Non-endoscopic biopsy techniques: a review

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Abstract

Introduction: Diseases of the stomach and small intestine account for approximately 20% of all gastrointestinal (GI)-related mortality. Biopsy of the stomach and small intestine remains a key diagnostic tool for most of the major diseases that affect the GI tract. While endoscopic means for obtaining biopsy is generally the standard of care, it has several limitations that make it less ideal for pediatric patients and in low resource areas of the world. Therefore, non-endoscopic means for obtaining biopsy samples is of interest in these settings.

Areas covered: We review non-endoscopic biopsy techniques reported thus far, and critically examine their merits and demerits regarding their suitability for obtaining biopsy samples in non-sedated subjects.

Expert commentary: Esophagogastroduodenoscopy (EGD) is the current standard for acquiring biopsy from the GI tract, however, its limitations include subject sedation, expensive endoscopy infrastructure, expert personnel, and a small but significant risk of complications. A less costly, minimally-invasive and non-endoscopic means for obtaining biopsy samples is therefore of interest for addressing these issues. Such a technology would be of significant impact in low- and middle-income countries where conducting endoscopy is challenging.

1. Introduction

Diseases of the stomach and the small intestine account for about 20% of all deaths attributable to gastrointestinal (GI) conditions in the US [1]. The financial cost associated with the treatment of these disorders, including gastric intestinal neoplasia, exceeds $500 billion annually [1,2]. One example, celiac disease (CD), is an autoimmune small intestinal condition resulting from ingestion of gluten by genetically predisposed people. While there are accurate serum markers for CD, a tissue diagnosis showing villous effacement and increased epithelial lymphocytes is still recommended [3,4] owing to the importance of placing those with CD on a lifelong gluten-free diet. Environmental enteric dysfunction (EED) is a poorly understood subclinical malabsorptive condition endemic to many developing countries, believed to result from poor sanitary and hygienic conditions [5]. This disorder may lead to stunting, inhibited mental development, and poor oral vaccine response. The debilitating effects from EED are hard to reverse once children grow pass the age of 2 years. Therefore, early and accurate diagnosis of this condition is imperative if EED is to be treated and proper growth in these children restored [6]. Biopsy is a key diagnostic tool for these and many other diseases that affect the stomach and small intestine. Currently, the preferred means for obtaining biopsy samples is esophagogastroduodenoscopy (EGD), where biopsies are obtained randomly or from discernible lesions. Endoscopic biopsy has several limitations as a diagnostic tool. Upper EGD often requires sedation of the subject which is inconvenient and carries nonnegligible risk. Second, endoscopy suites and requisite personnel contribute to health-care costs which limit EGD service provision in developing countries. Third, EGD/biopsy procedures are usually lengthy and, while infrequent, may lead to trauma, bleeding, or perforation of the small intestinal wall. Last, anesthesia may not be well tolerated by infants and children.

A less costly, minimally invasive, and non-endoscopic means for obtaining biopsy samples is therefore of interest to address these issues. Such a device would have a significant impact in low and middle-income countries where setting up an endoscopy facility and having appropriate personnel is challenging. In this article, we review non-endoscopic biopsy techniques reported thus far, and critically examine their merits and demerits regarding suitability for obtaining biopsy samples in non-sedated subjects.

2. Non-endoscopic small intestinal biopsy techniques

2.1. Kenamore forceps

In 1940, B. Kenamore made the first attempt to obtain biopsy samples from the gastric wall. He proposed using forceps to capture tissue while operating a rigid Schindler gastroscope.
for visualization [7,8]. In his design, shown in Figure 1, the forceps attached to a gastroscope had a cup type jaw for cutting and holding tissue with a maximum outer diameter of 3 mm. In 1946, Kenamore et al. obtained 35 gastric biopsy samples from anesthetized subjects with the aid of this instrument [9]. There were some drawbacks to this technique. The length of the gastroscope limited how far into the GI tract biopsies could be taken. The gastroscope also contained blind spots, hindering visibility. Further, the gastroscope was rigid, making it very difficult to reach the more hidden and distal portions of the GI tract.

