IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the *Inter Partes* Review of: Trial Number: To Be Assigned

U.S. Patent No. 6,258,044

Filed: July 23, 1999

Issued: July 10, 2001 Attorney Docket No.: 22344.04361

Inventor(s): Neal M. Lonky, et al.

Assignee: Oralscan/Trylon Joint Venture

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

Mail Stop *Inter Partes* Review
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PETITION FOR *INTER PARTES* REVIEW UNDER 37 C.F.R. 42.100

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On behalf of U.S. Endoscopy Group, Inc. (“U.S. Endoscopy”) and in accordance with 35 U.S.C. § 311 and 37 C.F.R. § 42.100, *inter partes* review is respectfully requested for claims 1-39 of U.S. Patent No. 6,258,044 ("the ‘044 Patent").

I. OVERVIEW OF THE PETITION

Patentees took a known brush that had been on the market for years, which was even trademarked, and through a series of machinations conjured up a patent. These machinations included simply ignoring a body of prior art and using functional language such as “non-lacerational” and “to collect cells from at least two layers of said epithelial tissue” to side-step the Patent Office and gain issued apparatus claims. (Ex. 1001, Claim 1 of the ‘044 Patent.) Numerous prior art references anticipate and render obvious the claims of the ‘044 Patent. As such Petitioner requests that this request for inter partes review be granted and that all claims of the ‘044 Patent be cancelled.

II. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8(a)(1)

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

The Petitioner, U.S. Endoscopy Group, Inc. (“U.S. Endoscopy”), is the Real Party-In-Interest. U.S. Endoscopy is a wholly-owned subsidiary of STERIS Corporation.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

The '044 Patent is currently the subject of litigation brought by its putative assignees/co-owners, CDx Diagnostics, Inc. ("CDx") and Shared Medical Resources, LLC against U.S. Endoscopy in the Southern District of New York, Case No. 1:13-cv-5669-NSR.

C. Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Lead Counsel: Todd R. Tucker (Registration No. 40,850)

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D. Service Information Under 37 C.F.R. § 42.8(b)(4)

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III. PAYMENT OF FEES UNDER 37 C.F.R. § 42.103

The undersigned authorizes the Office to charge the fees as set forth in 37 C.F.R. § 42.15(a) for this Petition for *Inter Partes* Review to Deposit Account No. 03-0172; any additional fees that might also be due are also authorized.

IV. REQUIREMENTS FOR *INTER PARTES* REVIEW UNDER 37 C.F.R. §§ 42.104

As set forth below and pursuant to 37 C.F.R. § 42.104, each requirement for *inter partes* review of the '044 Patent is satisfied.

A. Grounds for Standing Under 37 C.F.R. § 42.104(a)

Petitioner certifies pursuant to Rule 42.104(a) that the patent for which review is sought is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this Petition.

B. Identification of Challenge Under 37 C.F.R. § 42.104(b) and Relief Requested

1. *Claims for Which Inter Partes Review Is Requested Under 37 C.F.R. § 42.104(b)(1)*

Petitioner respectfully requests *inter partes* review of claims 1-39 of the '044 Patent and the cancellation of these claims as unpatentable.

2. *The Specific Art and Statutory Ground(s) on Which the Challenge Is Based Under 37 C.F.R. § 42.104(b)(2)*

Petitioner relies upon the following patents and printed publications:

Exhibit No.	**Description**
1001	U.S. Patent No. 6,258,044 to Lonky (the "'044 Patent")
1002	Prosecution History of the '044 Patent
1003	U.S. Patent No. 5,535,756 to Parasher ("Parasher"), issued on July 16, 1996. Parasher is available as prior art under 35 U.S.C. § 102(b).
1004	"Endoscopic Retrograde Wire-Guided Cytology of Malignant Biliary Structures Using a Novel Scraping Brush", Vinod K. Parasher, et al. ("Parasher Article"), GASTROINTESTINAL ENDOSCOPY Vol. 48, No. 3, 1998. The Parasher Article is available as prior art under 35 U.S.C. § 102(b).
1005	U.S. Patent No. 5,407,807 to Markus ("Markus"), issued on April 18, 1995. Markus is available as prior art under 35 U.S.C.

Exhibit No.	Description
	§ 102(b).
1006	Spirabrush Specimen and Declaration, submitted to the USPTO on March 18, 1993 ("Spirabrush"). Spirabrush is available as prior art under 35 U.S.C. § 102(b).
1007	U.S. Patent No. 4,759,376 to Stormby ("Stormby"), issued on July 26, 1988. Stormby is available as prior art under 35 U.S.C. § 102(b).
1008	"Exploiting the 'Toothpick Effect' of the Cytobrush by Plastic Embedding of Cervical Samples", by Mathilde Boon, et al. ("Boon"), ACTA CYTOLGICA, Jan-Feb 1991. Boon is available as prior art under 35 U.S.C. § 102(b).
1009	U.S. Patent No. 2,675,572 to Nomiya ("Nomiya"), issued on April 20, 1954. Nomiya is available as prior art under 35 U.S.C. § 102(b).
1010	U.S. Patent No. 5,067,195 to Sussman ("Sussman"), issued on November 26, 1991. Sussman is available as prior art under 35 U.S.C. § 102(b).

Supporting Materials:

Exhibit 1011 – Expert Declaration of Michel Kahaleh, M.D. ("Kahaleh".)

Petitioner requests cancellation of the challenged claims under the following statutory grounds:

Claim Nos.	Proposed Statutory Rejections for the '044 Patent
1-8, 11-17, 23-28, and 31-39	Claims 1-8, 11-17, 23-28, and 31-39 are anticipated by Parasher under 35 U.S.C. §102(b)
9-10 and 19-20	Claims 9-10 and 19-20 are rendered obvious by Parasher in view of Markus under 35 U.S.C. §103(a)
18, 21, and 22	Claims 18, 21, and 22 are rendered obvious by Parasher in view of Spirabrush under 35 U.S.C. §103(a)
1-8, 11-18, and 21-	Claims 1-8, 11-18, and 21-39 are rendered obvious by

Claim Nos.	**Proposed Statutory Rejections for the '044 Patent**
39	Stormby in view of the Boon Article, and further in view of Parasher under 35 U.S.C. §103(a)
9-10 and 19-20	Claims 9-10 and 19-20 are rendered obvious by Stormby in view of the Boon Article, and further in view of Parasher and Markus under 35 U.S.C. §103(a)
18, 21, and 22	Claims 18, 21, and 22 are rendered obvious by Stormby in view of the Boon Article, and further in view of Parasher and Spirabrush under 35 U.S.C. §103(a)
1-8, 11-18, and 21-39	Claims 1-8, 11-18, and 21-39 are rendered obvious by Spirabrush in view of Parasher under 35 U.S.C. §103(a)
9-10 and 19-20	Claims 9-10 and 19-20 are rendered obvious by Spirabrush in view of Parasher, and further in view of Markus under 35 U.S.C. §103(a)
18, 21, and 22	Claims 18, 21, and 22 are rendered obvious by Parasher in view of Nomiya under 35 U.S.C. §103(a)

Section V below demonstrates for each of the statutory grounds that there is a reasonable likelihood that Petitioner will prevail. See 35 U.S.C. 314(a).

3. *Overview of the '044 Patent*

The '044 Patent claims nothing more than a known brush for taking a biopsy and defining the brush by what it samples and how it collects that sample. The patent, however, does not claim the structure by which this is accomplished, but only states function in its apparatus claims. Additionally, both its apparatus claims and its methods can be found in several prior art references. All of the patents claims are invalid.

In order to overcome prior art rejections, the patentees were forced to hang their hat on the argument that the "the present invention is not directed to a surface abrading brush but is directed to a brush having bristles stiff enough to penetrate through the superficial layer [of the epithelium] into both the intermediate and basal layers in order to collect cells from all three layers." (Ex. 1002, Prosecution History Excerpts.) The problem with this argument, the prior art presented below shows exactly the feature that the patentees essentially argued as their point of novelty. And the result, all 39 claims of the '044 Patent are invalid and should be cancelled.

4. *How the Challenged Claim(s) Are to Be Construed Under 37 C.F.R. § 42.104(6)(3)*

In an *inter partes* review, the claim terms are presumed to have the meanings as detailed below. This Petition shows that the challenged claims of the '044 Patent are unpatentable when they are given their broadest reasonable interpretation in the light of the specification. *See* 37 C.F.R. 42.100(b); *see also In re Yamamoto*, 740 F.2d 1569, 1571 (Fed. Cir. 1984). Claim terms are also given their ordinary and customary meaning as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Additionally, an inventor may act as his or her own lexicographer, so long as the definition is set forth in the specification with reasonable clarity, deliberateness and precision. *Renishaw PLC v. Marposs*

Societa' Per Azioni, 158 F.3d 1243, 1249 (Fed. Cir. 1998). The chart below shows how the claim terms of the '044 Patent should be construed.

Term	**Claims**	**Proposed Construction**
Transepithelial	All Claims	"through the surface of the epithelium which, in the '044 Patent, is the squamous epithelium found in the oral cavity and into the esophagus" *See, e.g.*, '044 Patent, 4:62-5:25; *see also* Ex. 1011 at ¶15.
Non-lacerational	All Claims	"does not cut like a scalpel or laser, is minimally invasive and causes no more than minor discomfort and/or bleeding" *See, e.g.*, '044 Patent, 4:55-62.
Abrasive surface	4, 24	"capable of dislodging and removing cells when rubbed back and forth, includes materials that are finely ribbed or bumpy" *See, e.g.*, '044 Patent, 9:17-65.
Tip stiffness	9, 19	"cantilever or lateral tip deflection stiffness" Response to 3/15/00 Office Action dated 9/1/00, p. 5-6.

V. DETAILED EXPLANATION UNDER 37 C.F.R. §§ 42.104(b)(4) OF HOW THE CONSTRUED CLAIMS ARE UNPATENTABLE

A. Statement of Non-redundancy

The grounds raised in the following sections are meaningfully distinct from one another and rely upon fundamentally different types of cited prior art references. Petitioner urges the Board to adopt each ground of unpatentability presented in this Petition for at least the following reasons.

