

INNOVATION

Current and future applications of the capsule camera

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Scientific advances in areas such as nanotechnology and gene therapy promise to revolutionize the way we discover and develop drugs, as well as how we diagnose and treat disease. The 'camera in a pill' is one recent development that is generating considerable interest. Until recently, only the proximal (oesophagus, stomach and duodenum) and the distal (colon) portions of the gastrointestinal tract were easily visible using available technology. The twenty feet or so of small intestine in between these two portions was essentially unreachable. This hurdle might soon be overcome.

News about wireless capsule endoscopy first began to appear about three years ago when a paper in *Nature* described the development of a disposable capsule that takes pictures during its course through the digestive tract after being swallowed¹. Proprietary software loaded onto a desktop or laptop computer enables interpretation and storage of this data and generation of a report. This technology was initially used to look for sites of occult bleeding (see following section) from the gastrointestinal (GI) tract. It has since been used to study damage to the small intestine induced by both traditional nonsteroidal anti-inflammatory drugs (NSAIDs) and the newer cyclooxygenase-2 (COX-2) inhibitor NSAIDs. Its indications continue to evolve and now include evaluation of early small bowel disease such as **Crohn's disease**, diagnosis of **coeliac disease**

(particularly in asymptomatic patients not previously diagnosed with this condition) and monitoring of patients with certain premalignant conditions of the small bowel.

The wireless endoscopy system consists of three components: the capsule camera, an external receiving antenna and portable hard drive worn by the patient during the examination, and a personal computer workstation and proprietary software for review and interpretation of the images.

Transforming the idea into reality required miniaturization of the device and development of technology that could provide power for at least 6 hours. Another problem to overcome was internal light reflections within the dome of the capsule. The technologies developed were a complementary metal oxide silicon (CMOS) image sensor chip that requires much less current than a charge-coupled device for comparable image quality, advanced application-specific integrated circuit (ASIC) video transmitters and white-light-emitting diode light sources. Synchronous switching of the light source, CMOS chip and ASIC transmitter further

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minimized power consumption so that the battery power was sufficient for the duration of the capsule's trip through the GI tract.

The camera is pill-like (FIG. 1). Image features include a 140° field of view, 1:8 magnification allowing visualization of individual villi, 1–30 mm depth of view, and a minimum size of detection of about 0.1 mm. The capsule captures two images per second and transmits them as .jpg files. By the time battery power expires after about 8 hours, the camera will have captured about 55,000 images, which are transmitted to the hard drive worn by the patient. The propulsive force for the capsule is the natural motility of the intestine known as peristalsis. Unlike conventional endoscopy, no drugs are administered to the patient and air insufflation is not necessary. This might make the test more sensitive, as drug-induced drops in blood pressure or air tamponade (that is, compression of the blood vessels within the bowel lumen by insufflated air), which frequently occur during conventional endoscopy, can make it difficult to visualize small bleeding vessels. Some investigators maintain that use of the capsule camera is a more 'physiological' form of endoscopy (FIG. 2).

Before ingestion of the capsule, an antenna array is taped to the patient's anterior abdominal wall and connected to a 305 GB hard drive. This is carried in a shoulder-supported belt pack that also holds the power supply. In a group of healthy volunteers, mean transit times of the capsule camera were 63 minutes (range 10–319 minutes) for the stomach and 194 minutes (range 70–322 minutes) for the small bowel^{2,3}.

Captured images are reviewed at a rate that varies between 5 and 25 frames per second. The software also allows thumbnail annotated photos or short video clips to be stored for review or transmission to the patient's doctor. Two new software features might reduce reading time and improve accuracy. These features are a double screen on the playback 'Rapid' software and a suspected blood