2.2. Wood tube

In 1949, Wood et al. reported a biopsy technique using a flexible tube made of Bowden wire casing as shown in Figure 2 [10]. Providing suction at the proximal end using a pump caused the tissue to be pulled into a countersunk hole in the distal tubing. The cylindrical knife was actuated by pulling the attached wire to cut the tissue. This biopsy tube was used without the aid of a gastroscope. Wood and colleagues obtained 55 gastric specimens after 83 attempts from 48 subjects who were given topical anesthesia of the mouth and pharynx before the procedure [10,11]. Tomenius in 1950 reported a similar technique for obtaining biopsy samples from the stomach [12,13]. While this method effectively acquired biopsies from the stomach, the lack of guidance and the length of the tube limited its ability to access the small intestine.

2.3. Shiner capsule

Doig et al., Palmer et al., and Joske et al. [14–16] utilized the same biopsy suction mechanism as that proposed by Wood et al., but were not able to acquire biopsies from the duodenum. To pass through the pylorus and reach the duodenum, M. Shiner modified the wood suction tube, making it longer (128 cm), while shortening the sampling tube [17]. The sampling tube was attached to a heavier elliptical nickel piece to facilitate gastric emptying and entrance into the duodenum. The Shiner biopsy sampling device is shown in Figure 3. The use of X-ray fluoroscopy was essential for guiding the tube through the pylorus and confirming its position in the duodenum. Shiner used this tube for obtaining 12 successful duodenal biopsies from patients who gargled a topical anesthetic solution prior to the procedure. Pirola et al. also obtained biopsy samples from two patients using the Shiner capsule [18]. The tip of the tube was guided using fluoroscopy which is a limitation to this method for biopsy tissue acquisition.

2.4. Multipurpose Quinton tube

Brandborg, Rubin, and Quinton developed a sampling tube known as the multipurpose Quinton–Rubin tube, shown in Figure 4 [19]. This tube was similar to the Shiner capsule, but differed in that it could acquire four samples at any given time. The multipurpose Quinton–Rubin tube had four biopsy ports with two cylindrical knives as shown in Figure 4. The working mechanism of the multipurpose tube was the same as that for both Wood and Shiner tubes. Navigation into the intestine required X-ray fluoroscopy and weight increase of the tip of the device as well as a proper patient positioning technique [20]. The weight of the sampling tube was increased by a bag of mercury that was tied around the distal tip of the sampling tube. Ament et al. developed a biopsy tube for use in infants by reducing the outer diameter [21]. Reducing the biopsy port to 2.0 mm allowed adequate sizes of biopsy samples while reducing the risk of perforation. With this modification, biopsy samples were obtained from 69 children, of which 27 were less than 10 kg with a complication rate of less than 1% [22]. Liebman et al., Christie et al., and Kuitunen et al. also demonstrated small intestinal biopsy sampling using the multipurpose Quinton–Rubin tube [23–25]. This method was advantageous over the Shiner tube as four samples could be acquired during a single procedure. Safety in infants and children was also demonstrated. Nonetheless, fluoroscopy was still required for navigating and confirming its position in the intestine. Further, according to Anderson, the manipulation of the tube in young children could be emotionally traumatic and technically difficult unless the children are sedated [26].
Crosby and colleagues in the US army’s Sprue team felt that the rigidity of a wire-activated knife was less desirable, presumably for ease of use and safety reasons. Therefore, they proposed a mechanism that uses suction force to both pull tissue into the capsule and to activate a rotary spring-loaded knife \[27\]. The tissue acquisition device was comprised of a cylindrical capsule separated into two chambers by a rubber diaphragm. A knife was mounted on the proximal chamber and rotated around the axis of the capsule 90 degrees. This knife was actuated by a spring that was held loaded on the capsule wall by a key, as shown in Figure 6. When suction force was transmitted to the capsule, the surrounding tissue was first sucked through the biopsy ports on the capsule’s wall. Then, the vacuum created in the capsule caused the rubber diaphragm to bulge, kicking the spring off the key, sending the knife rotating past the herniated tissue and cutting it in the process. A standard Crosby capsule is 11 mm in diameter and 20 mm in length, however a variation of the capsule for pediatric use (8 mm × 17 mm) has also been reported \[28\]. An improvement and variation of the Crosby capsule known as the Watson capsule was developed by

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**Figure 3.** Suction biopsy tube variation developed by M. Shiner. Adapted from M. Shiner et al. (1955) [17].