B. Claims 1-8, 11-17, 23-28, and 31-39 are anticipated by Parasher

This section explains on an element-by-element basis how Parasher anticipates claims 1-8, 11-17, 23-28, and 31-39 of the '044 Patent. In short, Parasher recognized that the need for a non-lacerating device capable of collecting biopsy tissue samples was known as early as 1994. (Ex. 1003 at 2:12-20.) As explained below, Parasher satisfied this need with a non-lacerating brush having stiff or semi-rigid bristles. (*Id*. at Abstract, 4:46-59.)

1. Claim 1: "Apparatus to obtain cells in epithelial tissue of the body comprising:"

Parasher disclosed an apparatus to obtain cells in epithelial tissue of the body. Like the brush of the '044 Patent, the device 1 of Parasher has a brush 9 with stiff or semi- rigid bristles 11. (Ex. 1003 at Abstract, 4:46-59; *see also* Ex. 1001 at 8:20-21.) ("[I]n the present invention, bristles 40 of brush head 26 are each stiff or semi-rigid."). The bristles 11 permit the device 1 to collect biopsy tissue samples without laceration. (Ex. 1003 at 2:1-40.)

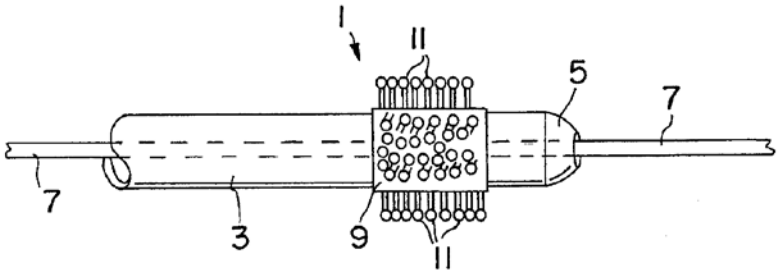
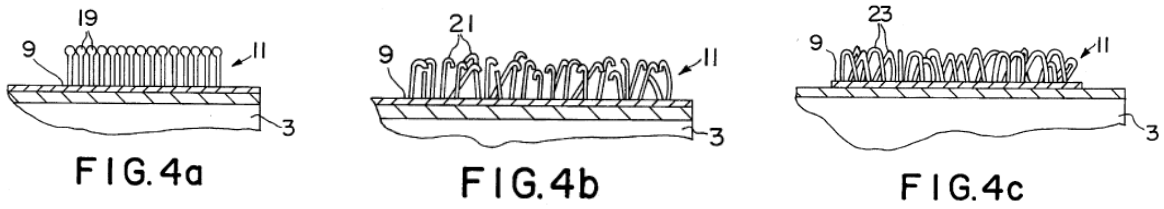


Fig. 1 of Parasher

In addition to the stiffness, the bristles 11 of the brush 9 include features that facilitate collection tissue. In Figures 4a-4c of Parasher, the bristles 11 have hook ends, ball-tips, mushroom tips, loops or the like that are specifically designed to maximize biopsy collection of the cells and tissue.



Figs. 4a-4c of Parasher

(*Id*. at Figs. 4a-4c, 5:46-57.) Thus, the brush 9 of Parasher is specifically designed to collect biopsy samples of epithelial tissue without laceration.

As also explained in Parasher, a biopsy sample is a gross tissue sample that includes the mucous lining of the duct, the tissue of the duct, and even adjacent connective tissues (*e.g.*, the submucosa). (Ex. 1003 at 1:54-67.) Previously, biopsy samples were taken using instruments such as biopsy forceps or scalpels that cut away and remove chunks of tissue from the diseased area. (*Id*. at 2:1-10.) Parasher recognized that these prior lacerational procedures run the risk of perforating the ducts. (*Id*. at 2:2-8.) The device of Parasher, however, permits the user to obtain the same biopsy tissue samples as these prior procedures without the risk of perforating the duct. (*Id*. at 2:1-40, 3:60-67.) Thus, because one of ordinary skill in the art would understand that a biopsy sample necessarily includes

fragments of the epithelial tissue, as well as portions of the basement membrane and submucosa below the epithelium they would also understand that Parasher is obtaining this sample. (Ex. 1011 at ¶ 10.)

Moreover, as explained in Parasher, the use of a guide wire with the device is optional and the brush may be used to obtain biopsy samples in any number of organs, including the esophagus, stomach, or the like. (Ex. 1003 at 2:30-50.) For example, the device of Parasher can be used to obtain biopsy samples of oral epithelia tissue (*e.g.*, within the oral cavity.) (Ex. 1011 at ¶ 17.)

Because the Parasher brush is capable of obtaining biopsy tissue samples of the entire epithelium of various organs where the sample includes portions of the basement membrane and submucosa below the epithelium, the brush of Parasher would be capable of obtaining samples of all three layers of oral epithelia tissue (*e.g.*, the superficial, intermediate, and basal layers). *Id.* The device of Parasher would also be capable of penetrating a keratinized layer of cells to collect epithelial tissue below the kerantized layer. *Id*. Thus, the device 1 of Parasher is an apparatus that may be used to obtain cells in epithelial tissue of the body as recited in the preamble of claim 1.

2. Claim 1: "transepithelial non-lacerational sampling apparatus to collect cells from at least two layers of said epithelial tissue, said transepithelial non-lacerational sampling apparatus comprising a brush, said

brush comprising bristles having sufficient stiffness to penetrate at least said two layers of said epithelial tissue."

The brush of Parasher is non-lacerational and capable of collecting tissue cells from at least two layers of epithelial tissue. The brush is capable of collecting biopsy-type samples, but in a manner that reduces the risk of perforating the duct as compared with known lacerational techniques. *See supra* sec. V(B)(1). Further, a biopsy sample collected by the bristles of the brush would necessarily include tissue located within two layers of epithelial tissue. *Id*. Parasher explains that a biopsy sample is a gross tissue sample that includes the mucous lining of the duct, the tissue of the duct, and even adjacent tissues (*e.g.*, the submucosa). *Id*.

The Parasher Article, authored by the sole inventor of Parasher '756, demonstrates that the brush can be used to obtain a biopsy sample of tissue located below the surface of the epithelium.[1] The Parasher Article describes patient trials of the brush. The brush used in the trials included a specially designed Velcro® pad having semi-rigid and rough bristles. (Ex. 1004 at 290-91.) The trials determined that the brush penetrated the ductal epithelium and obtained a biopsy sample and that the brush design could be used to generate even more scraping force. *Id*. As stated in the '044 Patent, "[b]y rubbing harder than normal cytological sampling, and using a device which penetrates epithelium but not very

[1] The Parasher Article is being used herein as a secondary reference to show the inherent characteristics of the brush disclosed in Parasher.

deep on each stroke, one can reach the basement membrane without lacerating." (Ex. 1001 at 4:65-5:3.) This is exactly what Parasher disclosed years before the '044 Patent. Claim 1 is anticipated by Parasher.

3. Claim 2: "Apparatus to obtain cells in epithelial tissue of the body according to claim 1, wherein said bristles 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."

The brush of Parasher can be used to obtain a biopsy sample of tissue. (Ex. 1003 at 2:1-40.) Parasher explains that a biopsy sample is a gross tissue sample that includes the mucous lining of the duct, the tissue of the duct, and even adjacent tissues (*e.g.*, the submucosa). (*Id*. at 1:54-65.) The device of Parasher permits the user to obtain the same biopsy tissue samples as prior lacerational procedures. (*Id*. at 2:1-40, 3:60-67.) The '044 Patent admits that the samples taken by its claimed brush are the same as those taken using the same prior art lacerational procedures described earlier by Parasher. (Ex. 1001 at 5:10-15.)

Thus, the bristles of the Parasher brush collect cells from three layers of the epithelial tissue and also have sufficient stiffness to penetrate the basement membrane and reach the submucosa. Claim 2 is anticipated by Parasher.

4. Dependent Claims 3-8, 11, and 14-17

The claim chart below shows where each of the features of claims 3-8, 11, and 14-17 are found in Parasher. As such, claims 3-8, 11, and 14-17 are anticipated by Parasher.

Claim	**Parasher**
3. Apparatus to obtain cells in epithelial tissue of the body according to claim 2, wherein said bristles of said brush have sufficient stiffness to penetrate said basement membrane and reach said submucosa.	*See supra* sec. V(B)(3). The bristles of the Parasher brush have sufficient stiffness to penetrate the basement membrane and reach the submucosa.
4. A transepithelial non-lacerational sampling apparatus according to claim 2, 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.	As shown in Fig. 1 of Parasher, the device 1 has a handle 3 having a distal and proximal end. The brush 9 is connected to the distal end of the handle. The bristles 11 form an abrasive surface. For example, in one embodiment, the brush is made of the hooked side of Velcro®. (Ex. 1001 at 4:59-61.) The '044 Patent lists Velcro® as an abrasive material that may be used. '044 Patent, 9:32-65.
5. Apparatus to obtain cells as set forth in claim 1, wherein said brush comprises a handle and a head portion, said head portion comprising bristles.	See claim 4 above. The handle 3 of the Parasher device 1 has a head portion that comprises bristles 11. (Fig. 1)
6. A transepithelial non-lacerational sampling apparatus according to claim 5, wherein said handle comprises a cylinder.	As shown in Fig. 1 of Parasher, the handle 3 is cylindrical.

Claim	**Parasher**
7. A transepithelial non-lacerational sampling apparatus according to claim 5, wherein said head portion comprises bristles directed outwardly from said head portion.	As shown in Fig. 1 of Parasher, the head portion of the handle 3 has bristles 11 directed outwardly from the head portion. (*See also* Ex. 1003 at 4:46-60.)
8. A transepithelial non-lacerational sampling apparatus according to claim 7, wherein said handle has a distal and a proximal end, said head portion comprises bristles directed radially outwardly from the distal end of said handle.	See claims 4, 5, and 7 above. The handle 3 has a distal and proximal end and the head portion of the handle has bristles 11 directed outwardly from the head portion.
11. Apparatus as set forth in claim 5, wherein said bristles have a tip stiffness, and wherein said bristles protrude between 0.05-0.2 inches.	The bristles 11 of the device 1 of Parasher inherently have a tip stiffness and also extend radially between 1 to 3 mm. (Ex. 1001 at 4:59-62.) This range converts to between .039 and .118 inches. The bristles 11 protrude between 0.05-0.2 inches.
14. A transepithelial non-lacerational sampling apparatus according to claim 4, wherein said brush comprises a handle and a head portion, said head portion comprising bristles.	See claims 4 and 5 above. The handle 3 of the Parasher device 1 has a head portion that comprises bristles 11.
15. A transepithelial non-lacerational sampling apparatus according to claim 14, wherein said handle comprises a cylinder.	See claim 6 above. As shown in Fig. 1 of Parasher, the handle 3 is cylindrical.

