invention therefore makes practical the routine testing of questionable lesions of the nasopharynx, hypopharynx, pharynx, trachea, larynx, and the upper esophagus, thus allowing early detection and treatment of cancer and pre-cancer of those areas.

While the preferred embodiment has been described with respect to a brush, the present invention generally describes a method and apparatus for obtaining transepithelial specimens of a body surface. The invention relates to a nonlacerational method and apparatus to obtain such a specimen. The reason one seeks to obtain a transepithelial sample is because suspect cells appear at the superficial layer of the epithelium originate at the basal layer within the tissue. With respect to the nasopharynx, hypopharynx, pharynx, trachea, larynx, and the upper esophagus, basal cells originate in the general area of the basement membrane separating the epithelial tissue from the tissue below the membrane known as the submucosa. In determining whether or not a patient has a precancerous or cancerous condition, it is important to reach down to the basement membrane and slightly therebelow because metastases may be suspected depending on the cellular architecture existing at just below or at the basement membrane through to the superficial layer.

The structure of the brush and bristles including the stiffness thereof as well as the shape of the bristle tips contribute to the effectiveness of the brushing or scrubbing action in retrieving cells from the transepithelial layers. The shape of the bristle tips is determined by the bristle cutting process. The bristle tips, preferably, have scraping edges. The tips of the brush and the brush itself may be considered as an assemblage of penetrating edges.

Although the preferred embodiment of the parent application, when filed, was to a hinged brush, a new preferred embodiment has been achieved. This new preferred embodiment is shown in FIG. 3, and will be described in the detailed description of this application. More importantly, the new preferred embodiment resembles, at least in appearance, a conventional endoscope with a brush carried therein, but is different from all prior art because of the stiffness of the bristles of the brush enabling a disaggregated specimen of the whole tissue to be achieved with nonlacerational brushing techniques.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a partial perspective and sectional view illustrating the retractable brush in an open position after passing through the endoscope;

FIG. 2 is an exploded partial perspective and sectional view showing the handle manipulating the brush and illustrating the retractable brush folding together as it is drawn into the endoscope;

FIG. 3 is a partial perspective and sectional view of a preferred embodiment of this invention in which a nonhinged brush is employed;

FIG. 4 is a figure of the esophagus showing a general boundary area between squamous epithelium and metaplastic glandular epithelium; and

FIG. 5 illustrates the metaplastic glandular epithelium being investigated.

DETAILED DESCRIPTION

The prior art has used brushes with endoscopes to sample the examined area by moving the bristles of the brush across the suspect tissue area. Such brushes are similar to those described above which remove cells from the superficial layer, and the bristles do not penetrate below such layer because there is no direct force applied pushing tips of the bristles into the tissue being examined. Further, the prior art brushes merely rub against the surface and the brush area is very limited. The present retractable brush opens to a large size, the bristles thereof directly bear on said tissue transversely thereto and are urged further into said tissue by direct pressure. The brush is then rotated to sample a large area while concurrently reaching through the basement membrane to the basal cell layer.

FIG. 1 is a partial perspective and sectional view of an embodiment of this invention comprising a brush **10** formed of two separate brush sections **12** and **14** hingedly connected together as at **16** and outwardly biased by a spring **17** connected to rigid backbones **18** and **19** to which are attached bristles **20**. The bristles **20** could be of different structures as in order to be more adapted to the environment in which the brushes will be employed. A cylindrical rigid rod **21** passes through a channel **22** in an endoscope **24** having a viewing lens or window **26** shown at the distal end of the endoscope. Endoscopes are commonly provided with channels through the instrument, such as **22** through which medical instruments pass in order to perform certain medical procedures which are employed in conjunction with the observational aspects of the endoscope **24**.

FIG. 2 is similar to FIG. 1 but shows the brush sections **18** and **19** being urged together against the pressure of spring **17** as the brush biopsy device of this invention is withdrawn in the endoscope as shown in dotted lines **28**. Of course, it is understood that FIG. 2 also shows how the brush **10** opens when it is inserted through channel **22** and spring **17** forces the brush sections **12** and **14** to open fully. The area to be sampled is maximized by employing the retractable brush structure which can be narrow when closed to pass through the endoscope but open fully when in position to sample the suspected tissue.

The spring **17** applies a constant biasing force to the brush sections **12** and **14**. In an equivalent structure, the force opening and closing the brush need not be continuous and need only be applied to open and close the brush sections **12** and **14** when they are in the proper position. The rigid rod **21** can be used for this purpose with conventional mechanical or hydraulic linkage. Before the brush is inserted in the patient, it is in a closed position with a distal front tip **26**. The closed brush passes through channel **22**, and the brush sections **18** and **19** are opened after they pass through the endoscope into the examining area. The rigid rod **21** permits direct transverse pressure by the brush bristles against the tissue being examined and enables the brush to be rotated in order to remove cells from the epithelium tissue being examined, arrows **30** and **32** indicating the reciprocating and rotational movement at handle **34** which is transmitted to brush **10** by rod **21**. Handle **34** is located at the proximal end. The rigid construction for backbone **17** and **18** assures a direct transfer of force from the user to the brush bristles **20** in order to effectively operate the brush. The retractable bristles in conjunction with the rigid rod allows a rotating or drilling action to be employed as desired.

As understood from the above, the bristles of the brush can penetrate through the basement membrane of the tissue under examination and reach into the basal cell layer so as to ensure that cells from all three layers are sampled. When the retractable brush closes either before or as it is withdrawn into the endoscope, the brush bristles also close retaining the sample cells. After the device is removed from the endoscope the brush again opens permitting the bristles to be wiped across a suitable carrier for later analysis of the cells deposited on the carrier.

The brush **10** is illustrative of a tissue removing structure, and other tissue removing structures may be employed. The size of the brush can be varied; the number and structure of bristles can be varied; the retractable brush structure can be

varied so that more than one pair of bristles may be employed, all of which would be available to one of ordinary skill in the art seeking to utilize the present non-lacerational cell sampling technique in conjunction with an endoscope. In essence, the retractable front end brush allowing non-lacerational removal of tissue from a desired area by manipulation of a rigid rod passing through a channel in an endoscope provides enhanced benefits to patients who may have suspected lesions without having to perform lacerational biopsies on such patients.

FIG. **3** is a view of a preferred embodiment of this invention showing a conventional endoscope having a channel through which a brush may pass. Although the brush illustrated in FIG. **3** may appear similar to cytological brushes, it is different from cytological brushes in the stiffness of the bristles, enabling a deeper removal of cells from merely the superficial cytological layer. In the prior art, the bristle strength of the brush merely is to brush the exfoliated top surface cells for examination, while in the present invention, the brush is stiff enough to reach in through the basement membrane whether for squamous or glandular epithelium, in order to be certain that the brush biopsy of the invention conducts a biopsy, not merely a superficial cytology. Endoscope **30** has a channel **32** for carrying suitable endoscopic instruments and a channel **34** through which the brush **36** biopsy of this invention is carried. The stiffness of the bristles permits reaching beyond the basement membrane, whether in squamous or glandular epithelium. Reference to reaching beyond squamous epithelium is the subject of parent application, U.S. Pat. No. 6,494,845. Described below is the glandular epithelium structure in order to further understand the biopsy aspects of this invention.

FIG. **4** shows adjacent squamous **40** and metaplastic glandular epithelium tissue **42** at the junction **44** of the glandular epithelium **42** and the normal squamous epithelium **40** in the esophagus **56**. The invention is seeking metaplastic glandular epithelium cells as part of a complete transepithelial biopsy of that area. The glandular epithelium includes columnar cells **48**.

The actual depth of the squamous epithelium **40** is perhaps 350 microns. The depth of the metaplastic glandular epithelium **42** which must be reached in order to do a complete biopsy is approximately 1000 microns. The brush bristle size penetration thus is at least 1000 microns, or approximately 3⁄32nds of an inch.

Referring now to FIG. **5**, a focus of a sample of glandular epithelium in FIG. **4** is shown. There is a basement membrane **52**, and columnar cells **48**. In order to be certain that a complete brush biopsy is performed, the pathologist or the computer will recognize that the brush biopsy has picked up a disaggregated specimen of the whole tissue, and the whole tissue is defined to be at least glandular cells plus basement membrane fragments plus elements of the submucosa. The submucosa exists below the basement membrane **52**. If all elements are in the brush biopsy, the brush biopsy of this invention is the equivalent of a lacerational biopsy which becomes substantially failsafe for medical diagnosis.

Other supplementary evidence of completeness of the biopsy of this glandular portion of the tissue is the fact that, in addition to the cellular disaggregated specimen, there are frequently microbiopsies which show all of the elements and their normal architecture present in this specimen as a function of the tissue itself.

This application as well as the parent application and patents upon which this application depends all describe various retractable endoscopes. Some of the retractable endoscopes have a brush structure which can be opened when the brush is fully inserted in the endoscope in the location in which sampling is to be conducted as illustrated in FIGS. **1** and **2** of this application, while other of the retractable brushes, such as shown in FIG. **3** of this application, have a brush structure which remains unchanged once it is fully inserted into the area in which sampling is to occur. Whether or not the brush structure is of the hinge type as in FIG. **2** or the fixed type as in FIG. **3**, the important aspect of the retractable feature is the ability to insert the brush and guide the brush to the area in which nonlacerational transepithelial sampling is to occur.

Having described this invention with regard to specific embodiments, it is to be understood that the description is not meant as a limitation since further modifications and variations may be apparent or may suggest themselves to those skilled in the art. It is intended that the present application cover all such modifications and variations as fall within the scope of the appended claims.

What is claimed is:

1. An apparatus to be used in conjunction with an endoscope to examine tissue cells located within glandular epithelium, said glandular epithelium comprising tissue at the outermost surface thereof and tissue area below said outermost surface, said apparatus comprising a channel extending the length of the endoscope; said apparatus comprising a rod passing through said channel having a distal and a proximal end; a retractable non-lacerational brush attached to the distal end of the rod, said brush being movable to bear against the tissue being examined and being controlled by said rod to remove tissue from a tissue area being examined, said brushing apparatus comprising bristles which exert sufficient pressure to dislodge cells and to pick up a specimen from said uppermost surface and said tissue area therebelow.

2. An apparatus as set forth in claim **1**, wherein said brush bristles are at least 1000 microns in length.

3. An apparatus as set forth in claim **1**, wherein said specimen picked up comprises a disaggregated specimen.

* * * * *

US006258044B1

(12) **United States Patent**
Lonky et al.