**Figure 4.** The multipurpose Quinton-Rubin tube for biopsy sampling; (a) is the handle and (b) the sampling tube. Adapted from L. L. Brandborg et al. (1959) [19].

**Figure 5.** Crosby-Kugler biopsy capsule, (a) when open and (b) when closed. Adapted from W. H. Crosby et al. (1957) [27].

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### 2.5. Crosby-Kugler capsule

Crosby and colleagues in the US army’s Sprue team felt that the rigidity of a wire-activated knife was less desirable, presumably for ease of use and safety reasons. Therefore, they proposed a mechanism that uses suction force to both pull tissue into the capsule and to activate a rotary spring-loaded knife [27]. The tissue acquisition device was comprised of a cylindrical capsule separated into two chambers by a rubber diaphragm. A knife was mounted on the proximal chamber and rotated around the axis of the capsule 90 degrees. This knife was actuated by a spring that was held loaded on the capsule wall by a key, as shown in Figure 6. When suction force was transmitted to the capsule, the surrounding tissue was first sucked through the biopsy ports on the capsule’s wall. Then, the vacuum created in the capsule caused the rubber diaphragm to bulge, kicking the spring off the key, sending the knife rotating past the herniated tissue and cutting it in the process. A standard Crosby capsule is 11 mm in diameter and 20 mm in length, however a variation of the capsule for pediatric use (8 mm × 17 mm) has also been reported [28]. An improvement and variation of the Crosby capsule known as the Watson capsule was developed by...
McCarthy et al., in which the knife block and the spring were one piece [29]. This method for biopsy tissue acquisition has the advantage of the capsule tether being flexible and long enough to access the jejunum; and swallowing the capsule is achievable without requiring anesthesia or sedation. Anderson reported that the capsule may not require more than one person to assist the operator and that fluoroscopy may be used sparingly as one can be reasonably sure that the capsule has entered the duodenum when clear yellow fluid siphons up the tubing [26]. One drawback to this method, aside from it being guided blindly, is that only one sample can be obtained before the capsule is retrieved.

Some safety concerns were also reported. A risk of the capsule getting stuck on the small intestinal wall was reported by Hoffman et al. [30]. Sheehy and Salem described the distal dome of the capsule detaching and having to be recovered in the feces after the procedure [31,32]. Saleem and Rankin described the Crosby capsule getting trapped at the pylorus, resulting in difficulty when pulling back the capsule [32,33]. Intestinal perforation in children was studied by Partin et al. They succeeded in decreasing the number of perforations to zero by reducing the biopsy port diameter from 3 to 2 mm [34]. They further decreased the biopsy port to 1.5 mm still obtain adequate specimens. Lack of capacity to swallow the capsule by some subjects, namely infants, posed a challenge. This issue was addressed by Pittman et al. where a polyethylene nasogastric tube was introduced over the capsule's tether to increase its rigidity. With this modification, the capsule could be pushed through the mouth and down the gut, decreasing the overall time of the procedure and enabling the use of the capsule in infants or subjects who would not voluntarily swallow the device [32].

### 2.6. Baker–Hughes tube

Baker et al. developed a double lumen tube that operated with a hydraulic mechanism to activate the knife (Figure 6). This device had a capacity to obtain multiple biopsy samples and deliver them within seconds to the exterior. Baker's version of the sampling device had the capability to sort the tissue samples by location [36]. The cutting head of the device consisted of a sampling tube with a smaller tube connected via three ports. When suction was applied, a section of the mucosa was sucked into the tube. About 100 ml of fluid was moved through the smaller tube to the distal end of the sampling tube. This fluid pushed the knife in the sampling tube past the biopsy port, cutting the suctioned section of tissue. The liquid then flowed past the knife and carried the severed tissue up the tube where it could be collected. The knife could be reset by applying negative pressure through the smaller tube, which pulled the knife back. Baker and group successfully applied this method to obtain biopsy samples in 36 cases, where in 32 cases satisfactory samples were obtained at multiple levels. Using the same principle, modified designs were tested by Lehmanna, Bolt et al. and Flick et al. [37–39]. Welsh et al. demonstrated the use of Baker–Hughes tube in children aged from ~10 months to 11 years [40]. This method is advantageous in that it offers the ability to acquire multiple sorted biopsy samples. However, it was somewhat more complex relative to other suction methods and still required intestinal introduction under fluoroscopic guidance. The tube is less well tolerated by young children owing to its relatively large diameter [26].