Claim	**Parasher**
16. A transepithelial non-lacerational sampling apparatus according to claim 14, wherein said head portion comprises bristles directed outwardly from said head portion.	See claim 7 above. As shown in Fig. 1 of Parasher, the head portion of the handle 3 has bristles 11 directed outwardly from the head portion. (*See also* Ex. 1003 at 4:46-60.)
17. A transepithelial non-lacerational sampling apparatus according to claim 16, wherein said handle has a distal and a proximal end, said head portion comprises bristles directed radially outwardly from the distal end of said handle.	See claims 4, 5, 7, and 8 above. The handle 3 has a distal and proximal end and the head portion of the handle has bristles 11 directed outwardly from the head portion.

5. Claim 12: "A transepithelial non-lacerational sampling apparatus to harvest cells in an oral cavity from the epithelial tissue, said epithelial tissue comprising superficial, intermediate and basal layers, and a basement membrane located between the basal layer and the submucosa, said non-lacerational sampling apparatus comprising means to traverse said superficial, intermediate and basal layers and to collect cells from said three layers."

The brush of Parasher is a transepthelial non-lacerational apparatus capable of harvesting cells from epithelial tissue in the oral cavity. *See supra* sec. V(B)(1-3). As explained herein, the bristles of the Parasher brush are capable of collecting cells from all three layers of the epithelial tissue (*e.g.*, the superficial, intermediate, and basal layers) and also have sufficient stiffness to penetrate the basement membrane and reach the submucosa. *Id*. Claim 12 is the anticipated by Parasher.

To the extent the Board finds that the language of claim 12 triggers a means plus function analysis under 35 U.S.C. § 112, ¶ 6, the Petitioner respectfully submits that the brush of Parasher still anticipates claim 12. In the specification, the only structure capable of traversing and collecting cells from the three layers of the epithelium is a non-lacerational brush with stiff bristles. Parasher discloses such a brush. As discussed above, the brush of Parasher is non-lacerational with bristles capable of collecting tissue cells from all three layers of the epithelial tissue (*e.g.*, the superficial, intermediate, and basal layers) that also have sufficient stiffness to penetrate the basement membrane and reach the submucosa. *See supra* sec. V(B)(1-3).

6. Dependent Claims 13 and 23-25

The claim chart below shows where each of the features of claims 13 and 23-25 are found in Parasher. Parasher anticipates these claims.

Claim	**Parasher**
13. A transepithelial non-lacerational sampling apparatus according to claim 12, wherein said means to traverse said three layers comprises sufficient stiffness to traverse said basement membrane and reach into said submucosa.	*See supra* sec. V(B)(5). The bristles of the Parasher brush have sufficient stiffness to penetrate the basement membrane and reach the submucosa.
23. A transepithelial non-lacerational sampling apparatus according to claim 12, wherein said bristles comprise tips, wherein said tips comprise scraping	The bristles 11 of the Parasher brush 9 have tips with edges that scrape, capture and hold cells and tissue. (*See*, *e.g.*, Ex. 1003 at Figs. 4a-4c, 5:46-57,

Claim	**Parasher**
edges.	6:5-10.)
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.	*See supra* sec. V(B), claim 4. The device 1 has a handle 3 having a distal and proximal end. The brush 9 is connected to the distal end of the handle. Also, the bristles 11 form 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.	As shown in Fig. 1 of Parasher, the brush 9 has a round head. (*Id*. at 1003, 4:45-59.) Further, the brush 9 of Parasher has stiff or semi-rigid bristles. (*Id*. at Abstract; 4:46-59.)

7. Claim 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."

Parasher disclosed a method to collect cells in epithelial tissue of the body. The brush of Parasher is non-lacerational and capable of collecting tissue cells from at least two layers of epithelial tissue. *See supra* sec. V(B)(1-3). Parasher explained how the brush could be used to penetrate the epithelial tissue to collect biopsy samples. (*Id*. at 3:7-32; 5:58-6:20.) For example, the brush is pushed and pulled, back and forth, several times such that sample scrapings of tissue from the stricture cling to bristles of the brush and are captured by the bristle structures. *Id*.

As such, Parasher disclosed a method of collecting cells in epithelial tissue of the body by passing a transipithelial non-lacerational sampling means through the epithelial tissue to collect cells from at least two layers of said epithelial tissue. Claim 26 is anticipated by Parasher.

8. Dependent Claims 27, 28, and 31-36

The claim chart below shows where each of the features of claims 27, 28, and 31-36 are found in Parasher. As such, claims 27, 28, and 31-36 are anticipated by Parasher.

Claim	**Parasher**
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.	*See supra* sec. V(B), claims 2 and 12. The bristles of the Parasher brush are capable of collecting cells from all three layers of the epithelial tissue.
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.	*See supra* sec. V(B), claims 3 and 13. The bristles of the Parasher brush have sufficient stiffness to penetrate the basement membrane and reach the submucosa.
31. A method to collect cells in epithelial tissue of the body according to claim 27, wherein said epithelial tissue comprises oral epithelial tissue.	*See supra* sec. V(B)(1-3). The Parasher device is capable of collecting cells from oral epithelial tissue.

Claim	**Parasher**
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.	*See supra* sec. V(B)(7). The brush of Parasher is pulled back and forth, several times, to scrape and scrub the epithelial tissue to collect biopsy tissue samples.
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.	*See supra* sec. V(B)(1-3). The Parasher device is capable of penetrating a keratinized layer and collecting cells from beneath the 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.	See claim 31 above. The Parasher device is capable of collecting cells from oral epithelial tissue.
35. A method to collect according to claim 26, further comprising abrading the epithelial tissue to collect cells.	See claim 32 above. The brush of Parasher may be used to abrade 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.	See claims 32 and 35 above. The bristles 11 of the Parasher brush form a scrubbing surface that contact the epithelial tissue to dislodge cells. (Ex. 1003 at 3:7-32, 4:45-59, 5:58-6:20.) Pushing and pulling the brush, back and forth, exerts sufficient pressure on the bristles to dislodge cells from the epithelial tissue. *Id*.

9. Claim 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."

Parasher disclosed an apparatus capable of obtaining cells in epithelial tissue of the body. As stated above, it disclosed a non-lacerational capable of collecting tissue cells from at least two layers of epithelial tissue. *See supra* sec. V(B)(1-3). The bristles 11 of the brush 9 have tips with edges that scrape, capture and hold cells of the epithelial tissue. (Ex. 1003 at Figs. 4a-4c, 5:46-57, 6:5-10.) As such, the bristles 11 form an assemblage of penetrating edges that penetrate at least two layers of epithelial tissue.

10. Dependent Claims 38 and 39

The claim chart below shows where each of the features of claims 38 and 39 are found in Parasher. As such, claims 38 and 39 are anticipated by Parasher.

Claim	**Parasher**
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.	*See supra* sec. V(B), claims 2, 3, 12, 13, 27, and 28 above. The bristles of the Parasher brush collect cells from all three layers of the epithelial tissue (*e.g.*, the superficial, intermediate, and basal layers) and have sufficient stiffness to penetrate the basement membrane and reach the submucosa.

Claim	**Parasher**
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.	*See supra* sec. V(B), claims 2, 3, 12, 13, 27, and 28 above. The bristles of the Parasher brush have sufficient stiffness to penetrate the basement membrane and reach the submucosa.

C. Claims 9-10 and 19-20 are rendered obvious by Parasher in view of Markus

Claims 9 and 19 recite that the "tip stiffness of each bristle is between 0.04 and 0.2 lbs/inch." Claim 10 depends from claim 9 and further recites that "said bristles protrude between 0.05-0.2 inches." Similarly, claim 20 depends from claim 19 and further recites that "said bristles protrude between 0.05-0.2 inches from the wires in which said bristles are held."

Parasher discloses the elements of claims 9, 10, 19, and 20 except the tip stiffness range. The Petitioner respectfully submits that it is a matter of routine experimentation for one of ordinary skill in the art to determine the optimal or workable range of cantilever or tip stiffness for the bristles. *See, e.g.*, MPEP 2144.05(II)(A) (*quoting In re Aller*, 220 F.2d 454, 456 (CCPA 1955)) ("Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."). As discussed above, the brush 9 of Parasher discloses all the claim limitations, and further discloses that the brush is capable of collecting cells from all three layers of

the epithelial tissue (*e.g.*, the superficial, intermediate, and basal layers) and that it has sufficient stiffness to penetrate the basement membrane and reach the submucosa. *See supra* sec. V(B)(1-3). As such, it is respectfully submitted that claims 9, 10, 19, and 20 are rendered obvious by Parasher in view of the common knowledge of one of ordinary skill in the art.

As shown below, Markus discloses a culturing brush 12 having a plurality of bristles 14 extending from at stainless steel wire stem 13 in which the bristles are held. (Ex. 1005 at Fig. 2, 4:40-55.) The bristles 14 of the brush 12 in Markus are made of Tynex®, the same material as the bristles of the brush in the '044 Patent, which has a tangent modulus (E) of 500,000 psi. (*Id.*; *see also* Ex. 1001 at 8:20-30.) The bristles 14 of the brush 12 in Markus have a length (L) of about .093 inch and a diameter (d) of about .005 inch.[2] *Id.*

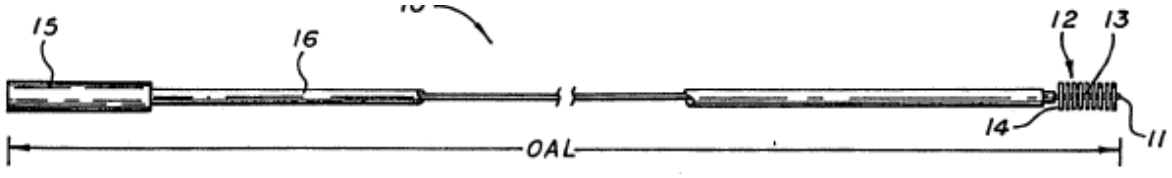


Fig. 2 of Markus

It would be routine and obvious to one of ordinary skill in the art to modify the brush of Parasher to have the brush bristles of Markus. Both brushes are used for sample collection, have a similar size and shape, and are capable of traversing

[2] The length (L) = ½ ((the diameter of the brush = 5 mm) - (the diameter of the stem (.01 inch))).

passages in an endoscope. Modifying the brush of Parasher with the brush bristles of Markus is a simple substitution to obtain predictable results. It is also no more than applying a known technique to a known device. MPEP § 2141(111).