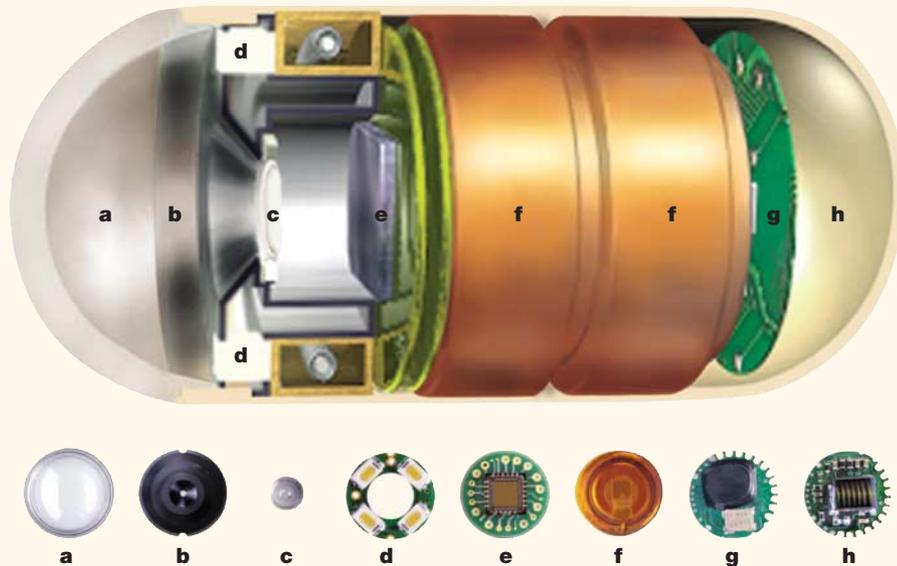


Figure 1 | **The M2A capsule camera.** The device consists of a disposable plastic capsule that weighs 3.7 grams and measures 11 mm in diameter by 26 mm in length. The contents include an optical dome (a), a lens holder (b), a short focal-length lens (c), six white-light-emitting diode illumination sources (d), a complementary metal oxide silicon (CMOS) chip camera (e), two silver oxide batteries (f), a UHF band radio telemetry transmitter (g) and an antenna (h).

indicator (SBI). The double screen increases the rate at which the clinician can view the images during playback. The SBI software directs the viewer to red-coloured areas that might indicate the presence of blood. Prior to a formal read, doctors can choose to go directly to these areas and create annotated thumbnails for later reference.

The patient fasts for 10 hours prior to the procedure. Cessation of anticoagulant therapy is unnecessary, in contrast to conventional endoscopy during which scope trauma, perforation of the bowel or biopsies can cause excessive bleeding that might require surgery. There is a less than 1% chance that the patient will require surgical intervention to retrieve the capsule. When intervention is necessary, it is not often urgent and the capsule can be removed during previously scheduled surgery for the pre-existing condition.

The antenna array taped to the patient's abdomen detects the signal from the capsule and stores it in the hard drive the patient is wearing. The position of the leads also helps to estimate the location of the capsule if an abnormality is seen. Location of the capsule is approximate and achieved by triangulation of the signals received by the three closest aerial ports. This information, together with the time that has elapsed since the capsule passed various 'landmarks' such as the pylorus or the outlet of the stomach, locates the capsule within the

small intestine with sufficient accuracy that surgery to remove a tumour or treat a bleeding vessel can be performed through a laparoscope. More accurate techniques for locating the capsule are necessary and are being developed.

Once the capsule is swallowed with a small amount of water, the patient can leave the treatment facility and return in about 8 hours. The patient is asked to avoid vigorous exercise during this period. He or she can drink clear liquids after 2 hours, and have lunch and/or medications from 4 hours after capsule ingestion.