### 2.7. Carey capsule

The Carey capsule could obtain multiple biopsy samples, but had no capacity to sort them according to the location where they were sampled [41]. The sampling capsule consisted of a proximal and distal concentric stainless-steel shells that closely slid past each other as shown in Figure 7. The two shells both had a biopsy port with a sharp knife edge. The proximal shell was connected to a suction tube and was also attached to the distal shell by a spring. Initially, the biopsy ports were aligned; when suction was applied, a section of the mucosa was sucked into the port. With the opening filled with tissue, the suction pulled the distal shell proximally, cutting the mucosa in the process. After releasing the suction force, the shells were then reset to the initial state by the spring. Additional biopsy sample could be obtained by repeating the process. Carey et al. successfully obtained 150 biopsy samples using this technique with no reports of complications [41,42]. This capsule was advantageous as it was simple in design and could be used to take multiple samples. Like other capsule devices, swallowability was an issue in subjects with no capacity to swallow such as infants, and fluoroscopic guidance was still needed for intestinal biopsies.

### 2.8. Choudhury capsule

Choudhury et al. realized that while maintaining the suction force and withdrawing the capsule, the suctioned tissue was severed from the intestinal wall creating a biopsy. Choudhury capsule's outer shell was very similar to that of the Crosby–Kugler capsule but had no movable knife to excise the tissue. As shown in Figure 8,
the distal edge of the biopsy port was sharp enough that when the capsule was withdrawn while suction was maintained the tissue was cut [43]. Choudhury et al., Ferguson et al., Saha et al., Sategna et al., and Cook et al. successfully used the Choudhury capsule to obtain small intestinal biopsies with no report of failure [43–47]. Cook et al. used the capsule in children with a median age of ~6 years. This capsule offered a few advantages such as ease in manufacturing, low cost, and the capacity to obtain multiple unsorted biopsy samples. The drawback to this method for biopsy tissue acquisition, like the Crosby–Kugler capsule, remains the need for fluoroscopic guidance.

2.9. Robotic biopsy device

The robotic biopsy device concept is a design that could be swallowed, excising tissue when electronically activated from outside the body [35]. The prototype consists of three modules: a tissue monitoring module, an anchoring module, and a biopsy module as shown in Figure 9. The camera onboard the device continuously monitors images through an aperture in the lateral direction. When an area of interest is observed, the anchoring module is activated and outriggers press onto the intestinal wall. By pressing on the intestinal wall, the mucosa herniates into the device through a biopsy port. The biopsy module then rotates a knife that cuts the tissue. The process could in principle be repeated as the device moves down the GI tract by peristalsis. This method for acquiring biopsies is attractive because the on-board camera makes it possible to target areas of interest before tissue excision. So far, only a bench top prototype of this device has been fabricated; to our knowledge, biopsies have not been acquired from living animals or human subjects with this method.

2.10. Rotational microbiopsy device

The rotational microbiopsy device operates as a wireless capsule that samples, seals, and fixes tissue in one operation [49]. The device shown in Figure 10 has an outer diameter of 10 mm and consists of a guillotine knife that is activated by a spring to sever tissue. An electrical signal activates a heater that melts a paraffin block within the device, once the block has melted, the spring is triggered. Tissue recovery occurs by retrieving the device after it passes naturally. Only one biopsy sample can be acquired per procedure. Since the device is still under development, no clinical demonstration has been reported to our knowledge.
2.11. Wireless biopsy capsule with a magnetic torsion spring (MTS)

The wireless biopsy capsule with MTS has a 9 mm diameter and a 24 mm length, like the Crosby–Kugler capsule [50]. A cylindrical knife rotates around the device’s longitudinal axis after being triggered by a MTS within the capsule as shown by the diagram in Figure 11. The MTS is a magneto-mechanical elastic element that stores elastic mechanical energy when brought near a strong magnetic field. The principle of operation is as follows: the capsule is swallowed and while in the GI tract, if a strong magnet is brought close to the body surface, the knife is rotated by the MTS opening the biopsy port. The magnetic force also causes the capsule to be pulled against the intestinal wall, in principle, causing the mucosa to bulge into the biopsy port. When the magnet is slowly withdrawn, the knife is triggered, rotating and cutting the bulging mucosa. This mechanism of tissue acquisition is simple and has potential to be inexpensive. We were unable to find any reports of this device being used in animals or patients at the time of writing this review.