(10) **Patent No.: US 6,258,044 B1**
(45) **Date of Patent: *Jul. 10, 2001**

(54) **APPARATUS AND METHOD FOR OBTAINING TRANSEPITHELIAL SPECIMEN OF A BODY SURFACE USING A NON-LACERATING TECHNIQUE**

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(73) Assignee: **Oralscan/Trylon Joint Venture**, Suffern, NY (US)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/360,425**

(22) Filed: **Jul. 23, 1999**

Related U.S. Application Data

(60) Provisional application No. 60/093,910, filed on Jul. 23, 1998.

(51) **Int. Cl.**[7] **A61B 10/00**
(52) **U.S. Cl.** **600/569**; 600/562
(58) **Field of Search** 600/562, 569, 600/570; 604/1; 606/161; 15/DIG. 6, 206, 207.2

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,675,572	*	4/1954	Nomiya	15/164
2,839,049		6/1958	MacLean	600/569
2,955,591		10/1960	MacLean	600/569
4,227,537	*	10/1980	Suciu et al.	600/569
4,759,376	*	7/1988	Stormby	128/756
4,873,992	*	10/1989	Bayne	600/569
5,067,195	*	11/1991	Sussman	15/167.001
5,184,626		2/1993	Hicken	600/569
5,257,182		10/1993	Luck et al.	382/224
5,623,941	*	4/1997	Hedberg et al.	600/569
5,713,369	*	2/1998	Tao et al.	600/569
5,761,760	*	6/1998	Dumler et al.	15/206
5,937,870	*	8/1999	Gueret	132/218

* cited by examiner

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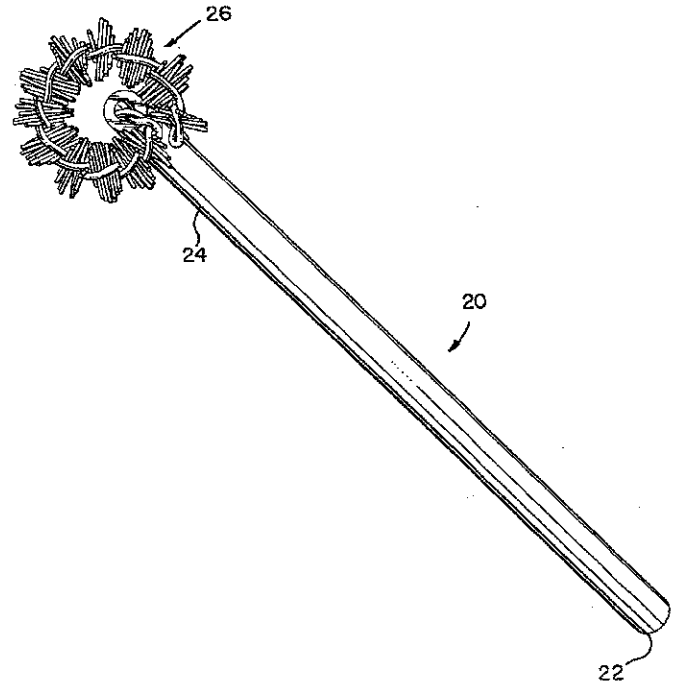
Assistant Examiner—Charles Marmor, II
(74) *Attorney, Agent, or Firm*—Levisohn, Lerner, Berger & Langsam

(57) **ABSTRACT**

A non-lacerational technique to collect cells in an oral mouth cavity utilizes a brush with bristles which have an abrading surface and collect cells from the superficial, intermediate and basal layers of the oral tissue.

