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READY TO INGEST
An endoscopy capsule: it has existed for more than 20 years, but in Italy it is not very widespread because many Regions have not charged for the service and there is a lack of trained personnel.

They have been performing non-invasive **endoscopy** for 20 years. Now "smart pills" dispense **medications** and monitor the **body's health** in real time.

by Vito Tartamella

The world of SMART PILLS

There is Vibes that, once it reaches the stomach, vibrates for half an hour, canceling hunger: it could make diets easier. Another, VM, monitors the patient from inside the body, signaling via radio if they stop breathing. And Capsulight will be able to cure gastritis without antibiotics: it will shoot beams of LED light capable of killing pathogenic bacteria.

These are the new "smart pills" (smart pills or ingestible sensors), that is, those that include electronic and mechanical parts. These devices, called "microelectromechanical" (MEMS), have already existed for almost 70 years. Now, thanks to progress in miniaturization, they have made giant steps. In fact, they are not limited to diagnosing diseases, as the endoscopic capsule, equipped with cameras capable of taking thousands of photos of the intestine, has done since 2001. Now smart pills can also cure, by conveying medicines into the digestive system. Like in the movie *Fantastic Voyage*, which in 1966 imagined shrinking a submarine to enter the arteries and cure a person from the inside.

Over the past 23 years, video capsule endoscopy «has become the first-line investigative method for suspected small-bowel bleeding. But it is also useful for diagnosing Crohn's disease and detecting tumors. And its future is bright», writes David Ralph Cave, a gastroenterologist at the University of Massachusetts, in a review study in *Frontiers in Robotics and AI*.

IN THE SECRETS OF THE INTESTINE

According to Grand View Research, the global capsule endoscopy market, worth $537 million in 2023, will grow by almost 10% annually until 2030. «The increase in the elderly population will provide a solid platform for growth: aging increases the risk of gastrointestinal disorders» and the pills are less invasive than the endoscope. Beyond some operational limitations (see below), smart pills are opening up new avenues in research, venturing into those 6 meters of the small intestine that are so important for our health, but largely unexplored: traditional endoscopy, the one with a flexible tube, only reaches the initial part. Therefore, the small intestine is considered one of the last "black boxes": «Better understanding the chemical environment of the intestine (gases and bacteria in the microbiota) could help us prevent diseases by identifying the factors that cause inflammation before it produces serious symptoms», says Timothy Lu, professor of bioengineering at MIT in Boston. Here is the MechE (Department of Mechanical Engineering), one of the most active laboratories in the world together with the Healthcare Mechatronics Laboratory of the Scuola Superiore Sant'Anna in Pisa.

But what is the scenario today and what can we expect? To- ▸

UNDER CONTROL
A doctor looks at images sent by a capsule endoscope swallowed by a patient: each exam produces 50,000 photos. Artificial intelligence helps study them.

A capsule that dispenses drugs for a month is being tested: it will help people comply with **chronic therapies**

day there are 6 very similar models of capsule endoscopes (see infographic on the side). In addition to these, there are two sensors for adherence to pharmacological treatments, i.e. pills that detect whether the patient has taken a medicine. The Hemopill signals bleeding in the digestive system in real time.

FROM ASTRONAUTS TO ENDOSCHOPSY

Finally, eCelsius, a pill capable of measuring body temperature from the inside: it is the oldest sensor. The first dates back to 1957, in Sweden: the engineer Ralph Stuart MacKay and the biochemist Bertil Jacobson invented an "endoradiosonde", a 2.8 cm long tablet with a diameter of 0.9 cm capable of detecting body temperature thanks to a transistor and a battery. The device could provide more reliable measurements on metabolism, and the authors thought of using it also as a "lie detector", believing that lies increased body heat. Other laboratories designed similar capsules, to monitor soldiers or divers, but no one tested them on humans.

The first pill used in clinical practice was funded by NASA and invented in 1988 by Protagoras Cutchis, Jeffery Lesho and Arthur Hogrefe of Johns Hopkins University: it contained a quartz crystal temperature sensor. In 1991 it was used to monitor astronauts on the Space Shuttle. The idea of creating an ingestible endoscope dates back to the early 1980s. It came to two Israelis: an army electronics engineer, Gavrial Iddan, and a gastroenterologist, Eitan Scapa. They built a swallowable endoscope with a video camera, but it consumed a lot of energy and needed a thin fiber optic cable to send the images, at a rate of 10 minutes for each. The project was shelved.