2.12. Microgrippers

Yim et al. developed a wireless technique for obtaining biopsies using a magnetically actuated untethered soft capsule endoscope that transports and releases thermally sensitive, untethered microgrippers in the lumen of the GI tract [51]. The microgrippers are thermosensitive submillimeter self-folding bilayers that fold and grab tissue as shown in Figure 12. The capsule moves down the GI tract and is activated magnetically to deliver the microgrippers to the area of interest. The microgrippers are also collected by the capsule once they have captured tissue. When the capsule has passed through the GI tract, the microgrippers can then be retrieved from the capsule, the tissue stripped off and...
studied. This is an elaborate method for obtaining biopsies, and, to our knowledge, the tissue yield and quality have yet to be demonstrated. As far as we know, in vivo biopsy sampling using this technology has also not yet been reported.

3. Discussion

Our analysis of the non-endoscopic biopsy tools is summarized in Table 1. Briefly, the Kenamore forceps and the Wood tube served as critical first steps demonstrating non-endoscopic biopsy, but have intrinsic limitations that prevent them from being used for obtaining the small intestinal biopsy samples. Of the non-endoscopic biopsy techniques that have been used to acquire small intestinal biopsies, the Shiner capsule, Quinton–Rubin tube, Crosby–Kugler capsule, Baker–Hughes tube, and Carey and Choudhury capsules all have been shown to acquire sufficient quality intestinal biopsies in relatively inexpensive and easy-to-use devices. Some of these devices (Baker-Multipurpose Quinton–Rubin tube, Hughes tube, Carey capsule, and Choudhury capsule) are further advantageous as they allow the acquisition of multiple intestinal biopsies during a single procedure. A major issue with these devices is that they require X-ray fluoroscopy for navigation to the small intestine and confirmation of proper positioning within the GI tract. Up and coming new devices such as the robotic and rotational biopsy devices, the MTS capsule, and the microgripper technology are very interesting and provide new concepts for actuation and biopsy and do not require sedation as indicated on Table 1. These biopsy devices could therefore be viable candidates for use in low resource settings where the cost of sedation and endoscopy would otherwise be prohibitive. Further, this review is intended as a point of reference for the development of next-generation non-endoscopic biopsy techniques. Looking toward the future, the next generation of technologies should leverage the cutting and actuation mechanisms of these devices while providing onboard imaging to navigate and confirm positioning.

4. Expert commentary

Biopsy is one of the major tools for medical diagnosis and treatment of diseases/conditions of the GI tract. EGD is the current standard for biopsy tissue acquisition from the GI tract, using forceps that operate through a working channel in the endoscope. A number of drawbacks to endoscopic biopsy limit its adoption as a diagnostic tool across the globe. One main limitation is patient discomfort, mandating that some subjects be consciously sedated or anesthetized during EGD. Sedation-related cardiorespiratory complications may arise from these endoscopy procedures. Also, the relatively high expense of EGD procedures, resulting from the increased cost of endoscopy infrastructure and the need for skilled endoscopist operators, can be prohibitive in low resource settings.

There is a need for a low-cost, minimally invasive, and non-endoscopic means for obtaining biopsy samples to address these issues. Such technologies would significantly impact low- and middle-income countries where provision of endoscopy services is challenging and where life-altering conditions such as EED are endemic. Development of minimally invasive technology will result in speedy diagnosis of GI conditions in these countries, more rapid assessment of interventions, and will also present an opportunity for a more inclusive provision of medical services in areas where cost and access are limiting factors.