39 Claims, 8 Drawing Sheets



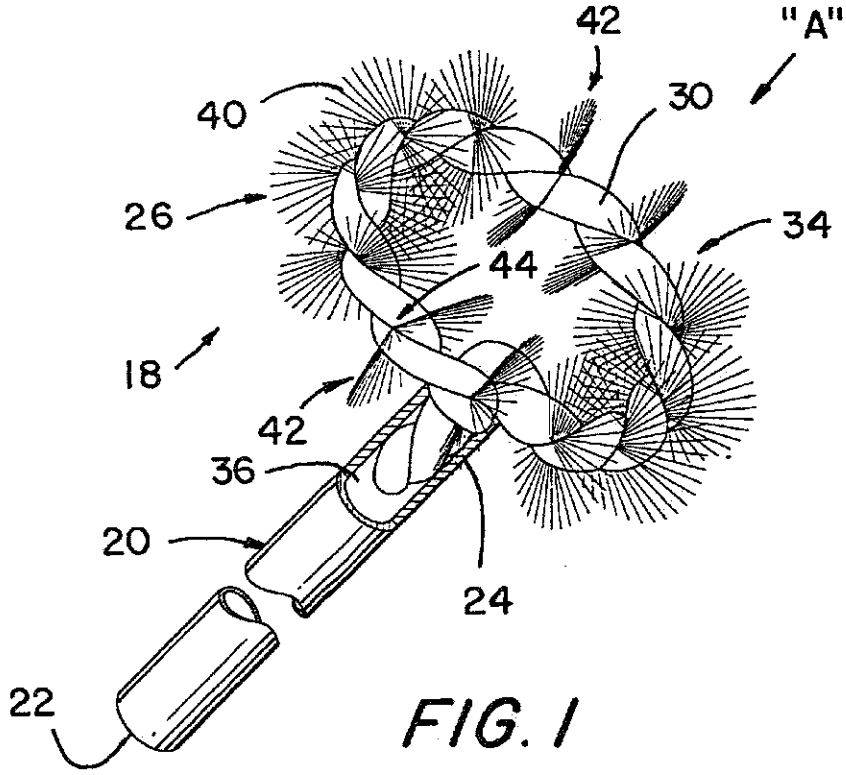


FIG. 1

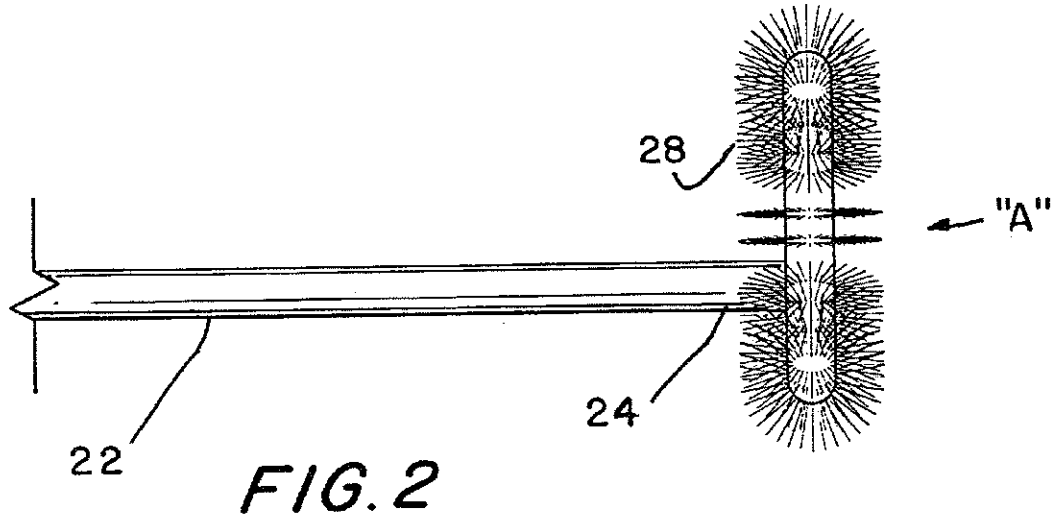


FIG. 2

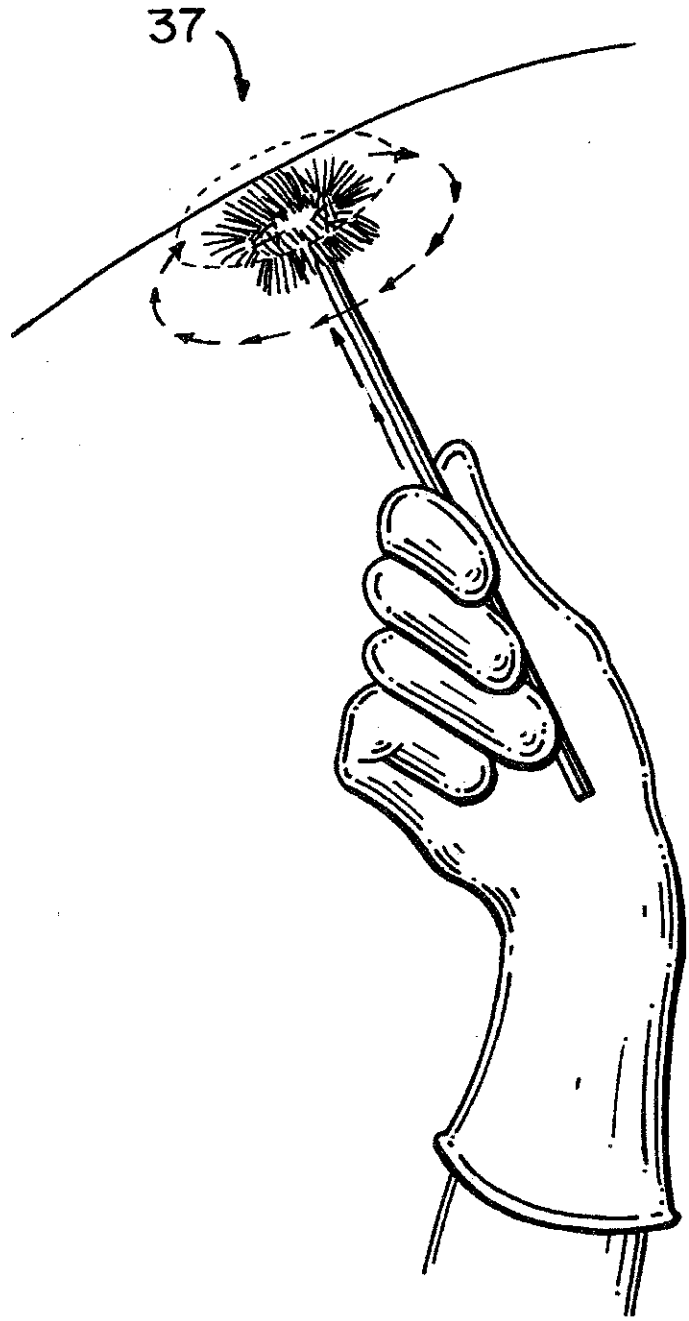


FIG. 3

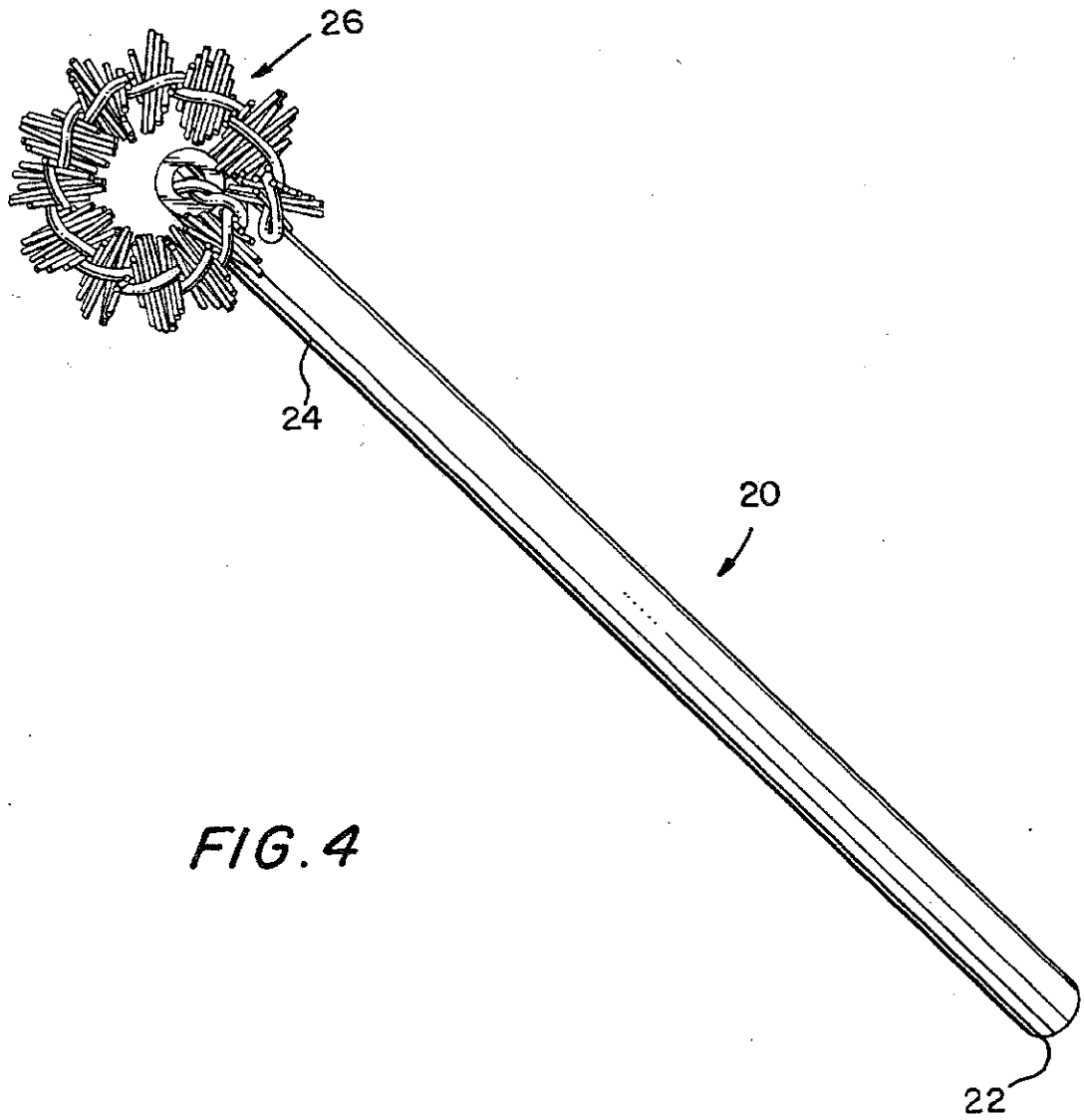


FIG. 4

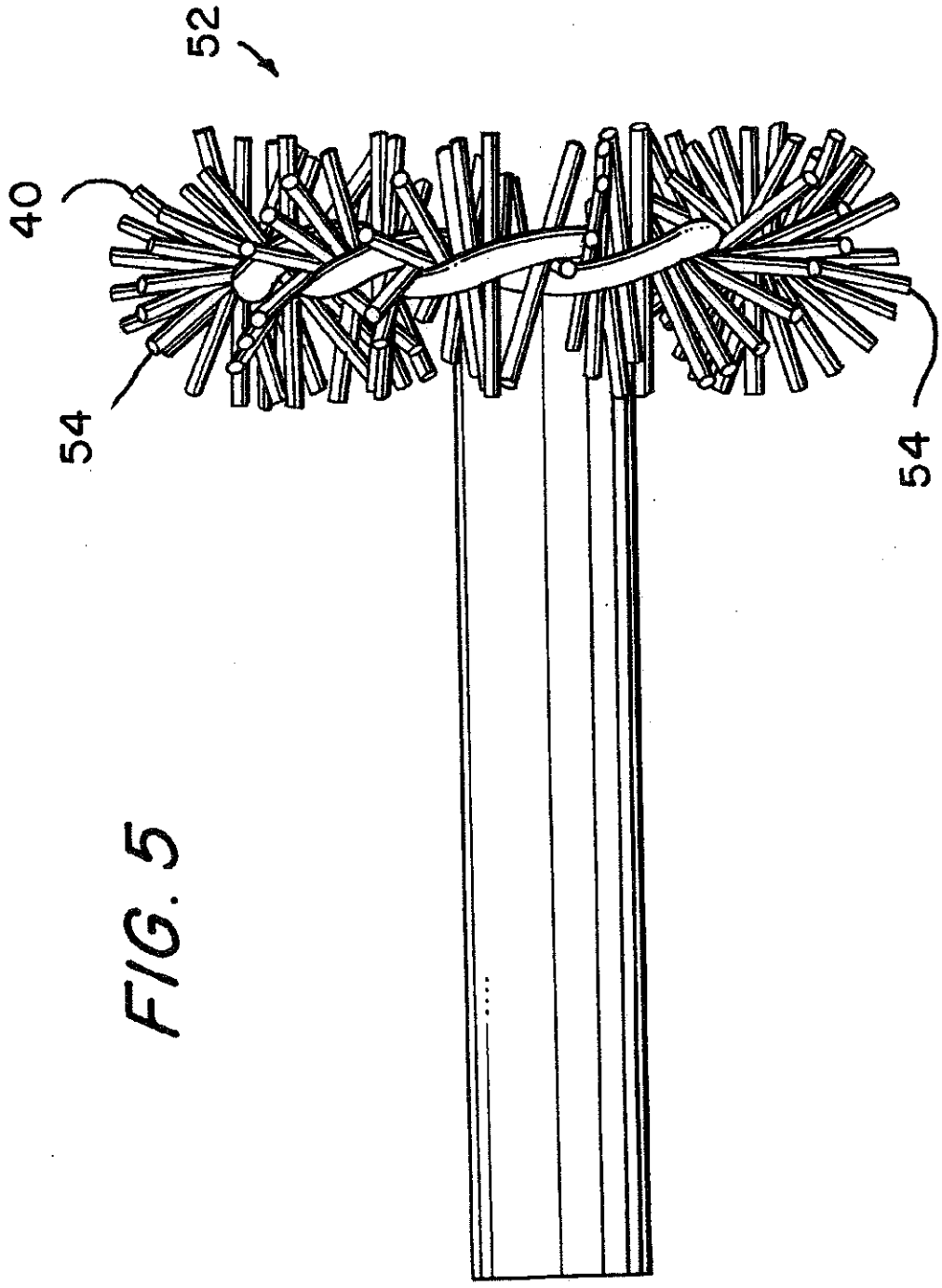
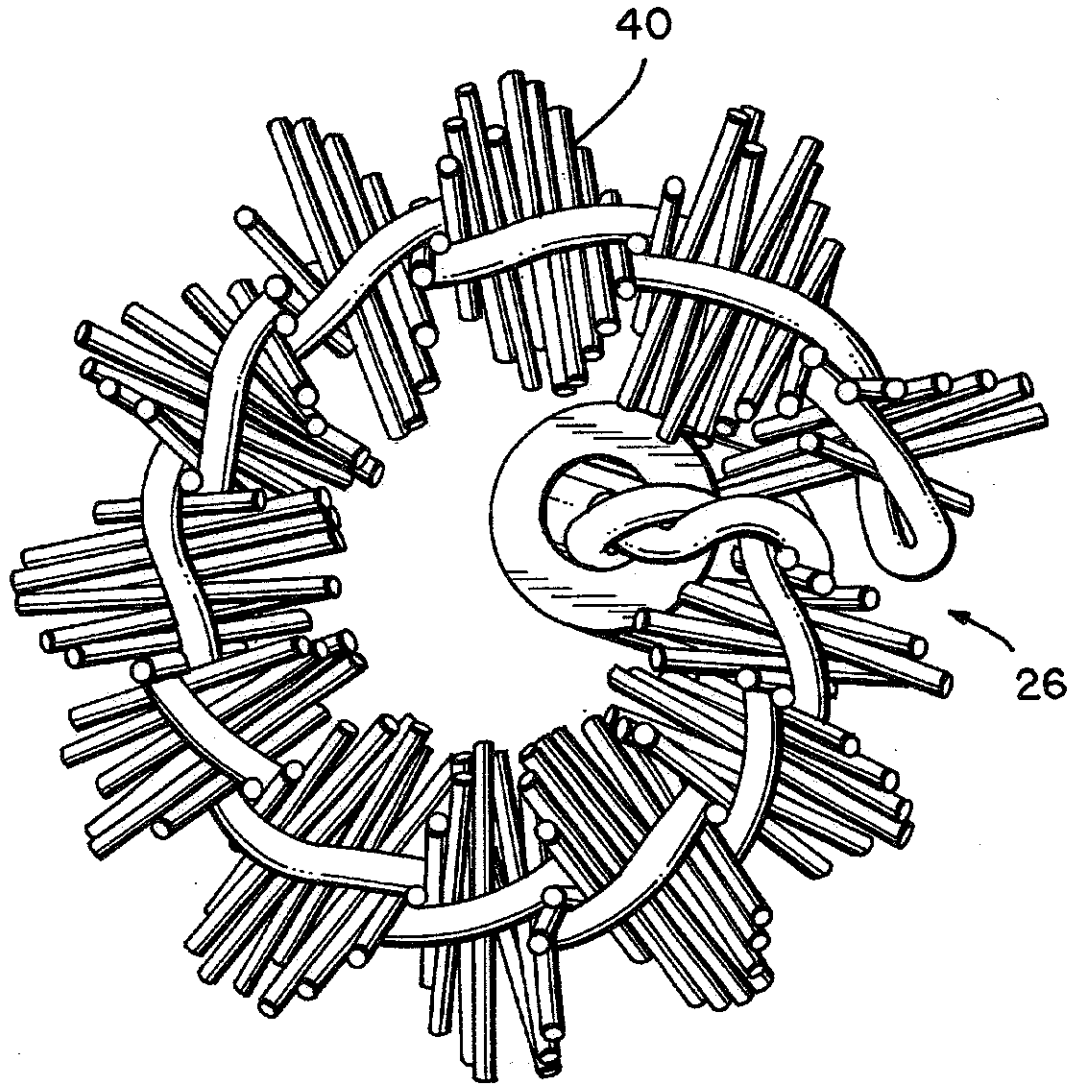