In 1993, Iddan split the system into two parts, to save space and energy: a capsule with the camera and antenna, and an image recorder on the patient's abdomen. But the video camera's sensor, a CCD (charge-coupled device), was bulky and consumed too much power. And the light bulbs in the capsule emitted a weak light. Years later, however, new optical sensors, CMOS (complementary metal oxide semiconductors), were invented, which were more sensitive and less energy-intensive. And LED lights provided efficient, low-consumption lighting. So in 1999 Scapa and Iddan, together with British gastroenterologist Paul Swain, founded Given Imaging in Israel.

The capsule was tested by Swain: he swallowed the pill, while the others kept their eyes glued to the monitor. But for more than 3 hours the capsule remained stuck in his stomach. Scapa had to use an endoscope to move it into the duodenum and see the images. In 2011, the FDA, the US regulatory body, authorized the use of the capsule; in 2014, Given Imaging was purchased by Medtronic for 860 million dollars, and today it is among the market leaders with the PillCam.

The debut, however, exposed a limit of capsule endoscopy: the risk of retention, which today occurs in 2% of cases. The caseload has been reduced because risk factors have been identified and a soluble test capsule is used before the test (*see box on last page*).

THE LIMITS: PASSIVE MOTION AND NO BIOPSIES

Today, technology is being revolutionized by artificial intelligence (AI). Capsule endoscopy exams produce over 50,000 images and take 3 hours to read: AI will shorten the time and be able to detect visible lesions in just a few frames.

But the capsule has two major limitations compared to traditional endoscopy: it cannot be maneuvered or located, and it does not allow interventions. That is, it cannot take a tissue sample to perform biopsies, nor remove intestinal polyps. In fact, the capsules move passively, driven by peristalsis (the contraction of the intestinal muscles): it is impossible to guide them to a specific area. So several attempts have been made ▸

SMART PILLS IN USE

ENDOSCOPES
Pillcam (Medtronic, Usa) 1
Mirocam (Intro Medic, South Korea) 2
Endocapsule (Olympus, Japan) 3
Capsocam + (Capsovision, Usa) 4
Omom (Jinshan, Cina) 5
Navicam (Anx robotics, Usa) 6

The capsule endoscopes weigh 2 to 6 g and are about the size of a vitamin pill. They are equipped with 1-2 cameras (Capsocam has 4, with a 360° field of view) that take images of the stomach and intestines, which are transmitted to an external sensor (a belt receiver or a patch with electrodes).
Olympus, Jinshan and Anx robotics have developed a system to guide the capsule from the outside using magnetic fields.

DRUG TREATMENT ADHERENCE SENSORS
Id-Cap (EtectRx, Usa) 7
Abilify MyCite (Otsuka, Japan) 8

These capsules signal whether a patient has taken a drug. Id-Cap is a capsule with a sensor: you put the drug in the capsule and when it reaches the stomach it transmits a radio signal to a smart watch. Abilify is an aripiprazole tablet (for the treatment of schizophrenia) with a sensor the size of a grain of sand: it signals the drug intake to a wearable receiver.

TEMPERATURE SENSORS
eCelsius (BodyCap, France) 9

They measure internal body temperature using a sensor powered by a small battery.

BLEEDING SENSORS
Hemopill (Ovesco, Germany) 10

An optical sensor detects bleeding in the stomach or upper and middle intestine.

PILLS BEING TESTED ON HUMANS

Drug release

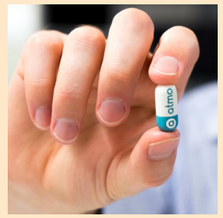
NAVICAP (Biora therapeutics, Usa)

When it reaches the colon (recognized by the reflection of the LED lights on the walls of the intestine), the capsule releases the anti-inflammatory drug, contained in a microreservoir.

LYNX (Lyndra therapeutics, United Kingdom)

The capsule, once in the stomach, dissolves, and opens in a star shape: its 6 arms contain the active ingredient. This shape blocks its passage into the pylorus. Once the dosage is finished, the arms dissolve. Useful for chronic therapies (HIV, Alzheimer's, diabetes, epilepsy).