The already developed and clinically tested minimally-invasive, unsedated biopsy techniques described in our review such as the Crosby, Choudhury, and Watson capsules, provide a good reference point for the development of the next-generation low-cost, minimally invasive biopsy devices. However, the use of fluoroscopy to provide positional guidance when deploying these devices is a drawback that hampers utilization in under-resourced communities. Hence, there is a motivation to combine these biopsy capsules with integrated imaging technologies to provide anatomic confirmation without fluoroscopy. One additional desirable input requirement for next generation biopsy devices is the capacity to acquire multiple biopsy samples during a single procedure.

We are interested in developing less invasive, less expensive, and rapid biopsy technologies for tissue acquisition in the GI tract. By providing sufficient amounts of tissue for histology, genome sequencing, and microbiome analysis, we anticipate that these new biopsy tools will enhance diagnosis and treatment of pathological conditions of the gut. Another critical aspect of this research is miniaturization so that these devices can be small enough to be safely used in young children and

| Table 1. Summary table of the different biopsy techniques. |
|----------------------------------------------------------|
| Device | Small intestinal biopsy | Number of samples | Require fluoroscopic guidance | Require sedation |
|--------|--------------------------|-------------------|-----------------------------|-----------------|
| Demonstrated in human subjects | Kenamore forceps | No | 1 | Yes | Yes |
| | Wood tube | No | 1 | Yes | Yes |
| | Shiner capsule | Yes | 1 | Yes | Yes |
| | Quinton–Rubin tube | Yes | 4 | Yes | Yes |
| | Crosby–Kugler Capsule | Yes | 1 | Yes | No |
| | Baker’s capsule | Yes | Multiple | Yes | Yes |
| | Carey capsule | Yes | Multiple | Yes | No |
| | Choudhury capsule | Yes | Multiple | Yes | No |
| | Rotational microbiopsy device | Possible | Multiple | No | No |
| | Magnetic torsion spring biopsy capsule | Possible | 1 | Yes | No |
| | Microgrippers | Possible | Multiple | No | No |
infants who are currently underserved by biopsy techniques in use today.

5. Five-year view

Biopsy is a key diagnostic tool for some of the major diseases that affect the stomach and small intestine. Currently, the preferred means for obtaining biopsy samples is EGD, where biopsies are obtained randomly or from discernible lesions. Endoscopic biopsy has several limitations as a diagnostic tool. Upper EGD often requires sedation of the subject which is inconvenient and carries nonnegligible risk. Second, endoscopy suites and requisite personnel contribute to health care costs that limit EGD service provision in developing countries. Third, EGD/biopsy procedures are usually lengthy and, while infrequent, may lead to trauma, bleeding, or perforation of the small intestinal wall. Last, anesthesia may not be well tolerated by infants and children. A less costly, minimally invasive and non-endoscopic means for obtaining biopsy samples is therefore of interest to address these issues. Such a device would have a significant impact in low- and middle-income countries where the resources required to conduct endoscopic biopsy can be prohibitive.

Key issues

- Diseases of the small intestine and stomach account for 20% of all the mortality that result from GI conditions in the US [1].
- The current preferred means for biopsy acquisition from the stomach and small intestine is EGD.
- EGD has several limitations such as subject sedation, duration of the procedures, the high cost of infrastructure, and elevated risk in pediatric subjects.
- Less costly and minimally invasive non-endoscopic biopsy is therefore attractive for areas of modest resource settings.
- In this paper, we review non-endoscopic biopsy techniques reported in literature thus far, and critically examine their merits and demerits regarding their suitability for obtaining biopsy samples in non-sedated subjects.

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Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (+) or of considerable interest (+) to readers.

1. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States, 2012 update. Gastroenterology. 2012 Nov;143 (5):1179–1187.

2. Yabroff KR, Lund J, Kepka D, et al. Economic burden of cancer in the US: estimates, projections, and future research. Cancer Epidemiol Biomarkers Prev. 2011 Oct;20(10):2006–2014.

3. Husby S, Koletzko S, Korponay-Szabo’ IR, et al. European society for pediatric gastroenterology, hepatology, and nutrition guidelines for the diagnosis of coeliac disease. Jgpn. 2012;54(1):136–160.