FIG. 5

FIG. 6



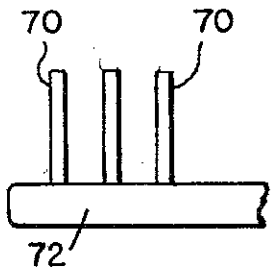


FIG. 7

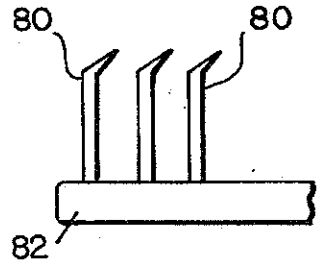


FIG. 8

FIG. 9

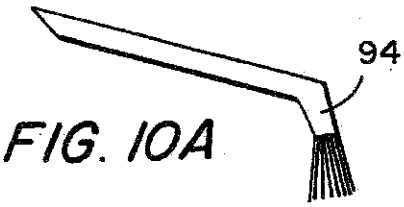


FIG. 10A

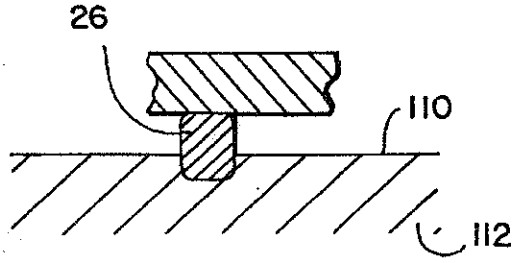


FIG. 11

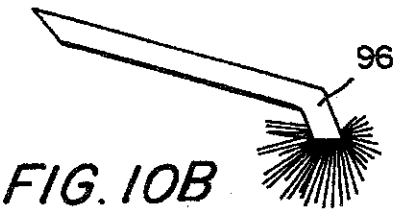


FIG. 10B

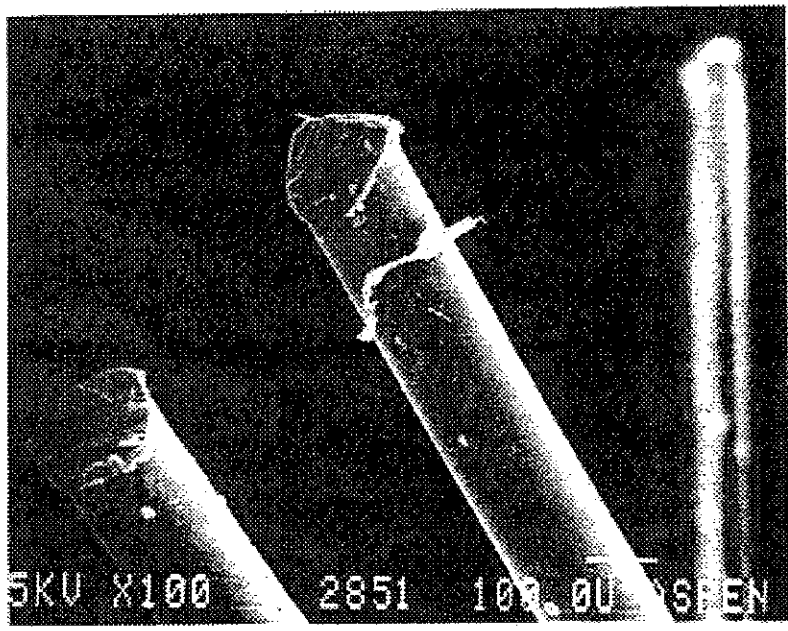


FIG. 12A

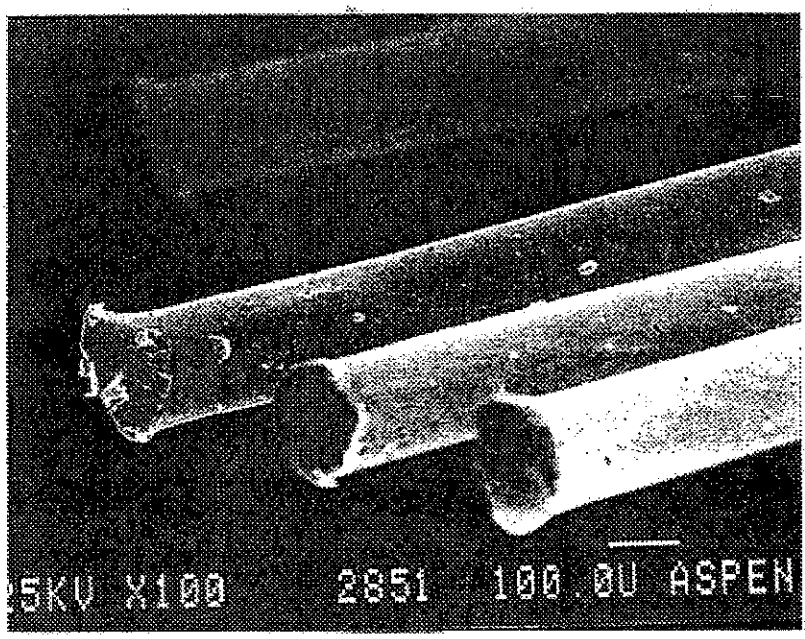


FIG. 12B

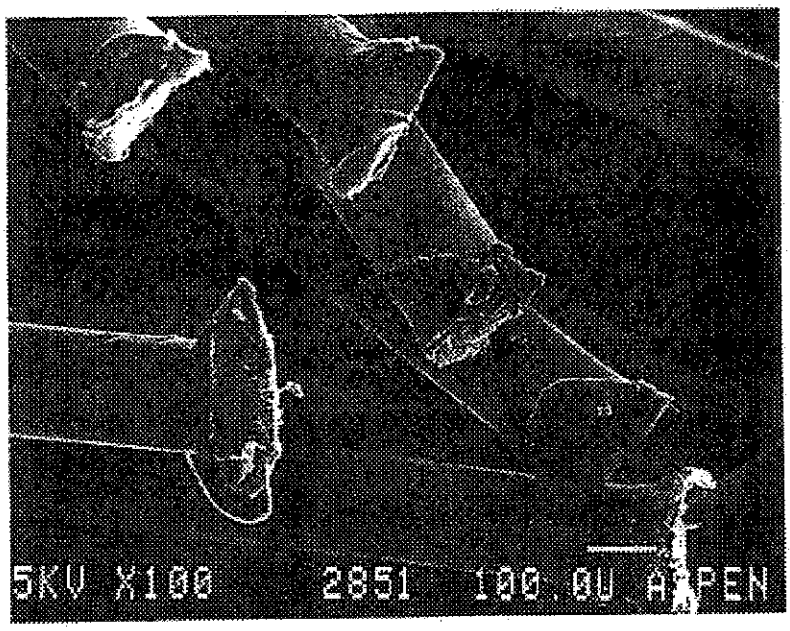


FIG. 13A

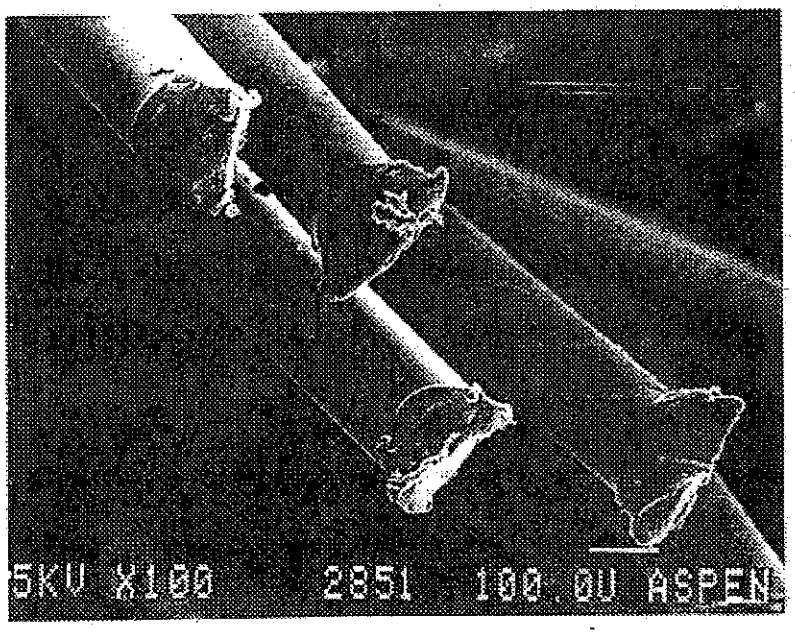


FIG. 13B

APPARATUS AND METHOD FOR OBTAINING TRANSEPITHELIAL SPECIMEN OF A BODY SURFACE USING A NON-LACERATING TECHNIQUE

This application claims the priority of U.S. provisional application Ser. No. 60/093,910 filed Jul. 23, 1998.

FIELD OF THE INVENTION

The present invention is directed to a method and apparatus for obtaining transepithelial specimens of body surfaces using a non-lacerating technique. Specifically, the invention is directed to tools for sampling squamous epithelium from lesions found in the oral cavity and in similar body tissues. The invention is also directed to an improved method of testing all lesions that involve the epithelium of the oral cavity and/or similar body tissues.

BACKGROUND OF THE INVENTION

Cancers of the oral cavity and pharynx are a major cause of death from cancer in the U.S., exceeding the U.S. death rates for cervical cancer, malignant melanoma and Hodgkin's disease. According to the American Cancer Society's Department of Epidemiology and Surveillance, an estimated 30,750 new cases of oral cancer were diagnosed in the U.S. during 1997, a figure which accounts for 2% to 4% of all cancers diagnosed annually.

Despite advances in surgery, radiation, and chemotherapy, the mortality rate of oral cancer has not improved in the last 20 years. Ultimately, 50% of patients die from their malignancy, and 8,440 U.S. deaths were predicted for 1997. There are several reasons for the high mortality rate from oral cancer, but undoubtedly, the most significant factor is delayed diagnosis. Studies have demonstrated that the survival and cure rate increase dramatically when oral cancer is detected at an early stage. For example, the 5-year survival rate for patients with localized disease approximates 79% compared to 19% for those with distant metastases. Unfortunately, approximately two thirds of patients at time of diagnosis have advanced disease, and over 50% display evidence of spread to regional lymph nodes and distant metastases.