Gas monitoring



ATMO-GAS
(Atmo Biosciences, Australia)

The capsule has sensors to detect gases (CO_2, H_2, O_2) in the intestine, which are useful for diagnosing various disorders. The sensors are sealed in a membrane that allows gas to enter but not digestive juices. The capsule transmits the data to a wearable receiver.

RANIPILL (Rani therapeutics, Usa)

When the capsule reaches the large intestine (detected by pH), the outer coating dissolves: a chemical reaction pushes a soluble needle into the intestinal wall, where the drug is released. Used to treat cancer, diabetes and other chronic diseases.

BREATHING MONITORING - MIT, 2023
Giovanni Traverso (MIT) hodling a VM pill: it works by monitoring the body vibrations associated with breathing and heartbeat. The pill can detect heart rate and signal in real time if a person stops breathing from inside the digestive tract.

An italian capsule can kill gastritis bacteria thanks to LED lights

to equip the capsules with a locomotion system: legs, flagella or propellers. They work, but absorb more energy, and more powerful batteries would be bulkier. To get around these obstacles, some capsules recently incorporate a magnet, so that they can be maneuvered (or recharged) with an external magnetic field. But the system needs a large magnet to guide them.

It is more complicated to equip the capsules with a system to collect tissue samples for examination: «The challenge is to miniaturize the mechanical components: "brushes" to sample the tissue selectively, and a tank to store the samples without contaminating them for later analysis», says Gastone Ciuti, scientific director of the Healthcare Mechatronics Laboratory in Pisa. «Ingenious prototypes have been created: now we need to demonstrate their effectiveness in the clinical setting».

MEDICATION DISPENSERS

This limitation is one of the factors that limit the use of smart pills. «In Italy, about 7,500 capsule endoscopies are performed each year», says Luca Elli, a gastroenterologist at the Policlinico in Milan. «It's a low average compared to the rest of Europe because several regions, especially in the South, have not charged for the service or do not have trained personnel. The equipment for the exam costs about 20 thousand euros, and the ingestible capsule about 500».

The high costs are another limitation: «A treatment with Abilify MyCite, a tablet with a sensor that signals its intake, costs 1,650 dollars a month compared to 20 dollars for the normal therapy: that's why it hasn't become widespread», adds Eugenio Santoro, head of the Digital Health Research Unit at the Mario Negri Institute in Milan.

In the meantime, smart pills are targeting new fields of application, such as the targeted release of drugs. Medicines for treating the intestine have coatings that resist the acidic pH of the stomach; but when they reach the intestine, chemical reactions reduce their availability to 1%. This is why Navicap and Ranipill are being tested on humans, which deliver drugs directly to the intestine without dispersion thanks to electronic systems (see box on the previous page).

The University of Florence and the Scuola Sant'Anna have instead patented a capsule that delivers a therapy without antibiotics for those suffering from Helicobacter pylori infections in the stomach: Capsulight. It emits a three-color LED light for 20 minutes, which kills pathogenic bacteria.

A pH sensor deactivates the capsule when it reaches the intestine, so as not to eliminate the beneficial bacteria of the microbiota. In vitro tests have demonstrated an efficacy of 97%. Now researchers are looking for funding to test it on humans: with 4 capsules and 8 days of treatment, bacteria could be eradicated without drugs.

And today smart pills could solve a long-standing problem: ensuring regular intake of drugs for patients suffering from chronic diseases (diabetes, epilepsy, Alzheimer's). In the US alone, failure to comply with prescriptions contributes to 125,000 preventable deaths and 50% of treatment failures, at a cost of over $100 billion a year.

FROM MALARIA TO HUNGER

To avoid these risks, a bioengineer from MIT, Giovanni Traverso, invented Lynx, a capsule with a slow-release active ingredient. To prevent the pill from being digested from day one, once in the stomach, it opens into a star shape with 6 arms impregnated with the drug. The shape allows the passage of food and water, but blocks the device in the stomach. «The pylorus, the exit orifice of the stomach, is 2 cm wide, so the star had to be wider», says Traverso. «In addition, the stomach compresses the food when digesting it, so we developed materials that can resist compression. But the segments that make up the star dissolve immediately in the intestine without causing obstructions».