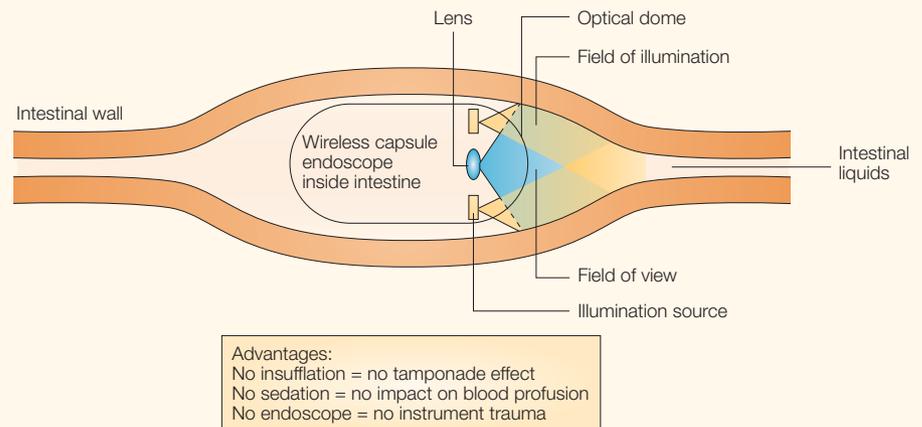


Figure 2 | **Physiological endoscopy.** This diagram shows the capsule camera as it is pushed along by the natural movements of the small bowel that move food. Some researchers think that as this procedure is performed without sedation or air insufflation, it approximates 'physiological endoscopy'.

At the end of the 8 hour recording period, the images are downloaded and processed, which takes about 30 minutes. A further 60–90 minutes is required to read the images. A video is created that can be viewed at varying rates depending on the pathology observed and the reader's experience. Reading the video requires a certain level of focus and concentration. When an abnormality is observed, an annotated and time-stamped thumbnail frame is created so that the image can be rapidly retrieved at a later time. Both .jpg and .avi files can be saved for later viewing or electronic transmission. We find it more convenient to store the findings on CD-readable or CD-readable/writeable disks.

Present indications

The indications for video capsule endoscopy continue to evolve. It is worth bearing in mind that this is a new technology, and indications for its use and its limitations are still being studied. There are four main indications.

First, there is the detection of obscure GI bleeding. Obscure GI bleeding is classified as 'occult' if it is not visible in stool or vomitus because of very small amounts of blood loss or its intermittent nature. It is termed 'overt' when blood is seen during a colonoscopy, a small bowel barium study, a normal upper endoscopy or a push enteroscopy (performed with a longer version of the upper endoscope pushed as far as it will go, which is usually not further than the first quarter of the small intestine). Patients with obscure GI bleeding account for about 5% of those with GI bleeding of all types. Preliminary data indicate that video capsule endoscopy might identify the cause of obscure bleeding in about 50% of cases⁴.

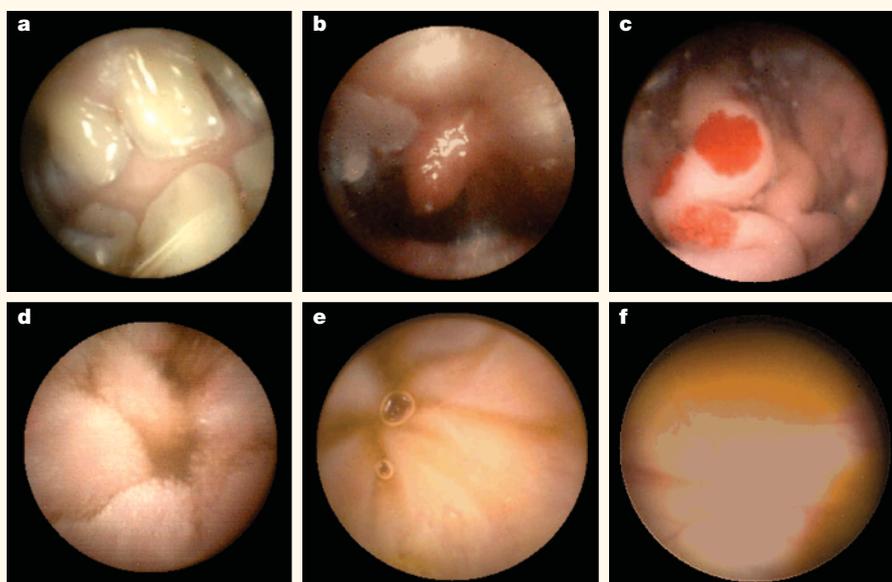


Figure 3 | **Visualizing the gastrointestinal tract.** These photographs show the appearance of various features during capsule endoscopy. **a** | Teeth. **b** | Epiglottis. **c** | Multiple telangiectasia on a gastric fold. **d** | Small intestine. **e** | Ileocecal valve. **f** | Wall of right colon.