Delay in the diagnosis of oral cancer is often the result of the limited diagnostic tools available in the prior art. The dentist or physician who detects an oral lesion which is not clearly suggestive of a precancer or cancer clinically, and who is limited to the prior art tools and methods, is faced with a quandary. Approximately 5–10% of adult patients seen in a typical dental practice exhibit some type of oral lesion, yet only a small proportion (approximately 0.5% to 1%) are precancerous or cancerous. These oral lesions are commonly evidenced as a white or reddish patch, ulceration, plaque or nodule in the oral cavity. The overwhelming majority of these lesions are relatively harmless; however, the multitude of poorly defined lesions in the oral cavity can be confounding to the clinician. A diverse group of oral lesions may be easily confused with malignancy, and conversely, malignancy may be mistaken for a benign lesion. Benign tumors, reactive processes, traumatic lesions, oral manifestations or systemic diseases, inflammatory oral disorders, and bacterial, viral and fungal infections all display similar oral features thereby impeding establishment of an accurate clinical diagnosis.

The only reliable means currently available in the prior art to determine if a suspect oral lesion is pre-cancerous or cancerous, is to incise or excise (i.e. lacerate) the lesion surgically with either a scalpel or a laser so that a histological section of the removed tissue can be prepared for microscopic evaluation. Histology can be generally defined as the microscopic inspection or other testing of a cross section of tissue. This prior art form of oral surgical biopsy is generally performed by a surgeon, and is often inconvenient, painful, and expensive. Furthermore, since the greatest number of oral cancers develop on the lateral border of the tongue and floor of the mouth, the difficulty and potential complications of biopsying these lesions, including pain, bleeding, and scar formation, can be significant. Not infrequently, biopsy is delayed either by the patient due to fear of the procedure, or by the clinician due to technical difficulty in obtaining an adequate specimen.

Since the majority of oral abnormalities detected clinically prove benign when tested microscopically, and given the limitations of biopsy, including cost, inconvenience, pain and potential for complications, relatively few oral lesions are subjected to biopsy. It is primarily for this reason that only oral lesions with clinical features strongly suggestive of cancer or precancer are referred for biopsy as described in the prior art. As a result, many patients with ominous, but visually less suggestive lesions are allowed to progress to advanced oral cancer, with their condition undiagnosed and untreated.

In many body sites, but not the oral cavity, a technique known as cytology is commonly utilized as an alternative to performing a lacerating biopsy and histological evaluation. In these body sites, pre-cancerous and cancerous cells or cell clusters tend to spontaneously exfoliate, or "slough off" from the surface of the epithelium. These cells or cell clusters are then collected and examined under the microscope for evidence of disease.

Since prior-art cytology is directed towards the microscopic examination of spontaneously exfoliated cells, obtaining the cellular sample is generally a simple, non-invasive, and painless procedure. Exfoliated or shed cells can often be obtained directly from the body fluid which is contiguous with the epithelium. Urine can thus be examined for evidence of bladder cancer, and sputum for lung cancer. Alternatively, exfoliated or shed cells may be obtained by gently scraping or brushing the surface of a mucus membrane epithelium to remove the surrounding mucus using a spatula or soft brush. This is the basis for the well known procedure known as the Pap smear used to detect early stage cervical cancer.

Because of the ease by which a cellular sample can be obtained from these body sites, prior-art cytology is typically utilized to screen asymptomatic populations for the presence of early stage disease. In the cervical Pap smear, for example, the entire surface area of the cervical regions where cancer generally occurs is gently scraped or brushed to collect and test the mucus from those regions. Abrasion of the underlying cervical epithelium is undesired, as it can cause bleeding and discomfort to the patient. This procedure is thus typically performed when no particular part of the cervix appears diseased, and when no suspect lesion is visible.

The design of prior art cytology sampling instruments reflects their use to sweep up cells which were spontaneously exfoliated and present on the superficial epithelial surface. Since prior-art cytology brushes need only to gently remove surface material, they are designed of various soft materials which can collect the cervical mucous with minimal abrasion to the underlying epithelium. These cytology sampling instruments therefore either have soft bristles, soft

flexible fimbriated or fringed ends, or even, as in the case of the cotton swab or spatula, no bristles at all.

Examples of prior art cytological sampling tools include the wooden, metal or plastic spatula. According to the traditional method of Pap smear sampling, the spatula is placed onto the surface of the cervix and lightly depressed or scraped across the surface of the cervix to pick up exfoliated cells.

Further examples of prior art cytological sampling tools include the Cytobrush®; a device which uses soft and tapered bristles to sample shed cells from the cervical canal. U.S. Pat. No. 4,759,376, which allegedly covers this product, likewise describes a conical tapered soft bristle brush (a mascara brush shape) which is placed into the cervical canal and rotated for endocervical sampling. U.S. Pat. No. 4,759,376 teaches that the bristles "are to be relatively soft such as that of a soft toothbrush to more readily bend and avoid damaging the tissues." By way of further example, physicians have long used the common swab, commercially known as the Q-Tip®, to perform endocervical sampling.

Other prior art cytological sampling tools designed to obtain a cytological sample from the cervix may combine both endocervical and exocervical sampling regions into one device. These devices swab the surface of mucous-covered tissue by soft brushing the mucous layer of the endocervix and exocervix at the same time, thereby collecting the cells contained in the mucous layer tissue of those surfaces. These devices include the Unimar®-Cervex Brush™, a brush that has a contoured flat comb-like head with a single layer of flexible plastic bristles (similar to a flat paint brush having only one row of bristles) in which the center bristles are longer than the bristles on the ends. According to the method of use for the device, the center bristles are inserted into the cervical canal until the lateral bristles bend against the exocervix. The device is then removed and the cells are swabbed across a microscope slide similar to painting with a paintbrush.

Similarly, the Bayne Pap Brush™, which Medical Dynamics, Inc. represents is covered by U.S. Pat. No. 4,762,133, contains a center arm, made of soft DuPont bristles, running horizontal to the cervical canal and a second arm of soft bristles at ninety degrees to the first arm, creating an L-shape. The center arm is placed within the cervical canal and then rotated. Upon rotation, the soft bristles of the second arm automatically sweep the surface of the exocervix in a circular motion thereby sampling the exocervix along with the endocervix.

Although cytology has been adopted for use in several other body sites, it has not been found useful to test questionable lesions of the oral cavity. This is in large part due to the fact that the prior art devices and methods used to obtain a cellular sample for cytology are unsatisfactory when used to sample lesions of the oral cavity and similar epithelia. Unlike the uterine cervix, questionable lesions of the oral cavity and similar epithelia may be typically coated with multiple layers of keratinized cells. This "keratin layer" forms a relatively hard "skin-like" coating over the surface of the lesion and may thus hide the abnormal cells lying underneath it and prevent their exfoliation from the surface.

As noted above, the design of prior art cytology sampling instruments reflect their use in tissues where spontaneously exfoliated abnormal cells are commonly present on the surface of an area of epithelium that harbors disease. These cytology sampling instruments therefore either have soft bristles, soft flexible fimbriated ends, or even no bristles at all. Since prior-art cytology brushes only need to gently remove surface material, they are designed of various soft materials which can collect the cervical mucous with minimal abrasion to the underlying epithelium.

While abnormal cells can spontaneously exfoliate to the epithelial surface and be gently removed by prior art instruments in the uterine cervix and other similar tissues, in many oral cavity lesions the abnormal cells never reach the surface because they are blocked by the keratin layer. This limitation is a major cause of the high false negative rate of prior art cytological testing to detect lesions of the oral cavity. That is, a large proportion of oral lesions found to be positive using lacerating biopsy and histology are found to be negative using cytology. In one major study, this false negative rate was found to be as high as 30%.

It is largely due to this lack of correlation between histology and prior art oral cytology that there is currently no significant use of oral cytology in the United States or elsewhere to test questionable oral lesions. Since it is well known that dangerous, truly cancerous oral lesions may commonly be reported as "negative" using prior art cytologic sampling techniques, prior art cytologic techniques offer little as a reliable diagnostic alternative to the lacerating biopsy and histology.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide an apparatus and method for sampling epithelial cells from the anatomy without the pain or injury of lacerational biopsies.

It is a further object of the present invention to provide an apparatus for sampling epithelial tissue in the oral cavity, the vulva, and similar keratinized epithelia.

It is a further object of the present invention to provide a non-lacerating apparatus for readily sampling cells from all levels of a surface epithelial lesion, including the basal, intermediate and superficial layers of the lesion.

It is a further object of the present invention to provide an apparatus for sampling cells from the entire surface of a lesion, to completely sample a suspect lesion which may be multifocal.

Further objects of the invention will become apparent in conjunction with the disclosure herein.

In accordance with the present invention, an apparatus is provided for sampling all types of epithelium, particularly squamous epithelium, from lesions found in the oral cavity, the vaginal cavity, and other similar keratinized epithelia. Further in accordance with the invention, an improved method is provided for testing questionable lesions found in the epithelium of the oral cavity and other body tissues. The method invented involves exerting sufficient pressure in the lesion area with a surface or edge capable of dislodging cells in and under a keratinized layer.

For purposes of this patent application, the prior art scalpel procedure is defined as lacerational, whereas the novel invention herein is non-lacerational and therefore minimally invasive. To the extent that an abrasive brush has characteristics that may cause minor discomfort and/or bleeding, there is substantial difference between the prior art scalpel trauma and the minimal trauma associated with the present invention.

In accordance with the present inventions, focal sampling of questionable lesions of the oral cavity and of similar epithelia is provided using a specialized, stiff-bristled, brush device disclosed herein. By rubbing harder than normal cytological sampling, and using a device which penetrates

epithelium but not very deep on each stroke, one can reach to the basement membrane without lacerating. As opposed to the prior art, use of the device allows cell sampling which can readily and consistently produce a transepithelial cytologic sample. That is, by utilizing the invention disclosed herein, cells can readily and consistently be obtained from all levels of the epithelium (basal, intermediate and superficial) of a suspect lesion, thus overcoming the limitation in the prior art of abnormal epithelial cells being inaccessible to cytology for a variety of reasons, including because they are covered by a keratin layer. The resulting cellular sample functionally approximates the cellular sample of a lacerating biopsy device, but is obtained with the ease of a swab application, and without discomfort to the patient. The subject invention therefore makes practical the routine testing of questionable lesions of the oral cavity, thus allowing early detection and treatment of oral cancer and pre-cancer. Furthermore, the invention can be utilized in testing benign neoplasms, a diverse group of inflammatory oral diseases such as pemphigus and lichen planus, oral lesions which represent manifestations of systemic diseases such as nutritional deficiencies and anemia, viral, bacterial, and fungal infections, reactive and traumatic processes, and chromosomal sex determination.

While the preferred embodiment has been described with respect to a brush, the present invention generally describes a method and apparatus for obtaining transepithelial specimens of a body surface. The invention relates to a non-lacerational method and apparatus to obtain such a specimen. The reason one seeks to obtain a transepithelial sample is because suspect cells appearing at the superficial layer of the epithelium originate at the basal layer within the tissue. With respect to the oral cavity, basal cells originate in the general area of the basement membrane separating the epithelial tissue from the tissue below the membrane known as the submucosa. In determining whether or not a patient has a precancerous or cancerous condition, it is important to reach down to the basement membrane and slightly therebelow because metastases may be suspected depending on the cellular architecture existing at just below or at the basement membrane through to the superficial layer.