Tip or cantilever stiffness (k) of a round member such as a bristle is determined using the following accepted — even the patentee referenced this equation in an Amendment:

$$k = \frac{P}{\delta} = \frac{3EI}{L^3}$$

Table 5.1: Spring Rate (k) of Cantilever Beam Loaded at End

$$I = \frac{\pi d^4}{64}$$

Appendix B-1: Moment of Inertia (I) for a Circular Section

("Fundamentals of Machine Component Design," 4th ed., R. Juvinal and K. Marshek, John Wiley, 2006, where E = tangent modulus, L = length, and d = diameter; *see also* Ex. 1002, Amendment at 6.) Applying the measurements from Markus and the tangent modulus for Tynex® into the equation above provides a stiffness of about .056 lbs/inch. This falls within the claimed range of 0.04 and 0.2 lbs/inch. Also, the length (L) of the bristles 14 extending from the wire stem 13 fall within the range of 0.05-0.2 inches recited in claims 10 and 20. As such, claims 9, 10, 19, and 20 are rendered obvious by Parasher in view of Markus.

D. Claims 18, 21, and 22 are rendered obvious by Parasher in view of SpiraBrush

As shown below, SpiraBrush disclosed a sampling brush made by the Trylon Corporation and having a round head with bristles held together with wires. Trylon filed for a trademark on "SpiraBrush." As part of this filing, Trylon submitted a declaration to the USPTO in March of 1993 – SpiraBrush specimen shown in the photo below. This trademark filing (and photo) is a publicly available publication catalogued and maintained by the USPTO. The declaration and photo are prior art under 35 U.S.C. § 102(b). The SpiraBrush bristles form brushing surfaces and the wires form a toroid that is substantially perpendicular to the axis of the handle. As seen below, the brush is in the form of a spiral shape substantially perpendicular to the axis of the handle:

SpiraBrush (Ex. 1006)

Comparing the photograph with Figs. 1-6 of the ‘044 Patent, the SpiraBrush brush has the same structure as the brush shown and described in the ‘044 Patent. Dr. Neil Lonky, the individual signing the declaration on behalf of the Trylon Corporation, knew that the Spirabrush CX was commercially available as of December 1992. Dr. Lonky, is also the first named inventor on the ‘044 Patent. The Trylon Corporation is also party to the joint venture assignee listed on the ‘044 Patent. Moreover, the other party to the joint venture explains in a patent (U.S. Patent 6,297,044 to Eisen (the “Eisen Patent”)) that the provisional application to which the ‘044 Patent claims priority, Provisional Appln. No. 60/093,910 (the “’910 application”), covers a brush that is the same as the SpiraBrush. (Eisen

Patent, 5:24-44.) As shown in the highlighted text below, the Eisen Patent states that the brush disclosed in the '910 application, or the SpiraBrush, is capable penetrating all three layers of the oral epithelium. *Id*.

In accordance with the preferred embodiment of the invention, it is important that a transepithelial sample be taken from the oral cavity or similar epithelia, the sample being obtained using a nonlacerational sampling device. This cytological or cellular sample of the entire epithelial thickness of an oral lesion is obtained using a non-scalpel instrument which is sufficiently abrasive to penetrate all three layers (basal, intermediate, and superficial) of the oral epithelium, preferably the sampling instrument disclosed in U.S. Provisional Patent Application Ser. No. 60/093,910, filed Jul. 23, 1998 and entitled "Apparatus and Method for Performing a Non-Lacerating Biopsy of Lesions of the Oral Cavity and of Similar Epithelium", the disclosure of which is provided below, or the Spirabrush™, available from The Trylon Corporation of Torrance, Calif., or the like. In the preferred embodiment, this trans-epithelial sample is obtained by means of pressing and rotating a circular stiff nylon brush several times over the entire lesion surface. This sample is then analyzed by an automated image processing system for detection of morphology or characteristics typical of dysplasia or cancer.

The Eisen Patent, 5:24-44

It is respectfully submitted that it would be routine and obvious to one of ordinary skill in the art to modify the brush of Parasher in view of the brush structure of SpiraBrush. Both brushes have the same purpose and perform the same function - obtaining samples of epithelia tissue within the body. Both brushes also have a similar size and shape, and are capable of traversing passages within the body. Modifying the brush of Parasher in view of Spirabrush is a simple substitution of one brush for another to obtain predictable results — the hallmark of obviousness.

The claim chart below shows where each of the features of claims 18, 21, and 22 are found in Parasher and SpiraBrush. As such, claims 18, 21, and 22 are rendered obvious by Parasher in view of SpiraBrush.

Claim	**Parasher/Spirabrush**
18. A transepithelial non-lacerational sampling apparatus according to claim 12, wherein said handle comprises a distal and a proximal end, further comprising wires connected to and extending from said distal end, said bristles held by said wires to form brushing surfaces at the tips of said bristles, said brushing surfaces abrading said epithelial tissue.	As shown above, the brush of SpiraBrush has wires extending from a distal end of a handle and the bristles are held by the wires to form brushing surfaces at the tips of the bristles. The brush of Parasher has brushing surfaces that abrade the epithelial tissue. *See supra* sec. V(B)(1-3).
21. A transepithelial non-lacerational sampling apparatus according to claim 18, wherein said wires form a toroid which is substantially perpendicular to the axis of said handle.	As shown above, the brush of SpiraBrush has wires that form a toroid which is substantially perpendicular to the axis of the handle.
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.	As shown above, the brush of SpiraBrush is in the form of a spiral shape substantially perpendicular to the axis of the handle.

E. Claims 1-8, 11-18, and 21-39 are rendered obvious by Stormby in view of the Boon Article, and further in view of Parasher

It was known prior to the filing date of the ‘044 Patent that a cytology brush can be used to sample epithelial tissue. For example, the Boon Article disclosed that a known cytology brush called the Cytobrush® can be used to remove and

sample fragments of epithelial tissue for the diagnosis of cancer. (Ex. 1004 at 57-58.) In particular, as shown below, the author of the Boon Article found that the bristles of the Cytobrush® have a "toothpick" effect that easily dislodges epithelial fragments. *Id*. One of ordinary skill in the art would understand that this "toothpick effect" is accomplished by rotating and drilling into the epithelial tissue with the brush. (Ex. 1011 at ¶¶ 16-17.)

Because these fragments were also present in large quantities in our correctly diagnosed cancer cases, we realized that the bristles of the Cytobrush have a "toothpick effect," easily dislodging these epithelial fragments from the endocervical canal. This is well illustrated by the scanning electron microscopy pictures of Glenthoj et al.[8]

Boon, p. 58

The Boon Article directly contradicts the patentee's statements in the background section of the '044 Patent that were relied upon by the Examiner during prosecution. In the background section, the patentee discussed prior art cytological sampling tools and, in particular, the Cytobrush®. (Ex. 1001 at 3:9-22.) The patentee distinguished these cytological sampling tools, including the Cytobrush®, on the basis that they only sweep exfoliated cells and are incapable of penetrating and sampling epithelia tissue. (*Id*. at 2:60-4:5.) This is, however, far from the actual case.

The '044 Patent identified U.S. Patent 4,759,376 ("Stormby") as being directed to the Cytobrush® discussed in the background section. (*Id*. at 3:9-22.)

Stormby disclosed a cytology brush 4 having a conically shaped tip 5 with spiraled nylon bristles.

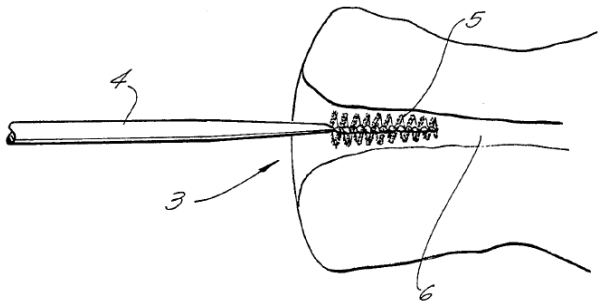


Fig. 2 of Stormby

(Ex. 1007 at 2:27-57.) The bristles are held by a wire and form a plurality of toroids substantially perpendicular to the handle. *Id*. at Fig. 2. Various properties of the brush are also disclosed in Stormby, including the number, length, diameter, stiffness, and density of the bristles. (*Id*. at 2:27-57.) Stormby discloses the Cytobrush® discussed in the Boon Article and the background section of the '609 Patent.

It is also known in the art that a cytology brush like the Cytobrush® of Stormby may be used in the oral cavity. (ex. 1011 at 17.) This is further evidenced by the '044 Patent inordinately discussing prior art cytology brushes in its background. (Ex. 1001 at 2:25-4:25.) As such, the Cytobrush® of Stormby may be used to penetrate and remove oral epithelial tissue.

One of ordinary skill in the art would readily recognize that it could modify the Cytobrush® in view of Stormby and further in view of Parasher. The brushes have the same purpose and perform the same function - obtaining epithelial tissue samples within the body. The brushes have a similar size and shape, and are designed to traverse passages within the body. Modifying the Cytobrush® in view of Stormby and in view of Parasher is a simple substitution of one brush for another to obtain predictable results. Moreover, it is nothing more than applying a known technique to a known device. *See* MPEP § 2141.