4. Rubio-Tapia A, Hill ID, Kelly CP, et al. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol. 2013;108:656–676.

5. Kelly P, Menzies I, Crane R. Responses of small intestinal architecture and function over time to environmental factors in a tropical population. Am J Trop Med Hyg. 2004;70:412–419.

6. Lundeen EA, Behrman JR, Crookston BT, et al. Growth faltering and recovery in children aged 1–8 years in four low- and middle-income countries: young lives. Public Health Nutr. 2014 Sep;17 (9):2131–2137.

7. Kenamore B. A biopsy forceps for the flexible gastroscope. Am J Dig Dis. 1940;7(12):539.

- First description of in human biopsy acquisition from the stomach of living humans with the aid of a gastroscope.

8. Schindler R, Renshaw J. Experimental study with certain tips used on the Wolf-Schindler flexible gastroscope. Am J Dig Dis. 1936;3 (10):747–751.

9. Kenamore B, Scheff H, Womack N. A study of gastric lesions by means of biopsy specimens removed endoscopically. Arch Surg. 1946;52(1):50–58.

10. Wood LJ, Motteram R, Doig RK, et al. Gastric biopsy report on fifty-five biopsies using a new flexible gastric biopsy tube. The Lancet. 1949;253(6540):18–21.

- Description of the wood biopsy tube; a more flexible and simple biopsy device that does not require a gastroscope for navigation and guidance.

11. Wood LJ, Doig RK, Motteram R, et al. The relationship between the secretions of the gastric mucosa and its morphology as shown by biopsy specimens. Gastroenterology. 1968;54(4):Suppl 732–734.

12. Tomenius J. An instrument for gastrobiopsies. Gastroenterology. 1950;15:498.

13. Tomenius J. Suction biopsy of the gastric mucosa. Acta Med Scand. 1957;159(9):353–367.

14. Doig RK. Gastric biopsy and gastritis. Proc R Soc Med. 1954;47 (6):423–424.

15. Joske RA, Finchk ES, Wood LJ. Gastric biopsy: a study of 1,000 consecutive successful gastric biopsies. Q J Med. 1955;24(95):269–294.

16. Palmer DE. Gastric mucosal biopsy findings correlated with gastroscopic diagnoses: preliminary report based on 50 patients. Am J Med Sci. 1950;219(6):648–650.

17. Shiner M. Duodenal biopsy. The Lancet. 1955;267(6906):17–19.

- A report on the first duodenal biopsy device. They employed a longer biopsy tube with a weighted tip.

18. Pirola R. Rapid duodenal intubation with metoclopramide. Am J Dig Dis. 1967;12(9):913–915.

19. Brandborg LL, Rubin GE, Quinton WE. A multipurpose instrument for suction biopsy of the esophagus, stomach, small bowel, and colon. Gastroenterology. 1959;37(1):1–16.

20. Rosson RS. Peroral small bowel biopsy. Conn Med. 1965;29 (1):31–34.

21. MacDonald WC, Dobkins WO, Rubin CE. Studies of the familial nature of celiac sprue using biopsy of the small intestine. N Engl J Med. 1965;272:448–456.

22. Ament AE, Rubin CE. An infant multipurpose biopsy tube. Gastroenterology. 1973;65:205–209.

23. Liebman WM. Xylose test in malabsorption. J Pediatr. 1979;94 (3):508–509.

24. Christie DL. Use of the one-hour blood xylose test as an indicator of small bowel mucosal disease. J Pediatr. 1978;92(5):725–728.

25. Kuitunen P, Visakorpi JK. Pyloric spasm complicating peroral intestinal biopsy in infants. The Lancet. 1965;285(7398):1276–1277.

26. Anderson CM. Intestinal malabsorption in childhood. Arch Dis Child. 1966;41(220):571–596.
27. Crosby WH, Kugler H. Intraluminal biopsy of the small intestine. Am J Dig Dis. 1957;2(5):236–241.

- A description of the Crosby–Kugler capsule device that can acquire biopsy samples from the jejunum.

28. Pittman FE, Ores C, Denning CR, et al. A new method for use of the Crosby-Kugler intestinal mucosal biopsy capsule. Pediatrics. 1964;34(2):276–278.

29. Read AE, Gough KR, Bones JA, et al. An improvement to the Crosby peroral intestinal biopsy capsule. The Lancet. 1962;1:894.