Alternate ways to obtain such a transepithelial specimen without laceration include electromagnetic, optical, microwave, ultrasound, mechanical and chemical. With regard to chemical, it is possible that the enzyme hyaluronadase could be used since this chemical could separate the epithelium from between the basement membrane. If one could actually obtain the entirety of a transepithelial layer, the cell architecture would be readily apparent, but such an approach would also materially harm the patient. Therefore, obtaining a more limited specimen and collection of cells is what is desired, and the preferred embodiment of using the brush is identified.

In accordance with the present invention, a toroidal or donut shaped brush is provided for cell sampling, as disclosed below. The brush provides a more complete sampling of the epithelium than the brushes of the prior art. In accordance with the present invention, a method is further provided for sampling epithelial cells. According to the method, the brush of the present invention may be rotated against or brushed parallel to, an epithelial surface, to burrow into and deeply sample epithelial cells. A rotation motion or other scrub motion essentially operates to scrub across the lesion thereby causing cells to be lifted from the surrounding tissues and adhere to the bristles of the brush.

The structure of the brush and bristles including the stiffness thereof as well as the shape of the bristle tips contribute to the effectiveness of the brushing or scrubbing action in retrieving cells from the transepithelial layers. The shape of the bristle tips is determined by the bristle cutting process. The bristle tips, preferably, have scraping edges.

The tips of the brush and the brush itself may be considered as an assemblage of pentrating edges.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a perspective view of an apparatus for sampling epithelial tissue in accordance with the present invention.

FIG. **2** is a side view of the apparatus for sampling epithelial tissue shown in FIG. **1**.

FIG. **3** is a perspective view of using the brush of the present invention to sample a lesion, in accordance with the method of the present invention.

FIG. **4** is an enlarged perspective view of the brush of this invention.

FIG. **5** is a side view of the enlarged view of the brush of this invention shown in FIG. **4**; and

FIG. **6** is an end view showing the bristles of the brush shown in FIG. **4**.

FIGS. **7** and **8** are side views of alternate structures for the bristles showing the bristle tips.

FIG. **9** is a side view of an alternate structure for abrading.

FIGS. **10**A and **10**B are alternate brush structures.

FIG. **11** is a sectional view of the tissue in the oral cavity showing the brush penetrating the basement membrane and reaching to the submucosa.

FIGS. **12**A and **12**B are electron microscopic enlargements of the blunt or square cut bristle ends.

FIGS. **13**A and **13**B are electron microscopic enlargements of the wedge or chisel cut bristle ends.

DETAILED DESCRIPTION OF THE INVENTION AND THE PREFERRED EMBODIMENTS

FIGS. **1**–**3** were submitted with the original provisional patent application. FIGS. **4**–**6** are more detailed and more accurate representations of the brush and bristle structure including its specific construction. Submitted in this detailed description are photographs taken by an electron microscope of the ends of the bristles further illuminating the structural aspects of the bristles which contribute to the effectiveness of the brush in obtaining transepithelial samples.

A preferred embodiment of the invention is provided in FIG. **1**. In accordance with the invention, a device **18** is provided which comprises a handle or elongate member **20**, having both a proximal end **22** and a distal end **24**. In the preferred embodiment, the total length of the device is approximately six inches.

Handle **20** is designed for gripping by a user, and is of a sufficient length to allow the user to manipulate the device within a body cavity from a location just outside the body. In the preferred embodiment, handle **20** is semi-rigid so as to assist in reaching the target tissue notwithstanding difficult angles or narrow passages. In the preferred embodiment, the handle is approximately 5 inches long.

The brush handle can be constructed of a plastic, such as polypropylene, or any other suitable semi-rigid material. The handle can be solid, but is hollow in the preferred embodiment. It is further preferred that handle **20** also have at least one area whose cross-section is substantially circular such that the elongate member may be readily twirled

between the thumb and forefinger while pressed against a lesion. Another way to reach areas that are somewhat difficult in the oral cavity would be to hold the handle short and rotate and scrub the side of the brush, rather than its end, against the lesion area. This will also be effective in the brush bristles passing through the transepithelial layers to retrieve cells in the lesion area.

At or around the distal end **24** of the handle or elongate member **20**, the device is provided with a brush head **26**. Brush head **26** is preferably a substantially toroidal or "donut" shaped brush which presents bristles both towards its end and side, and can be formed from one or more twisted or braided wires, backbone or cables **30**. Wires or cables **30** are preferably secured to handle **20** by affixation to backbone or the wire **30** in a recess **36** located in the distal end **24** of the handle. The brush can be formed from conventional twisted wire brush construction. In a preferred embodiment, the total length of the twisted wire is approximately 1.1 inches, with approximately 0.2 inches inserted in the handle, and approximately 0.9 inches exposed as part of the toroid.

Wires or cables **30** are preferably bent to form an incomplete toroid **34** which is perpendicular to the longitudinal axis of handle **20**. In other words, toroid **34** preferably defines a circular plane, the plane being provided perpendicular to the longitudinal axis of the handle **20** of brush head **26**. Alternatively, a cross-section of the brush forms a nautilus or spiral shape at ninety degrees to the handle or elongate member **20**. The brush could be curled into an outward spiral in the same plane. The metallic spine of the brush spirals out in a plane which is perpendicular to the handle. This is more clearly seen in FIGS. **4–6**.

Brush head **26** may be integral with handle **20**, or may be detachable. It may be a reusable sterilizable or surgical holder. Alternatively, the proximal end **22** of the handle **20** may be detachable from the distal end **24**. The detachable portion of the brush may be scored, to easily break away, may be provided with screw threads to screw off the remainder of the device, or so forth. In either embodiment, detachment of either the brush head or of a portion of the handle connected to the brush head, can allow the distal end of the brush, having sampled cells collected therein, to be separated from the proximal end. This allows the handle or the proximal end thereof to be discarded while the distal end of the apparatus is forwarded to the laboratory for analysis. The bristles are also used to collect cells as well as perform the transepithelial activity. For example, the distal portion of the device can be dropped into a transfer solution, while the proximal portion is thrown away.

Brush head **26** is further provided with a plurality of bristles **40**. In the preferred embodiment, bristles **40** are approximately 0.25 inches from tip to tip, protrude 0.05–0.2 inches from the toroidal wire and have a stiffness of between 0.04–0.2 lbs/inch. The stiffness is better identified as a cantilever or lateral tip deflection stiffness. Each end of the bristle protrudes a distance of about 0.10 inches from the wire spine. The bristles are approximately 0.006 inches (0.16 mm) thick.

Although in the prior art, the sampling brushes provided have been soft brushes with soft bristles, in the present invention, bristles **40** are specifically made stiff or semi-rigid, going against the teachings of the art. As described above, for example, U.S. Pat. No. 4,759,376 teaches that the bristles of the brush should be relatively soft and should readily bend Likewise, the brush disclosed in U.S. Pat. No. 4,762,133, is also meant to be soft, as is it provided for sampling the exocervix along with the endocervix. This preference heretofore in the art to use a soft brush prevents damage to tissue. While this is generally desirable in the cervix, it is not helpful when the lesions are keratinized, as in the oral cavity.

Moreover, sampling below the superficial layer of the epithelium is not known to have been achieved with prior art brushes. In contrast, in the present invention, it is specifically desired to disrupt the tissue of a lesion and penetrate beneath the superficial layer of the epithelium to sample all three epithelial layers. Whereas the prior art brushes are generally designed for the cervix where no keratin is present, the present brush can penetrate through keratin covered lesions to provide a suitable tissue sample. It may be preferable to have a plurality of scratches or furrows in the tissue from the brush, one of which will penetrate the basement membrane over a substantial area of the lesion. In the present invention, each stroke penetrates a little so that the depth of penetration can be controlled by the appearance of spot bleeding.

Accordingly, in the present invention, bristles **40** of brush head **26** are each stiff or semi-rigid. The bristles are preferably made of Tynex® brand nylon laid in a double layer and have a diameter of between 0.010 cm and 0.022 cm. The Tynex® brand bristles have their own cantilever stiffness which may be at a modulus of 500,000 psi. Preferably, the bristles have a diameter of approximately 0.016 cm and protrude 0.10 inches from the wire spine. Although triple and single row densities may be used, double row density bristles are preferred. A range of protruding lengths of 0.08 to 0.16 inches could be used.

Bristles **40** are preferably provided in a series of arrays **42**. As shown in FIG. **1**, each array **42** is composed of a series of bristles **40**, the bristles extending radially from a center **44**, to form each of the arrays **42**. At center **44**, the end of each bristle **40** is secured within the twisted wire **30** backbone.

Arrays **42** preferably extend around the entire perimeter of toroid **34**. In one embodiment, viewing the apparatus head-on, from the perspective "A" in FIGS. **1** or **2**, tufts of bristles are evenly arranged around the perimeter of the toroid. Thus, the arrays are arranged at 30 degrees spacings along the twisted wire of the brush head.

The bristles do not form a plane, but rather preferably extend upward from center **44** at an acute angle to wire **30**. As a result of this bristle orientation, rotation will result in a degree of bristle abrasion that is effected by the bristles splaying under load. Rotation in the opposite direction will result in abrasion that is greatly accentuated by maximizing the direct piercing of the skin with the stiff bristle ends. While the unique drilling combination of bristle pressure, tip shape, stiffness, brushing and rotation results in provision of the trans-epithelial cytologic sample of the lesion as noted above, rotation in the direction which moderates direct surface piercing by the bristle ends (clockwise, in the case of the preferred embodiment) allows this trans-epithelial cytologic sample to be obtained with minimal discomfort to the patient.

Further, an advantage and feature of this invention achieved with the brush is that a rather large area around the lesion area is subject to the action of the brush which enhances the cell collection process to provide a more effective sampling.

The photographs of FIGS. **12A–12D** are electron microscope enlargements of the front edge or tips of the bristles of this invention. The tips of the bristles provide good scraping or cutting surfaces. These scraping or cutting

surfaces help to dislodge the cells from the surrounding tissue to be collected on the bristles. The sharp edges do not dig too deeply into the epithelial tissue and avoid severe injury.

FIGS. **7** and **8** are cross sectional views of alternate brush structures with the front edges of the bristles **70** being squared as in FIG. **7** or "file card wire brush type edges" **80** which are aligned as in FIG. **8**. The squared britles of FIG. **7** form non-penetrating scraping edges and even generate negative rake angles when the bristles bend over. Both brushes are attached to handles **72** and **82** respectively. It is preferable to have a large number of such bristles to spread the pressure as the brush structure is being used. An alternative structure in FIG. **9** illustrates a plurality of small rigid scrapers **90** which could be employed at the edge of the brush and attached to handle **92**. Such scrapers would extend from handle **92**.