1. Claim 1: "An apparatus to obtain cells in epithelial tissue of the body comprising:"

The Boon Article disclosed that the Cytobrush® of Stormby can be used to remove and sample fragments of epithelial tissue for the diagnosis of cancer. (Ex. 1008 at 57-58.) Thus, the brush of Stormby is an apparatus that may be used to obtain cells in epithelial tissue of the body as recited in the preamble of claim 1.

2. Claim 1: "transepithelial non-lacerational sampling apparatus to collect cells from at least two layers of said epithelial tissue, said transepithelial non-lacerational sampling apparatus comprising a brush, said brush comprising bristles having sufficient stiffness to penetrate at least said two layers of said epithelial tissue."

The '044 Patent considered brushes, such as the Cytobrush® of Stormby, as a simple, non-invasive brush that was an alternative to lacerating. (Ex. 1001 at 2:26-34.) Further, as explained in the Boon Article, the Cytobrush® can be used to

penetrate and remove epithelial tissue in a biopsy-type sample. (Ex. 1008 at 57-58.) Also, the brush of Parasher is non-lacerational and capable of collecting tissue cells from at least two layers of epithelial tissue. *See supra* sec. V(B)(1-3). As discussed above, the brush is capable of collecting tissue samples sufficient to qualify as a biopsy. *Id*. Additionally, the Parasher Article shows that the brush of Parasher can be used to obtain a biopsy sample of tissue located below the surface of the epithelium. *Id*. The Cytobrush® of Stormby modified in view of Parasher would yield transepithelial, non-lacerational brush with bristles having sufficient stiffness to collect cells from at least two layers of epithelial tissue. Claim 1 is rendered obvious by Stormby in view of the Boon Article, and further in view of Parasher.

3. Claim 2: "Apparatus to obtain cells in epithelial tissue of the body according to claim 1, wherein said bristles 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."

As discussed above, the Cytobrush® of Stormby may be used to penetrate and remove oral epithelial tissue. In particular, the bristles of the Cytobrush® have a "toothpick" effect that easily dislodges epithelial fragments. (Ex. 1008 at 57-58.) In addition, the brush of Parasher may be used to obtain biopsy samples of oral epithelia tissue (*e.g.*, within the oral cavity) that would necessarily include all three

layers (*e.g.*, the superficial, intermediate, and basal layers) of the tissue. *See supra* sec. V(B)(1-3). The bristles of the Parasher brush have sufficient stiffness to penetrate the basement membrane and reach the submucosa. *Id*. Thus, claim 2 is rendered obvious by Stormby in view of the Boon Article and further in view of Parasher.

4. Dependent Claims 3-8, 11, and 14-17

The claim chart below shows where each of the features of claims 3-8, 11, and 14-17 are found in Stormby, the Boon Article, and/or Parasher. Claims 3-8, 11, and 14-17 are rendered obvious by Stormby in view of the Boon Article and further in view of Parasher.

Claim	**Stormby-Boon-Parasher**
3. Apparatus to obtain cells in epithelial tissue of the body according to claim 2, wherein said bristles of said brush have sufficient stiffness to penetrate said basement membrane and reach said submucosa.	*See supra* sec. V(E), claim 2. The bristles of the Cytobrush® penetrate and remove oral epithelial tissue. In addition, the bristles of the Parasher brush have sufficient stiffness to penetrate the basement membrane and reach the submucosa.
4. A transepithelial non-lacerational sampling apparatus according to claim 2, 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.	As shown in Fig. 2 of Stormby, the brush 4 has a handle with a distal and proximal end. The bristles of the brush 4 are connected to the distal end and form an abrasive surface. The bristles 11 of the Parasher brush form an abrasive surface. *See supra* sec. V(B), claim 4.

Claim	**Stormby-Boon-Parasher**
5. Apparatus to obtain cells as set forth in claim 1, wherein said brush comprises a handle and a head portion, said head portion comprising bristles.	See claim 4 above. The handle of the brush 4 in Stormby has a head portion that comprises bristles.
6. A transepithelial non-lacerational sampling apparatus according to claim 5, wherein said handle comprises a cylinder.	As shown in Fig. 2 of Stormby, the handle of the brush 4 is cylindrical.
7. A transepithelial non-lacerational sampling apparatus according to claim 5, wherein said head portion comprises bristles directed outwardly from said head portion.	As shown in Fig. 2 of Stormby, the head portion of the handle has bristles directed outwardly from the head portion.
8. A transepithelial non-lacerational sampling apparatus according to claim 7, wherein said handle has a distal and a proximal end, said head portion comprises bristles directed radially outwardly from the distal end of said handle.	See claims 4, 5, and 7 above. The handle of the brush 4 has a distal and proximal end and the head portion of the handle has bristles directed outwardly from the head portion.
11. Apparatus as set forth in claim 5, wherein said bristles have a tip stiffness, and wherein said bristles protrude between 0.05-0.2 inches.	The top bristles of the brush 4 in Stormby inherently have a tip stiffness and protrude about 5.4 mm, which converts to about 0.2 in. Stormby, 2:40-50. The bristles also protrude between 0.05-0.2 inches. Further, the bristles 11 of the device 1 of Parasher protrude between 0.05-0.2 inches. *See supra* sec. V(B), claim 11.

Claim	**Stormby-Boon-Parasher**
14. A transepithelial non-lacerational sampling apparatus according to claim 4, wherein said brush comprises a handle and a head portion, said head portion comprising bristles.	See claims 4 and 5 above. The handle of the brush 4 in Stormby has a head portion that comprises bristles.
15. A transepithelial non-lacerational sampling apparatus according to claim 14, wherein said handle comprises a cylinder.	See claim 6 above. As shown in Fig. 2 of Stormby, the handle of the brush 4 is cylindrical.
16. A transepithelial non-lacerational sampling apparatus according to claim 14, wherein said head portion comprises bristles directed outwardly from said head portion.	See claim 7 above. As shown in Fig. 2 of Stormby, the head portion of the handle has bristles directed outwardly from the head portion.
17. A transepithelial non-lacerational sampling apparatus according to claim 16, wherein said handle has a distal and a proximal end, said head portion comprises bristles directed radially outwardly from the distal end of said handle.	See claims 4, 5, 7, and 8 above. The handle of the brush 4 in Stormby has a distal and proximal end and the head portion of the handle has bristles directed outwardly from the head portion.

5. Claim 12: "A transepithelial non-lacerational sampling apparatus to harvest cells in an oral cavity from the epithelial tissue, said epithelial tissue comprising superficial, intermediate and basal layers, and a basement membrane located between the basal layer and the submucosa, said non-lacerational sampling apparatus comprising means to traverse said superficial, intermediate and basal layers and to collect cells from said three layers."

As discussed above, both the Cytobrush® and the brush of Parasher are transepthelial non-lacerational apparatuses capable of harvesting cells from epithelial tissue in the oral cavity. *See supra* sec. V(B)(1-3). Moreover, the bristles of the Parasher brush collect cells from all three layers of the oral epithelial tissue (*e.g.*, the superficial, intermediate, and basal layers) and also have sufficient stiffness to penetrate the basement membrane and reach the submucosa. *Id*. Thus, claim 12 is rendered obvious by Stormby in view of the Boon Article, and further in view of Parasher.

To the extent the Board finds that the language of claim 12 is subject to 35 U.S.C. § 112, paragraph 6, the Petitioner respectfully submits claim 12 is still rendered obvious by Stormby in view of the Boon Article, and further in view of Parasher. In the specification of the '044 Patent, the only structure disclosed for traversing and collecting cells from the three layers of the epithelium comprises a non-lacerational brush with stiff bristles. Both Stormby and Parasher disclose such a brush. Likewise, the Cytobrush® of Stormby is a non-lacerational brush capable of harvesting cells from epithelial tissue in the oral cavity. Additionally, the brush of Parasher is non-lacerational with bristles capable of collecting tissue cells from all three layers of the epithelial tissue (*e.g.*, the superficial, intermediate, and basal layers) that also have sufficient stiffness to penetrate the basement membrane and reach the submucosa. *See supra* sec. V(B)(1-3).

6. Dependent Claims 13, 18, and 21-25

The claim chart below shows where each of the features of claims 13, 18, and 21-25 are found in Stormby, the Boon Article, and/or Parasher. As such, claims 13, 18, and 21-25 are rendered obvious by Stormby in view of the Boon Article, and further in view of Parasher.

Claim	**Stormby/Boon/Parasher**
13. A transepithelial non-lacerational sampling apparatus according to claim 12, wherein said means to traverse said three layers comprises sufficient stiffness to traverse said basement membrane and reach into said submucosa.	*See supra* sec. V(E), claim 12. The bristles of the Cytobrush® of Stormby may be used to penetrate and remove oral epithelial tissue. In addition, the bristles of the Parasher brush have sufficient stiffness to penetrate the basement membrane and reach the submucosa.
18. A transepithelial non-lacerational sampling apparatus according to claim 12, wherein said handle comprises a distal and a proximal end, further comprising wires connected to and extending from said distal end, said bristles held by said wires to form brushing surfaces at the tips of said bristles, said brushing surfaces abrading said epithelial tissue.	As shown in Fig. 2 of Stormby, the handle of the brush 4 has a distal and proximal end with wires connected to and extending from the distal end. The bristles of the brush 4 are held by the wires to form brushing surfaces at the tips of the bristles that abrade the epithelial tissue. The brush of Parasher has brushing surfaces that abrade the epithelial tissue. *See supra* sec. V(B)(1-3).
21. A transepithelial non-lacerational sampling apparatus according to claim 18, wherein said wires form a toroid which is substantially perpendicular to the axis of said handle.	As shown in Fig. 2 of Stormby, the bristles of the brush 4 are held by a wire and form a plurality of toroids substantially perpendicular to the handle.