30. Hoffman GM, McDougal JL, Voss WH, et al. Use of the Crosby-Kugler intestinal biopsy capsule: case reports. J Am Osteopath Assoc. 1965;64:1238–1248.

31. Sheehy TW. An improvement to the Crosby peroral intestinal biopsy capsule. The Lancet. 1962;279(7244):1404–1405.

32. Salem SN. Small-intestinal biopsy. The Lancet. 1965;285(7387):674–675.

33. Rankin GB, Owens FJ. Crosby-Kugler capsule in bowel twenty-seven days. Report of a case. Bull Gastrointest Endosc. 1964;11:29–30.

34. Partin JC, Schubert K. Precautionary note on the use of the intestinal-biopsy capsule in infants and emaciated children. N Eng J Med. 1966;274:94–95.

35. Baker SJ, Hughes A. MULTIPLE-RETRIEVING SMALL-INTESTINAL BIOPSY TUBE. The Lancet. 1960;276(7152):686–687.

- A report on a small-intestinal biopsy device that can acquire multiple biopsy samples.

36. Lehmann KE. Instrument for multiple transoral biopsies of gastrointestinal tract. Acta Med Scand. 1961;169:205.

37. Bolt RJ, Parrish JA, French AB, et al. Adult coeliac disease. Histologic results of long-term low gluten diet. Ann Intern Med. 1964;60:581–586.

38. Flick AL, Quinton WE, Rubin CE. A peroral hydraulic biopsy tube for multiple sampling at any level of the gastro-intestinal tract. Gastroenterology. 1961;40:120–126.

39. Welsh J, Rohrer G, Porter M. The Baker-Hughes gastrointestinal biopsy tube. Am J Dig Dis. 1966;11(7):559–563.

40. Carey JB. A simplified gastrointestinal biopsy capsule. Gastroenterology. 1964;46:550–557.

- A simplified form of the small-intestinal biopsy capsule.

41. Achkar E, Carey WD, Petras R, et al. Comparison of suction capsule and endoscopic biopsy of small bowel mucosa. Gastrointest Endosc. 1986;32(4):278–281.

42. Choudhury DCR, Nicholson GI, Cooke WT. Simple capsule for multiple intestinal biopsy specimens. The Lancet. 1964;284(7352):185–186.

- Another variation of the small-intestinal biopsy capsule.

43. Cook GC, Kajubi SK. Tribal incidence of lactase deficiency in Uganda. The Lancet. 1966;287(7440):725–730.

44. Roy-Choudhury DC, Cooke W, Banwell J, et al. Multiple jejunal biopsies in adult celiac disease. Am J Dig Dis. 1967;12(7):657–663.

45. Ferguson R, Allan RN, Cooke WT. A study of the cellular infiltrate of the proximal jejunal mucosa in ulcerative colitis and Crohn’s disease. Gut. 1975;16:205–208.

46. Saha K, Agarwal SK, Misra RC. Gut-associated IgA deficiency in lepromatous leprosy. Scand J Immunol. 1978;8:397–402.

47. Sategna-Guidetti C, Grosso S, Pulitano R, et al. Celiac disease and insulin-dependent diabetes mellitus. Dig Dis Sci. 1994;39(8):1633–1637.

- References 48-51 describe up and coming non-endoscopic biopsy techniques in the research phase of development.

48. Kong K, Yim S, Choi S, et al. A robotic biopsy device for capsule endoscopy. ASME J of Med Device. 2012;6(3):031004.

49. Kong K, Cha J, Jeon D et al. A rotational micro biopsy device for the capsule endoscope. Proc. IEEE/RSJ Int. Conf. Intell. Robots Syst., Aug. 2–6, Edmonton, Can. pp. 1839–1843. Piscataway, NJ: IEEE.

50. Simi M, Gerboni G, Menciassi A, et al. Magnetic mechanism for wireless capsule biopsy. J Med Devices. 2012;6(1):017611.

51. Yim S, Gultepe E, Gracias DH, et al. Biopsy using a magnetic capsule endoscope carrying, releasing, and retrieving untethered micro-grippers. IEEE Trans Biomedic. 2014;61(2):513–521.