FIGS. **10**A or **10**B illustrate conventional brush arrangements **94** and **96** adjoined to a handle allowing end or side pressure. These brushes can be rubbed back and forth to dislodge and remove the cells for their collection. A plurality of different abrasive materials such as finely ribbed or bumpy materials could be employed, where the protrusions may be shaped with edges to apply highly localized pressure, and catch against cell clusters rather than sliding over them. FIGS. **4** through **6** are respectively perspective side and end views of an enlargement of the brush of this invention. The bristles **40** are seen collected and captured in the metallic wire **30** to form a relatively irregular surface although the side view in FIG. **5** illustrates that the front plane **52** of the brush head **26** presents a relatively flat planar surface. In use, only the outer front plane **52** or the edge planes **54** of the brush head will be used to retrieve cells from the epithelial tissue structure. The following is a list of alternative models for materials which could sample cells. Such materials would generally not be introduced into a patient's mouth.

Abrasive Materials/Tools	
brillo pad, fine steel wool pad	
gauze, sterile pads,	
file, pumice,	
sponges, loofah	Brushes
velcro, hook and loop	radial Dremel brush
cotton swab with salt, steel wool or	bristle brush
glass fiber	bristles that poke out slightly, similar
cat tongue, shark skin	to 5 o'clock shadow, (light beard)
powder/abrasive	
other types of abrasive put on	
a flexible backing	
	Other
Scraper or File Tools	abrasion other test methods, wear
Metal or plastic blades, file molded	testing rubber ball to squeeze out
out of plastic	material onto slide
toothpick	small pads that have adhesive on
two pronged tool, one to break	them that can be pulled off
layer, one with pad to absorb	chemical process (weak acids)
triangular shaped wire loop, dental	
scraper	
dental burr, regular burr	
fresnel lens like instrument (fine	
molded ridges)	
plastic helix	
file made out of cuttle fish bone	
sintered glass, aerator stone	

The present invention allows for limited space between the points of abrasive contact upon brush rotation, while maintaining enough separation between the bristles to trap a clinically effective amount of cells. The length of the stiff bristles of the brush may also vary but is similarly balanced between: 1) the requirement to keep the bristles stiff enough to grind the tissue into its cellular components during rotation; 2) the requirement that the bristles be long enough to trap the removed cells with these extending 0.1 inch from the wire toroid; and 3) soft enough to bend.

As shown in FIG. **3**, according to the method of the present invention, the flat distal end of the handle of the brush is placed directly on the site of the suspect lesion **37**. The stiff dense bristles are then pushed firmly against the lesion site while the handle is simultaneously rotated clockwise at least once, and preferably several times about its axis. The metal or twisted wire of the brush head assists in the application of pressure to the epithelial surface. The trained user will continue rubbing until pinpoint bleeding is observed.

Rotation of the bristles against the lesion results in the scraping detachment of cells from multiple layers of the epithelium. The detached cells become collected between the stiff bristles and are trapped there. These cells can then be inspected by a suitable laboratory.

The method of the present invention is particularly advantageous due to the fact that, as no laceration of the epithelium is required, the discomfort experienced by the patient is considerably less than that of a surgical biopsy, and is generally minimal. Further, this invention effects sampling over a large area.

The method of the present invention is in contrast to the method of the prior art, in which the technique has been to "sweep" the soft bristles of a brush or other non-abrasive instrument over and across the surface of a lesion. In the present invention, the stiff bristles are pressed down and brushed or rotated into a lesion of potential concern to penetrate or "drill" into the lesion. This drilling presents the ability to thoroughly sample all layers of the epithelium without the necessity of performing a surgical laceration. Specifically, the preferred embodiment's unique combination of: 1) sufficient manual pressure transferred directly by the handle of the device to the interface between the flat surface of the brush and the surface of the lesion; 2) keeping the sharp bristle edge in contact with the epithelium and, 3) rotation of the device, provide this superior "drilling" action in the epithelium which has previously been unknown in the art of cytology. It is this unique drilling action which results in the unique and improved ability of the subject invention to provide a cytological sample of a keratinized lesion which contains cells from all layers of the underlying epithelium. As such, the cytologic sample obtained by the present invention is the functional equivalent of the tissue section type of sample taken by the prior art lacerating biopsy technique, and yet is obtained without the patient discomfort, scarring, and other difficulties potentially associated with a lacerating biopsy.

Moreover, in addition to avoiding patient discomfort and scarring, the present invention poses yet a further advantage over the prior art lacerating technique. In the present invention, a sample can be obtained from the entire surface of a multifocal lesion to provide a broad sample of cells from the entire lesion for further testing. In contrast, in the prior art incision surgical biopsy a tissue core is taken of only a section of a lesion to test the lesion for malignancy. Accordingly, due to the fact that the particular portion of the lesion sampled by the surgical technique may be benign, while a non-sampled portion of the lesion may be malignant,

22. A transepithelial non-lacerational sampling apparatus according to claim 21, wherein said brush is in the form of a spiral shape substantially perpendicular to the axis of said handle.

23. A transepithelial non-lacerational sampling apparatus according to claim 12, wherein said bristles comprise tips, wherein said tips comprise scraping edges.

24. A transepithelial non-lacerational sampling apparatus according to claim 12, wherein said brush comprises a handle, said handle comprises a distal and a proximal end, said brush is connected to said distal end, said bristles of said brush forming an abrasive surface.

25. A transepithelial non-lacerational sampling apparatus according to claim 12, wherein said brush has a round head, said bristles being stiff.

26. A method to collect cells in epithelial tissue of the body comprising:

passing a transipithelial non-lacerational sampling means through the epithelial tissue to collect cells from at least two layers of said epithelial tissue.

27. A method to collect cells in epithelial tissue of the body according to claim 26, wherein said transepithelial non-lacerational sampling means collects cells from three layers of said epithelial tissue, said three layers comprising superficial, intermediate and basal layers.

28. A method to collect cells in epithelial tissue of the body in which a basement membrane is located below said basal layer according to claim 27, wherein said transepithelial non-lacerational sampling means penetrates said basement membrane.

29. A method to collect cells in epithelial tissue of the body according to claim 28, wherein said transepithelial sampling means is rotated and drilled into said tissue.

30. A method to collect cells in epithelial tissue of the body according to claim 28, wherein said transepithelial sampling means is moved substantially perpendicularly into said tissue.

31. A method to collect cells in epithelial tissue of the body according to claim 27, wherein said epithelial tissue comprises oral epithelial tissue.

32. A method to collect cells in epithelial tissue of the body according to claim 27, further comprising abrading the epithelial tissue to collect cells.

33. A method to collect cells in epithelial tissue of the body according to claim 32, wherein said epithelial tissue has a keratinized layer and said cells are collected from beneath said keratinized layer.

34. A method to collect cells in epithelial tissue of the body according to claim 26, wherein said epithelial tissue comprises oral epithelial tissue.

35. A method to collect according to claim 26, further comprising abrading the epithelial tissue to collect cells.

36. A method to collect cells in epithelial tissue of the body according to claim 26, wherein said method comprises the step of exerting sufficient pressure on a scrubbing surface in contact with said epithelial tissue to dislodge cells.

37. Apparatus to obtain cells in epithelial tissue of the body comprising:

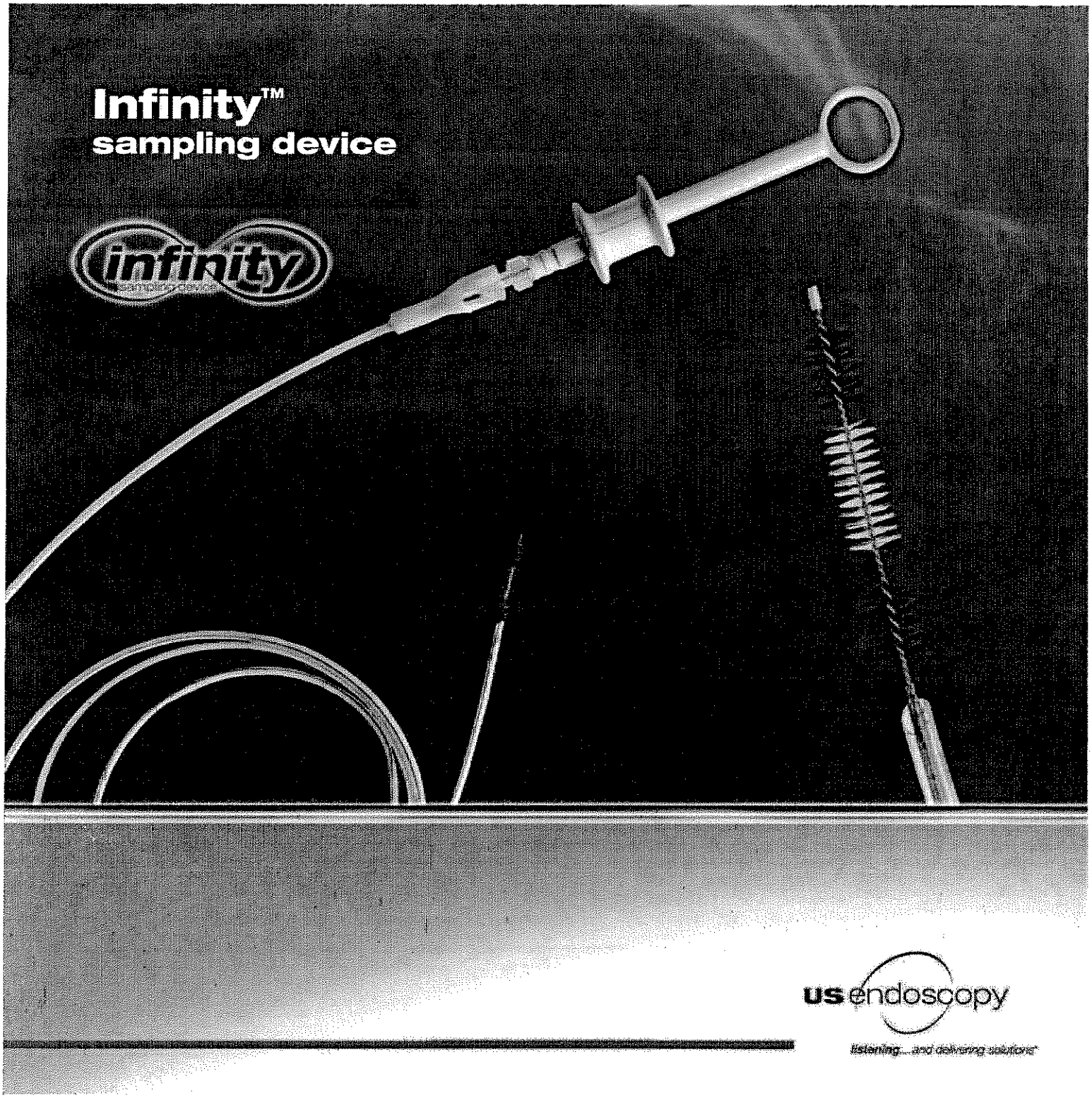
transepithelial non-lacerational sampling apparatus to collect cells from at least two layers of said epithelial tissue, said transepithelial non-lacerational sampling apparatus comprising an assemblage of penetrating edges to penetrate at least said two layers of said epithelial tissue.