Second, it is indicated for the evaluation of malabsorptive, inflammatory or infiltrative conditions that are incompletely diagnosed or require the use of intraoperative enteroscopy.

A third indication is the surveillance in patients with polyposis syndromes.

Last, there is the evaluation of abnormal radiological imaging of the small intestine. Several studies comparing video capsule endoscopy with push enteroscopy and barium imaging have demonstrated that capsule endoscopy is a superior modality for the diagnosis of diseases in the small intestine⁴⁻⁷. Lesions observed by video capsule endoscopy include angioectasia of the stomach and intestine, erosions and ulcers in the GI tract, small bowel tumours, and stenotic lesions. A selection of photographs from capsule endoscopy are shown in FIG. 3. FIG. 4 is a picture of bleeding in the distal small intestine that could only be diagnosed by capsule endoscopy. A normal small bowel barium study does not exclude the presence of strictures that might restrict the movement of a video capsule. Conversely, lesions such as a very narrow lumen, seen as a 'string sign', have been traversed by capsule cameras without incident. In some instances, video capsule endoscopy helps by ruling out disease processes that are being considered as possibilities.

Emerging indications

The use of capsule endoscopy is enabling earlier diagnosis in patients who might previously

have had to live with recurrent anaemia or ill health because the technology did not exist for easy observation of the lining of the small bowel. Capsule endoscopy is clearly superior to barium radiography of the small intestine for the detection of tumours of the small intestine and abnormal blood vessel formations causing obscure bleeding. Several studies have shown that it will detect early Crohn's disease in patients who present with abdominal pain and/or diarrhoea but have normal results on conventional studies^{8,9}. Capsule endoscopy is also helping to confirm the suspicion that coeliac disease (allergy to the wheat protein gluten) is more common than once thought. Many patients with coeliac disease have mild symptoms and present with a 'failure to thrive' that might not be recognized as a disease at all. More rapid diagnosis will hopefully improve the quality of life for many patients and appropriate management might delay or prevent some of the complications of the disease. In the future, capsule endoscopy might be used to evaluate the small bowel during serious enteric infections. It might also serve as an early detection tool for small bowel ischaemia, particularly in very sick patients, permitting intervention before gangrene develops.

Studying drugs

NSAIDs such as Motrin and Advil (ibuprofen) cause ulcers in the stomach and duodenum and sometimes in the colon.

Conventional endoscopy of the upper GI tract (oesophagus, stomach and duodenum) and the colon might not detect blood loss in patients taking NSAIDs. Autopsy studies indicated that the incidence of small intestine ulceration in patients taking NSAIDs was about 8.4% compared to 0.6% in those not taking NSAIDs¹⁰.

We were the first to show in a controlled study that NSAIDs cause significant damage to the small intestine¹¹. In this open-label, endoscopist-blinded prevalence study, we observed patients who had arthritis and had been on painkillers for at least three months. They were divided into one group that took NSAIDs and a second group that took acetaminophen. All patients underwent capsule endoscopy and the results were read by investigators who were blinded to the type of painkiller being taken by the patients. A scoring system was devised, as the terminology for lesions observed during capsule endoscopy is still being formulated. We found that 70% of patients taking NSAIDs for at least three months had damage to the small intestine — 33% had severe damage, mainly in the form of ulcers. Suppression of acid is unlikely to heal or provide prophylaxis against NSAID-induced damage in the small intestine as there is no acid present. In theory, synthetic prostaglandins could be administered to strengthen the lining of the small intestine in patients prone to symptomatic damage from NSAID use. A recent study indicated that newer COX-2 inhibitor NSAIDs, such as celecoxib and rofecoxib, cause less damage in similar circumstances than non-selective NSAIDs¹².



Figure 4 | **The terminal ileum.** The presence of blood in the terminal portion of the small bowel indicates that there is a source of blood loss nearby. A normal colonoscopy would confirm this suspicion and rule out reflux of blood backwards from a colonic source.