Claim	**Stormby/Boon/Parasher**
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.	As shown in Fig. 2 of Stormby, the brush 4 has a conically shaped tip 5 with spiraled nylon bristles extending substantially perpendicular to the axis of the handle.
23. A transepithelial non-lacerational sampling apparatus according to claim 12, wherein said bristles comprise tips, wherein said tips comprise scraping edges.	The brush 4 of Stormby has tips with scraping edges. In addition, the bristles 11 of the Parasher brush 9 have tips with edges that scrape, capture and hold cells and tissue. *See supra* sec. V(B), claim 23.
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.	*See supra* sec. V(E), claim 4. As shown in Fig. 2 of Stormby, the brush 4 has a handle with a distal and proximal end. The bristles of the brush 4 are connected to the distal end and form an abrasive surface. Further, the bristles 11 of the Parasher brush form an abrasive surface. *See supra* sec. V(B), claim 24.
25. A transepithelial non-lacerational sampling apparatus according to claim 12, wherein said brush has a round head, said bristles being stiff.	As shown in Fig. 2 of Stormby, the brush 4 has a round head. The brush 9 of Parasher has a round head and stiff or semi-rigid bristles. *See supra* sec. V(B), claim 25.

7. Claim 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."

Both Stormby/Boon and Parasher disclosed a method to collect cells in epithelial tissue of the body. As discussed above, both the Cytobrush® of Stormby and the brush of Parasher are non-lacerational and capable of collecting tissue cells from epithelial tissue. The Boon Article explained how the Cytobrush® could be used to collect fragment of epithelial tissue. (Ex. 1008 at 57-58.) Parasher also explained in detail how the brush could be used to penetrate the epithelial tissue to collect biopsy samples. *See supra* sec. V(B)(1-3). In particular, Parasher disclosed a method of collecting cells in epithelial tissue of the body by passing a transipithelial non-lacerational brush through the epithelial tissue. *Id*. Thus, claim 26 is rendered obvious by Stormby in view of the Boon Article, and further in view of Parasher.

8. Dependent Claims 27-36

The claim chart below shows where each of the features of claims 27-36 are found in Stormby, the Boon Article, and/or Parasher. As such, claims 27-36 are rendered obvious by Stormby in view of the Boon Article, and further in view of Parasher.

Claim	**Stormby/Boon/Parasher**
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,	*See supra* sec. V(E), claims 2 and 12. The bristles of the Parasher brush are capable of collecting cells from all three layers of the epithelial tissue.

Claim	**Stormby/Boon/Parasher**
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.	*See supra* sec. V(E), claims 3 and 13. The bristles of the Parasher brush have sufficient stiffness to penetrate the basement membrane and reach the submucosa.
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.	As discussed above, the Boon Article describes use of the Cytobrush® of Stormby such that the bristles have a "toothpick" effect that easily dislodges epithelial fragments. Boon, pp. 57-58. As discussed above, this "toothpick effect" is accomplished by rotating and drilling into the epithelial tissue with the Cytobrush®.
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.	Rotating and drilling into the epithelial tissue using the Cytobrush® of Stormby includes moving the brush substantially perpendicularly to the epithelial 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.	As discussed above, both the Cytobrush® of Stormby and the Parasher device are capable of collecting cells from oral epithelial tissue.
32. A method to collect cells in epithelial tissue of the body according to claim 27, further comprising	The Cytobrush® of Stormby abrades the epithelia tissue as it is rotated and drilled in the tissue (*i.e.*, the toothpick

Claim	**Stormby/Boon/Parasher**
abrading the epithelial tissue to collect cells.	effect). Further, the brush of Parasher abrades the epithelial tissue. *See supra* sec. V(B), claim 32.
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.	The Parasher device is capable of penetrating a keratinized layer and collecting cells from beneath the keratinized layer. *See supra* sec. V(B), claim 33.
34. A method to collect cells in epithelial tissue of the body according to claim 26, wherein said epithelial tissue comprises oral epithelial tissue.	See claim 31 above. Both the Cytobrush® of Stormby and the Parasher device are capable of collecting cells from oral epithelial tissue.
35. A method to collect according to claim 26, further comprising abrading the epithelial tissue to collect cells.	See claim 32 above. The brush of Parasher may be used to abrade 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.	See claims 32 and 35 above. The bristles of the Cytobrush® of Stormby form a scrubbing surface that contact the epithelial tissue to dislodge cells. Boon, pp. 57-58. Rotating and drilling into the epithelial tissue with the Cytobrush® of Stormby exerts sufficient pressure on the bristles to dislodge cells from the epithelial tissue. Further, the bristles 11 of the Parasher brush form a scrubbing surface that contact the epithelial tissue to dislodge cells. *See supra* sec. V(B), claim 36.

9. Claim 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."

Both Stormby and Parasher disclosed an apparatus capable of obtaining cells in epithelial tissue of the body. The Cytobrush® of Stormby and the brush of Parasher are also non-lacerational and capable of collecting tissue cells from epithelial tissue. The bristles of the Cytobrush® of Stormby have tips with edges that are used to penetrate the epithelial tissue. Further, the bristles 11 of the brush 9 of Parasher have tips with edges that scrape, capture and hold cells of the epithelial tissue. *See supra* sec. V(B)(1-3). As such, the bristles form an assemblage of penetrating edges that penetrate at least two layers of epithelial tissue. Claim 37 is rendered obvious by Stormby in view of the Boon Article, and further in view of Parasher.

10. Dependent Claims 38 and 39

The claim chart below shows where each of the features of claims 38 and 39 are found in Stormby, the Boon Article, and/or Parasher. As such, claims 38 and 39 are rendered obvious by Stormby in view of the Boon Article, and further in view of Parasher.

Claim	**Stormby-Boon-Parasher**
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.	*See supra* sec. V(E), claims 2, 3, 12, 13, 27, and 28. The bristles of the Parasher brush collect cells from all three layers of the epithelial tissue (*e.g.*, the superficial, intermediate, and basal layers) and also have sufficient stiffness to penetrate the basement membrane and reach the submucosa.
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.	*See supra* sec. V(E), claims 2, 3, 12, 13, 27, and 28. The bristles of the Parasher brush have sufficient stiffness to penetrate the basement membrane and reach the submucosa.

F. Claims 9-10 and 19-20 are rendered obvious by Stormby in view of the Boon Article, and further in view of Parasher and Markus

Claims 9 and 19 recite that the "tip stiffness of each bristle is between 0.04 and 0.2 lbs/inch." Claim 10 depends from claim 9 and further recites that "said bristles protrude between 0.05-0.2 inches." Similarly, claim 20 depends from claim 19 and adds that "said bristles protrude between 0.05-0.2 inches from the wires in which said bristles are held."

As discussed above, the Cytobrush® of Stormby modified with the brush of Parasher discloses these claim elements besides the cantilever or tip stiffness of the bristles of the brush. The Petitioner respectfully submits that it is a matter of

routine experimentation for one of ordinary skill in the art to determine the optimal or workable range of cantilever or tip stiffness for the bristles. *See, e.g.*, MPEP 2144.05(II)(A). Furthermore, as discussed above, Markus discloses a culturing brush having a plurality of bristles extending from at stainless steel wire stem in which the bristles are held. *See supra* sec. V(C). It is respectfully submitted that it would be routine and obvious to one of ordinary skill in the art to further modify the Cytobrush® in view of Stormby and further in view of Markus. Both brushes are used for sample collection and have a similar size and shape. Modifying the Cytobrush® of Stormby to be the brush of Markus is a simple substitution of one brush for another to obtain predictable results.

Moreover, the bristles of the brush in Markus are made of Tynex®, the same material as the bristles of the brush in the '044 Patent, and have a stiffness of about .056 lbs/inch, which falls within the range of 0.04 and 0.2 lbs/inch recited in claims 9 and 19. *See supra* sec. V(C). The length of the bristles extending from the wire stem fall within the range of 0.05-0.2 inches recited in claims 10 and 20. *Id*. As such, claims 9-10 and 19-20 are rendered obvious by Stormby in view of the Boon Article, and further in view of Parasher and Markus.

G. Claims 18, 21, and 22 are rendered obvious by Stormby in view of the Boon Article, and further in view of Parasher and Spirabrush

As described above, the Stormby-Boon-Parasher combination discloses each and every limitation of claims 18, 21, and 22. If this combination is found by the

Board not to disclose the features of these claims, then such features are clearly disclosed in Spirabrush. As discussed above, Spirabrush discloses a brush having a structure that is substantially the same as the brush shown in the '044 Patent. *See supra* sec. V(D). It is respectfully submitted that it would be routine and obvious to one of ordinary skill in the art to further modify the Cytobrush® of Stormby to be the brush of Spirabrush. Both brushes have the same purpose and perform the same function - obtaining samples of epithelia tissue within the body. Both brushes also have a similar size and shape, and are capable of traversing passages within the body. Modifying the Cytobrush® in view of Stormby and further in view of Spirabrush is a simple substitution of one for another to obtain predictable results — hallmark of obviousness.