38. Apparatus to obtain cells in epithelial tissue of the body according to claim 37, wherein said assemblage of penetrating edges collect cells from three layers of said epithelial tissue, said three layers comprising superficial, intermediate and basal layers, said basal layer separated from the submucosa by a basement membrane.

39. Apparatus to obtain cells in epithelial tissue of the body according to claim 38, wherein said assemblage of penetrating edges penetrates said basement membrane and reach said submucosa.

* * * * *

Exhibit 2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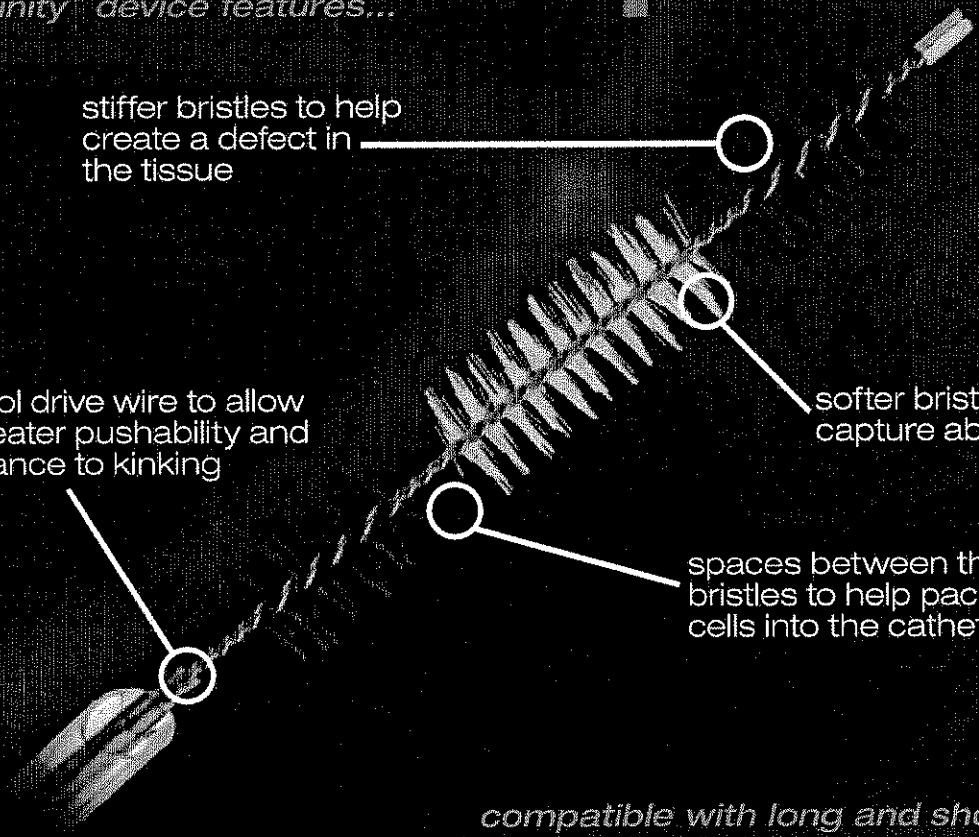

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product number	sheath diameter (mm)	length (cm)	sterile	units/box
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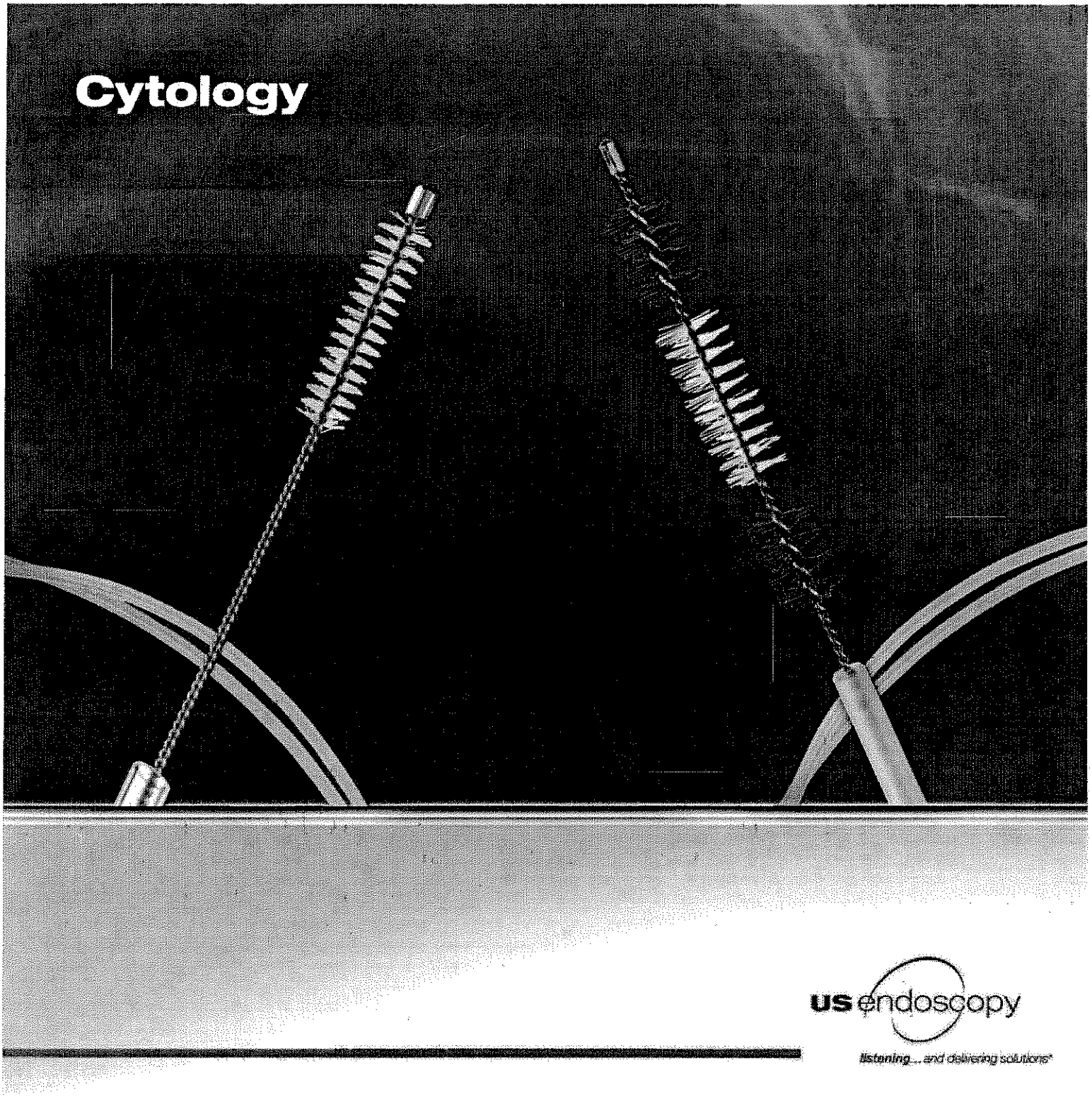
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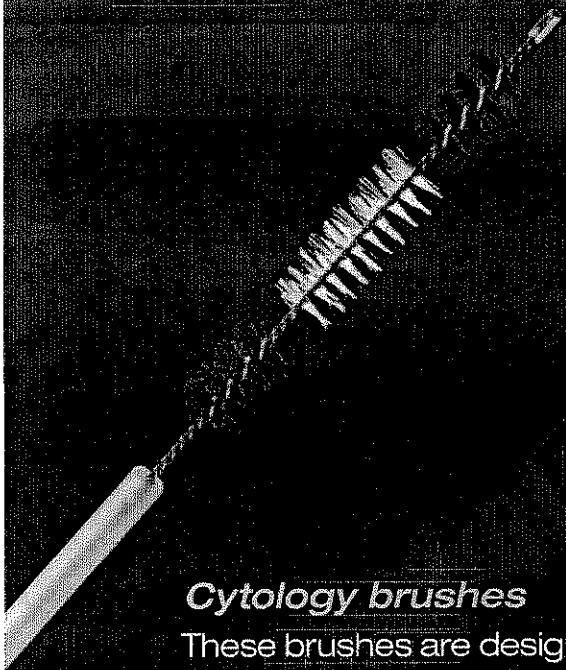

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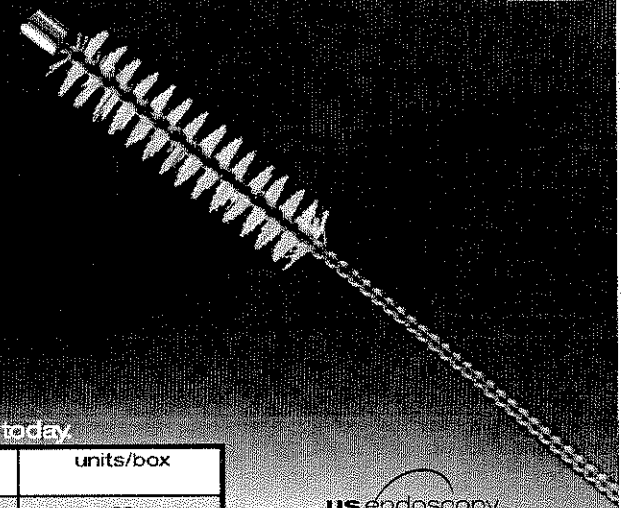
- features a unique bristle configuration
  - stiffer bristles to help create a defect in the tissue
  - softer bristles to capture abraded material
- designed with spaces between the bristles to help pack cells into the catheter



Cytology brushes

These brushes are designed to collect cell samples in the bronchus as well as the GI tract.

- features a rotatable handle to facilitate an abundant sample

For more information on cytology devices, contact US Endoscopy today.

product number	description	sheath diameter (mm)	length (cm)	units/box
00711401	bronchoscope	1.8	120	20
00711402	gastroscope	1.8	160	20
00711403	colonoscope	2.4	230	20
00711405	enteroscope	2.4	350	10
00711499	Infinity® cytology device	2.4	230	5

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