The effect of drugs on the mucosa of the small intestine has not attracted much research attention as it has been difficult to study damage in this area. Now that capsule endoscopy allows non-invasive study of the small intestine, the effects of drugs that are known to cause abdominal symptoms will hopefully be studied in more detail. It is possible that the intolerance of some drugs in certain patients is related to small bowel damage. The evaluation of new drugs should perhaps include study of their effects on the small intestine. To date, damage to the small intestine has been indicated indirectly by measuring blood or protein loss in stool. Alternatively, molecule-tagging tools, such as ¹¹¹indium for labelling leukocytes or ^{99m}Tc-porphyrin, detect increased permeability or 'leakiness' of the small bowel after damage to the lining. Consensus on the visual indicators of small intestine damage due to NSAID use has now been reached, but the effects of other

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classes of drugs on the small bowel might be quite varied. Direct visualization might enhance our understanding of drug toxicities that we are presently unaware of. Some chemotherapeutic agents are toxic to the lining of the small bowel. Capsule endoscopy might be used to classify these drugs according to their GI side-effect profiles in patients whose oral nutrition is important. The same rationale might apply to radiation treatments directed to or near abdominal organs.

Video capsule endoscopy could have a role in the screening of patients with hereditary conditions that have an increased propensity to develop cancers such as polyposis syndromes. As it is not practical to remove large sections of the intestine, the development of cancerous lesions must be detected early. Video capsule endoscopy might provide a means of achieving this aim. It could also be used to monitor patients that are receiving drugs that are thought to cause polyp regression.

Possible complications

The main complication with video capsule endoscopy is capsule retention proximal to a

stricture. Patients with retained capsules usually remain asymptomatic because the capsule does not generally cause obstruction but tumbles around and eventually passes the stricture. Surgical removal is rarely necessary. The 'delayed excretion' rate is about 5%, and the surgical retrieval rate less than 1%. A capsule might also be delayed because of motility disorders or narrowing of the outlet of the stomach (pyloric stenosis). If transit to the caecum does not occur, a plain film of the abdomen 24 to 48 hours later will pinpoint the location of the capsule. In my view, the only contraindications to swallowing the capsule are a patient who would not survive surgery if it were necessary, one who would not give consent for surgery, or the presence of clinical bowel obstruction. There are reports of the capsule being retained in the bowel for up to a year without adverse outcome. Clearly, if abdominal pain develops in a patient known to have retained a capsule, urgent evaluation is indicated and prompt surgery might be required. The FDA prefers that video capsule endoscopy not be used in patients with implanted cardiac defibrillators or pacemakers, but there is no evidence to date that the capsule poses any danger to these patients. Obviously, magnetic resonance imaging should not be performed while the capsule is inside the body.

Conclusions

As the future of medical micro-devices in medicine unfolds, video capsule endoscopy has established itself as a valuable diagnostic tool for doctors and their patients. It is a relatively non-invasive method of visualizing the small bowel mucosa and helps to diagnose or direct management in many cases of small bowel disease. Research is underway to develop capsules with propulsive and therapeutic capabilities¹³. Technology already exists that could enable the capsule camera to measure pH, temperature, blood perfusion and intestinal motility during its journey through the gut. In the not-too-distant future, capsules that can be manoeuvred by remote control, transmit real-time images and have injection, laser, microwave and radiation capabilities will be available. Other micro-devices that are being developed include implantable pulse generators for stomach walls for weight reduction, implantable biosensor drug delivery systems, and devices that control insulin production, dispense chemotherapeutic agents or filter 'bad' cholesterol from the blood. Current-generating bacteria could provide long-term power for these and many more

as-yet-unexplored biomedical devices¹⁴. Advances in nanobiotechnology will create surprising and exciting possibilities for improving care of the sick. The 'camera in a pill' might one day make major surgery unnecessary in many cases.

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doi:10.1038/nrd1385

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Competing interests statement
The author declares that he has no competing financial interests.

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