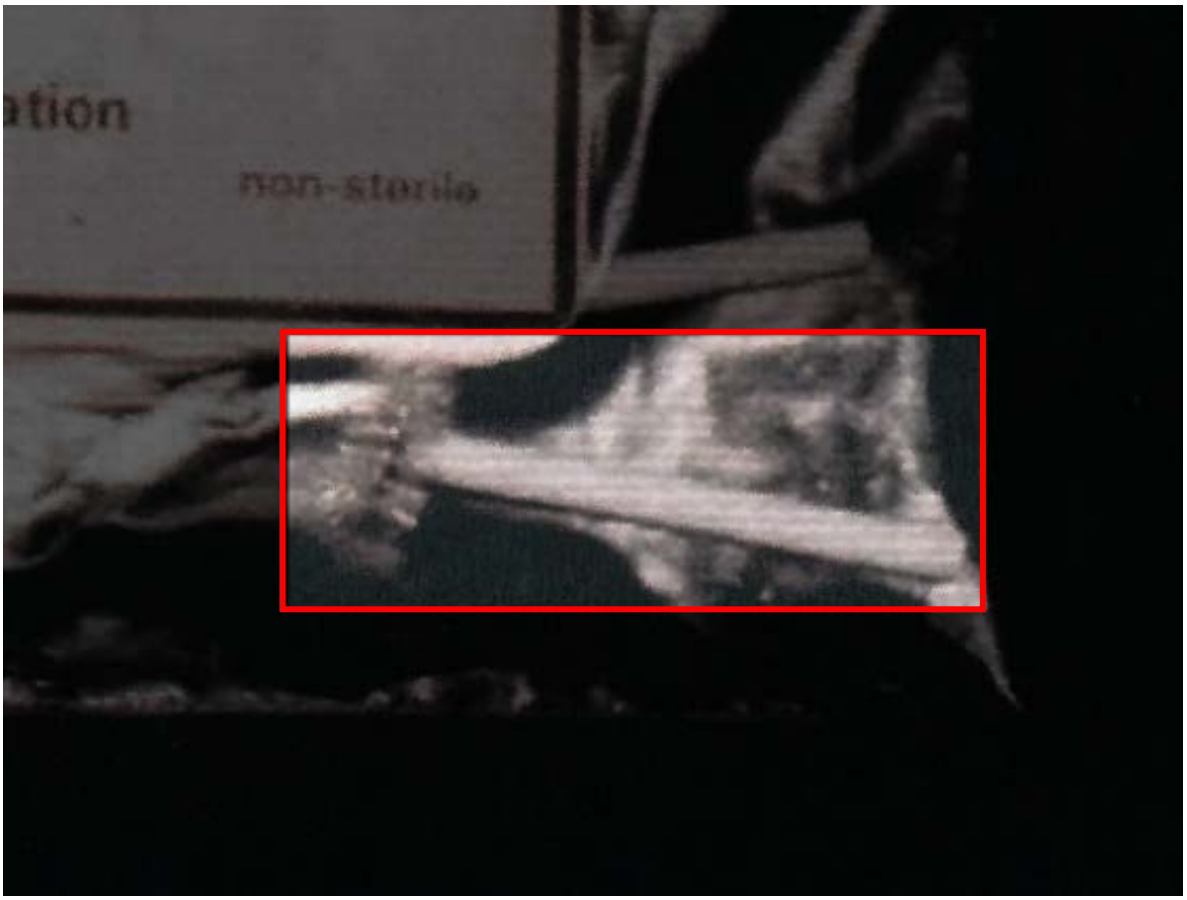
The claim chart below shows where each of the features of claims 18, 21, and 22 are found in the combination of Stormby-Boon-Parasher and Spirabrush. As such, claims 18, 21, and 22 are rendered obvious by the combination of Stormby-Boon-Parasher in view of Spirabrush.

Claim	**Stormby-Boon-Parasher and Spirabrush**
18. A transepithelial non-lacerational sampling apparatus according to claim 12, wherein said handle comprises a distal and a proximal end, further comprising wires connected to and extending from said distal end, said bristles held by said wires to form	The brush of Spirabrush has wires extending from a distal end of a handle and the bristles are held by the wires to form brushing surfaces at the tips of the bristles. *See supra* sec. V(D). The brush of Parasher has brushing surfaces that abrade the epithelial tissue. *See*

Claim	**Stormby-Boon-Parasher and Spirabrush**
brushing surfaces at the tips of said bristles, said brushing surfaces abrading said epithelial tissue.	*supra* sec. V(B)(1-3).
21. A transepithelial non-lacerational sampling apparatus according to claim 18, wherein said wires form a toroid which is substantially perpendicular to the axis of said handle.	The brush of Spirabrush has wires that form a toroid which is substantially perpendicular to the axis of the handle. *See supra* sec. V(D).
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.	The brush of Spirabrush is in the form of a spiral shape substantially perpendicular to the axis of the handle. *See supra* sec. V(D).

H. Claims 1-8, 11-18, and 21-39 are rendered obvious by Spirabrush in view of Parasher

Spirabrush discloses the following sampling brush:



Spirabrush - Ex. 1006

As explained above in Section V(D), a comparison of the photograph above with Figs. 1-6 of the ‘044 Patent shows that the SpiraBrush brush has the same structure as the brush shown and described in the ‘044 Patent. Further, the Eisen Patent indicates that the SpiraBrush™ is capable penetrating all three layers of the oral epithelium. (Eisen Patent, 5:24-44.) Also, as previously discussed, it is known in the art that a cytology or sampling brush like the brush in Spirabrush may be used in the oral cavity. *See supra* sec. V(D). As such, the Spirabrush may be used to penetrate and remove oral epithelial tissue.

It is respectfully submitted that it would be routine and obvious to one of ordinary skill in the art to modify the brush of SpiraBrush in view of Parasher. Both brushes have the same purpose and perform the same function - obtaining epithelial tissue samples within the body. Further, both brushes have a similar size and shape, and are designed to traverse passages within the body. Modifying the brush of SpiraBrush in view of Parasher is a simple substitution of one brush for another to obtain predictable results.

1. Claim 1: "An 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 a brush, said brush comprising bristles having sufficient stiffness to penetrate at least said two layers of said epithelial tissue."

As discussed in the '044 Patent, cytology or sampling brushes are considered by the Applicant to be non-lacerational. (Ex. 1001 at 2:26-4:25.) Further, the '044 Patent states that the brush shown in the '044 Patent, which is the same as the Spirabrush brush, is non-lacerational. (*Id*. at 55-62.) Moreover, the brush of Parasher is non-lacerational and capable of collecting tissue cells from at least two layers of epithelial tissue. *See supra* sec. V(B)(1-3). As discussed above, the brush is capable of collecting tissue samples sufficient to qualify as a biopsy, which would necessarily include tissue located within two layers of epithelial tissue. *Id.* As such, the brush of SpiraBrush modified in view of Parasher is a

transepithelial, non-lacerational brush with bristles having sufficient stiffness to collect cells from at least two layers of epithelial tissue. Claim 1 is rendered obvious by SpiraBrush in view of Parasher.

2. Claim 2: "Apparatus to obtain cells in epithelial tissue of the body according to claim 1, wherein said bristles 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."

As discussed above, the brush of Parasher may be used to obtain biopsy samples of oral epithelia tissue (*e.g.*, within the oral cavity) that would necessarily include all three layers (*e.g.*, the superficial, intermediate, and basal layers) of the tissue. *See supra* sec. V(B)(1-3). The bristles of the Parasher brush collect cells from all layers of the epithelial tissue and also have sufficient stiffness to penetrate the basement membrane and reach the submucosa. *Id*. As such, claim 2 is rendered obvious by Spirabrush in view of Parasher.

3. Claims 3-8, 11-18, and 21-39

The claim chart below shows where each of the features of claims 3-8, 11-18, and 21-39 are found in SpiraBrush or Parasher. As such, claims 3-8, 11-18, and 21-39 are rendered obvious by SpiraBrush in view of Parasher.

Claim	**SpiraBrush and Parasher**

Claim	**SpiraBrush and Parasher**
3. Apparatus to obtain cells in epithelial tissue of the body according to claim 2, wherein said bristles of said brush have sufficient stiffness to penetrate said basement membrane and reach said submucosa.	See claim 2 above. The bristles of the Parasher brush have sufficient stiffness to penetrate the basement membrane and reach the submucosa.
4. A transepithelial non-lacerational sampling apparatus according to claim 2, 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.	As shown in Spirabrush, the brush has a handle with a distal and proximal end. The bristles of the brush are connected to the distal end and form an abrasive surface. Further, as explained above, the bristles 11 of the Parasher brush form an abrasive surface.
5. Apparatus to obtain cells as set forth in claim 1, wherein said brush comprises a handle and a head portion, said head portion comprising bristles.	See claim 4 above. The handle of the brush in Spirabrush has a head portion that comprises bristles.
6. A transepithelial non-lacerational sampling apparatus according to claim 5, wherein said handle comprises a cylinder.	As shown in Spirabrush, the handle of the brush is cylindrical.
7. A transepithelial non-lacerational sampling apparatus according to claim 5, wherein said head portion comprises bristles directed outwardly from said head portion.	As shown in Spirabrush, the head portion of the handle has bristles directed outwardly from the head portion.

Claim	**SpiraBrush and Parasher**
8. A transepithelial non-lacerational sampling apparatus according to claim 7, wherein said handle has a distal and a proximal end, said head portion comprises bristles directed radially outwardly from the distal end of said handle.	See claims 4, 5, and 7 above. The handle of the brush in Spirabrush has a distal and proximal end and the head portion of the handle has bristles directed outwardly from the head portion.
11. Apparatus as set forth in claim 5, wherein said bristles have a tip stiffness, and wherein said bristles protrude between 0.05-0.2 inches.	The bristles 11 of the device 1 of Parasher inherently have a tip stiffness and also extend radially between 1 to 3 mm. Parasher, 4:59-62. This range converts to between .039 and .118 inches. As such, the bristles 11 protrude between 0.05-0.2 inches.
12. A transepithelial non-lacerational sampling apparatus to harvest cells in an oral cavity from the epithelial tissue, said epithelial tissue comprising superficial, intermediate and basal layers, and a basement membrane located between the basal layer and the submucosa, said non-lacerational sampling apparatus comprising means to traverse said superficial, intermediate and basal layers and to collect cells from said three layers.	See claim 2 above. The brush of Parasher is a transepthelial non-lacerational apparatus capable of harvesting cells from epithelial tissue in the oral cavity. *See supra* sec. V(B)(1-3). The bristles of the Parasher brush collect cells from all three layers of the oral epithelial tissue (*e.g.*, the superficial, intermediate, and basal layers) and also have sufficient stiffness to penetrate the basement membrane and reach the submucosa. *Id.*[3]

[3] To the extent the Board finds that the language of claim is subject to 35 U.S.C. § 112, paragraph 6, the Petitioner respectfully submits claim 12 is still rendered obvious by Spirabrush in view of Parasher. In the specification, the structure the Applicant contends is capable of traversing and collecting cells from the three

Claim	**SpiraBrush and Parasher**
13. A transepithelial non-lacerational sampling apparatus according to claim 12, wherein said means to traverse said three layers comprises sufficient stiffness to traverse said basement membrane and reach into said submucosa.	See claim 12 above. The bristles of the Parasher brush have sufficient stiffness to penetrate the basement membrane and reach the submucosa.
14. A transepithelial non-lacerational sampling apparatus according to claim 4, wherein said brush comprises a handle and a head portion, said head portion comprising bristles.	See claims 4 and 5 above. The handle of the brush in SpiraBrush has a head portion that comprises bristles.
15. A transepithelial non-lacerational sampling apparatus according to claim 14, wherein said handle comprises a cylinder.	See claim 6 above. As shown in SpiraBrush, the handle of the brush is cylindrical.
16. A transepithelial non-lacerational sampling apparatus according to claim 14, wherein said head portion comprises bristles directed outwardly from said head portion.	See claim 7 above. As shown in SpiraBrush, the head portion of the handle has bristles directed outwardly from the head portion.
17. A transepithelial non-lacerational sampling apparatus according to claim 16, wherein said handle has a distal and a proximal end, said head portion comprises bristles directed radially outwardly from the distal end of said handle.	See claims 4, 5, 7, and 8 above. The handle of the brush in SpiraBrush has a distal and proximal end and the head portion of the handle has bristles directed outwardly from the head portion.

layers of the epithelium is a brush that has the same structure as the brush in SpiraBrush. *See, e.g.,* '044 Patent, Figs. 1-6.

Claim	**SpiraBrush and Parasher**
18. A transepithelial non-lacerational sampling apparatus according to claim 12, wherein said handle comprises a distal and a proximal end, further comprising wires connected to and extending from said distal end, said bristles held by said wires to form brushing surfaces at the tips of said bristles, said brushing surfaces abrading said epithelial tissue.	As shown in SpiraBrush, the handle of the brush has a distal and proximal end with wires connected to and extending from the distal end. The bristles of the brush are held by the wires to form brushing surfaces at the tips of the bristles that abrade the epithelial tissue. Moreover, as discussed above, the brush of Parasher has bristles with brushing surfaces that abrade the epithelial tissue. *See supra* sec. V(B)(1-3).
21. A transepithelial non-lacerational sampling apparatus according to claim 18, wherein said wires form a toroid which is substantially perpendicular to the axis of said handle.	As shown in SpiraBrush, the wires of the brush form a toroid which is substantially perpendicular to the axis of the handle.
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.	As shown in SpiraBrush, the brush is in the form of a spiral shape substantially perpendicular to the axis of the handle.
23. A transepithelial non-lacerational sampling apparatus according to claim 12, wherein said bristles comprise tips, wherein said tips comprise scraping edges.	The brush of SpiraBrush has tips with scraping edges. In addition, the bristles 11 of the Parasher brush 9 have tips with edges that scrape, capture and hold cells and tissue. *See supra* sec. V(B)(1-3).

Claim	**SpiraBrush and Parasher**
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.	See claim 4 above. As shown in SpiraBrush, the brush has a handle with a distal and proximal end. The bristles of the brush are connected to the distal end and form an abrasive surface. Further, as explained above, the bristles 11 of the Parasher brush form 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.	As shown in SpiraBrush, the brush has a round head. The brush 9 of Parasher has a round head and also has stiff or semi-rigid bristles. *See supra* sec. V(B)(1-3).
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.	As discussed above, the brush of Parasher is non-lacerational and capable of collecting tissue cells from epithelial tissue. Parasher also explained in detail how the brush could be used to penetrate the epithelial tissue to collect biopsy samples. A biopsy sample collected by the bristles of the Parasher brush would necessarily include tissue located within two layers of epithelial tissue. *See supra* sec. V(B)(1-3).
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.	See claims 2 and 12 above. The bristles of the Parasher brush are capable of collecting cells from all three layers of the epithelial tissue.

Claim	**SpiraBrush and Parasher**
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.	See claims 3 and 13 above. The bristles of the Parasher brush have sufficient stiffness to penetrate the basement membrane and reach the submucosa.
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.	Because the brush of SpiraBrush is substantially the same as the brush shown in the '044 Patent, the brush of SpiraBrush is capable of being rotated and drilled into epithelial 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.	See claim 29 above. Rotating and drilling into the epithelial tissue using the SpiraBrush includes moving the brush substantially perpendicularly to the epithelial 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.	As discussed above, both the SpiraBrush and the Parasher device are capable of collecting cells from 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.	As discussed above, the brush of Parasher is pulled back and forth, several times, to scrape and scrub the epithelial tissue to collect biopsy tissue samples. *See supra* sec. V(B)(1-3).

Claim	**SpiraBrush and Parasher**
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.	As discussed above, the Parasher device is capable of penetrating a keratinized layer and collecting cells from beneath the keratinized layer. *See supra* sec. V(B)(1-3).
34. A method to collect cells in epithelial tissue of the body according to claim 26, wherein said epithelial tissue comprises oral epithelial tissue.	See claim 31 above. Both the SpiraBrush and the Parasher device are capable of collecting cells from oral epithelial tissue.
35. A method to collect according to claim 26, further comprising abrading the epithelial tissue to collect cells.	See claim 32 above. The brush of Parasher may be used to abrade 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.	See claims 32 and 35 above. The bristles of the SpiraBrush form a scrubbing surface that contact the epithelial tissue to dislodge cells. Rotating and drilling into the epithelial tissue with the SpiraBrush exerts sufficient pressure on the bristles to dislodge cells from the epithelial tissue. Further, the bristles 11 of the Parasher brush form a scrubbing surface that contact the epithelial tissue to dislodge cells. *See supra* sec. V(B), claim 36.

Claim	**SpiraBrush and Parasher**
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.	As discussed above, the brush of SpiraBrush and the brush of Parasher are non-lacerational and capable of collecting tissue cells from epithelial tissue. The bristles of the brush in SpiraBrush has tips with edges that are used to penetrate the epithelial tissue. Further, the bristles 11 of the brush 9 of Parasher have tips with edges that scrape, capture and hold cells of the epithelial tissue. *See supra* sec. V(B), claim 37.
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.	See claims 2, 3, 12, 13, 27, and 28 above. The bristles of the Parasher brush collect cells from all three layers of the epithelial tissue (e.g., the superficial, intermediate, and basal layers) and also have sufficient stiffness to penetrate the basement membrane and reach the submucosa. *See supra* sec. V(B), claim 38.
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.	See claims 2, 3, 12, 13, 27, and 28 above. The bristles of the Parasher brush collect cells from all three layers of the epithelial tissue and also have sufficient stiffness to penetrate the basement membrane and reach the submucosa. *See supra* sec. V(B), claim 39.

I. Claims 9-10 and 19-20 are rendered obvious by SpiraBrush in view of Parasher, and further in view of Markus

Claims 9 and 19 recite that the "tip stiffness of each bristle is between 0.04 and 0.2 lbs/inch." Claim 10 depends from claim 9 and further recites that "said

bristles protrude between 0.05-0.2 inches." Similarly, claim 20 depends from claim 19 and further recites that "said bristles protrude between 0.05-0.2 inches from the wires in which said bristles are held."

As discussed above, the brush of SpiraBrush modified in view of Parasher discloses the elements of these claims besides the cantilever or tip stiffness of the bristles of the brush. The Petitioner respectfully submits that it is a matter of routine experimentation for one of ordinary skill in the art to determine the optimal or workable range of cantilever or tip stiffness for the bristles. *See, e.g.*, MPEP 2144.05(II)(A). As explained above, Markus discloses a culturing brush having a plurality of bristles extending from at stainless steel wire stem in which the bristles are held. *See supra* sec. V(C). Modifying the SpiraBrush in view of Markus is a simple substitution of one brush for another to obtain predictable results.

The bristles of the brush in Markus are made of Tynex®, the same material as the bristles of the brush in the '044 Patent, and have a stiffness of about .056 lbs/inch, which falls within the range of 0.04 and 0.2 lbs/inch recited in claims 9 and 19. *See supra* sec. V(C). Moreover, the length of the bristles extending from the wire stem fall within the range of 0.05-0.2 inches recited in claims 10 and 20. *Id*. As such, claims 9-10 and 19-20 are rendered obvious by Spirabrush in view of Parasher, and further in view of Markus.

J. Claims 18, 21, and 22 are rendered obvious by Parasher in view of Nomiya

As shown in Fig. 1, Nomiya discloses an annular brush for cleaning cylindrical vessels. The brush has a round head with bristles held together with wires forming a loop 7. The bristles form brushing surfaces and the wires form a toroid that is substantially perpendicular to the axis of the handle. The brush is in the form of a spiral shape substantially perpendicular to the axis of the handle.

It is respectfully submitted that it would be routine and obvious to one of ordinary skill in the art to modify the brush of Parasher in view of the brush structure of Nomiya. Both brushes are capable of traversing passages and are similar size and shape. Modifying the brush of Parasher in view of Nomiya is a simple substitution of one brush for another to obtain predictable results — the hallmark of obviousness.

The claim chart below shows where each of the features of claims 18, 21, and 22 are found in Parasher and Nomiya. As such, claims 18, 21, and 22 are rendered obvious by Parasher in view of Nomiya.

Claim	**Parasher/Nomiya**
18. A transepithelial non-lacerational sampling apparatus according to claim 12, wherein said handle comprises a distal and a proximal end, further comprising wires connected to and extending from said distal end, said bristles held by said wires to form brushing surfaces at the tips of said bristles, said brushing surfaces	As shown in Fig. 1 of Nomiya, the brush of Nomiya has wires extending from a distal end of a handle and the bristles are held by the wires to form brushing surfaces at the tips of the bristles. The brush of Parasher has brushing surfaces that abrade the epithelial tissue. *See supra* sec. V(B)(1-3).

Claim	**Parasher/Nomiya**
abrading said epithelial tissue.	
21. A transepithelial non-lacerational sampling apparatus according to claim 18, wherein said wires form a toroid which is substantially perpendicular to the axis of said handle.	As shown in Fig. 1 of Nomiya, the brush has wires that form a toroid which is substantially perpendicular to the axis of the handle.
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.	As shown in Fig. 1 of Nomiya, the brush is in the form of a spiral shape substantially perpendicular to the axis of the handle.

VI. CONCLUSION

For the foregoing reasons, *inter partes* review of claims 1-39 of U.S. Patent No. 6,258,044 is respectfully requested.

Respectfully submitted,

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CERTIFICATE OF SERVICE ON PATENT OWNER UNDER 37 C.F.R. § 42.105(a)

Pursuant to 37 C.F.R. §§ 42.8(e) and 42.105(b), the undersigned certifies that on the 15th day of April, 2014, a complete and entire copy of this Petition for *Inter Partes* Review and all supporting exhibits were provided via Federal Express, postage prepaid, to the Pater Owner by serving the correspondence address of record for the '044 Patent:

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