So, to follow a therapy it will be enough to take one capsule a week or a month. The British company Lyndra Therapeutics, founded by Traverso, has received funding for 260 million dollars (including from the Bill & Melinda Gates Foundation) and is doing the first tests on humans. Lynx could also help defeat malaria. In fact, to exterminate the mosquitoes that spread it, all residents of an area must take ivermectin every day, an antiparasitic that kills the insects that bite those who have caught it. Administering the drug in a single dose would make it easier to clean up.

Also promising is the use of smart pills to monitor intestinal gases produced by inflammation. These gases have a short life: knowing precisely where they develop is essential to diagnose a disease. A capsule, Atmo-gas, is being tested on humans: it measures the concentrations of hydrogen and CO_2.

Recently, MIT created a capsule that contains special bacteria: in the presence of gas, they emit light, which is then transformed into a radio signal.

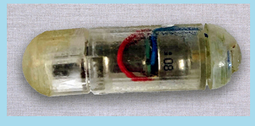
And Traverso has invented two smart pills for hunger: one, Flash, triggers it, stimulating with mini electric shocks the receptors in the stomach that produce ghrelin, the appetite hormone. And another, Vibes, turns it off by vibrating for 30 minutes: the pigs it was tested on ate 40% less. If the two pills work on humans, they could revolutionize diets.

«The important thing», warns Santoro, «is that these new devices are supported by studies that demonstrate their safety, efficacy and sustainability on a large scale. Even compared to existing therapies».

PILLS TESTED ON ANIMALS

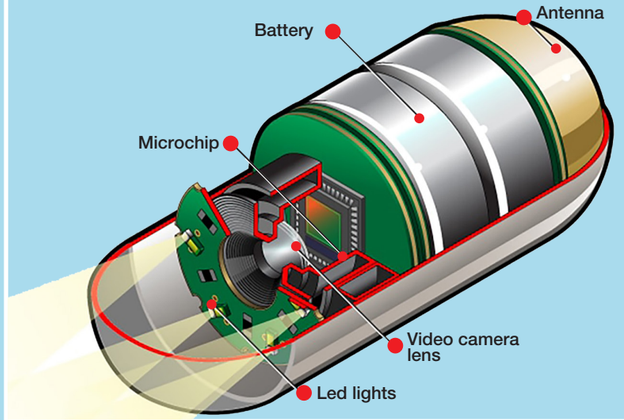
GAS MONITORING - MIT, 2023
The pill contains bacteria that emit light when they detect nitric oxide and hydrogen sulfide byproducts, which mediate intestinal inflammation. The pill's electronic circuitry converts the light into a wireless signal that is transmitted to a smartphone.

STIMULATION OF HUNGER - MIT, 2023
The Flash capsule is coated with gold wire: the grooves absorb stomach fluid, so the wire can electrically stimulate receptors in the stomach that release ghrelin, the hormone that makes you feel hungry. It may be useful for anorexia.



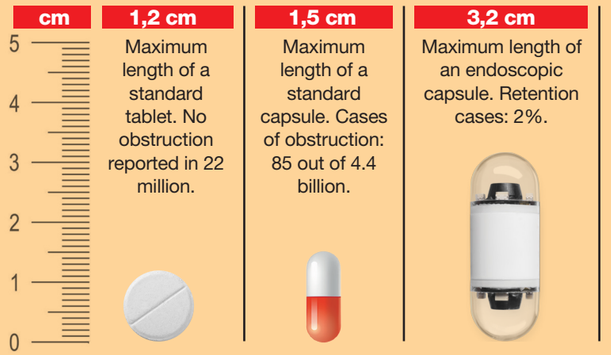
APPETITE CONTROL - MIT, 2023
When the Vibes pill reaches the stomach, gastric fluids activate an electrical circuit: the capsule vibrates for 30 minutes, stimulating the nerves in the stomach that give the sensation of fullness. The animals tested ate 40% less.

HOW THEY ARE MADE



The endoscopy capsule, about the size of a vitamin pill, contains a tiny camera that takes pictures of the inside of your digestive tract.
It is taken on an empty stomach, after taking a laxative the night before.
The capsule takes about 8 hours to travel through your body and can capture more than 50,000 images.
You cannot eat for 4 hours after taking it.
The images are transmitted to a recorder via sensors attached to your body with electrodes or a receiver on your belt.
This data can help a gastroenterologist see and diagnose a variety of gastrointestinal conditions, such as polyps, ulcers and bleeding.
After the exam, the capsule goes down the toilet.

THE RISKS



The risk of retention is one of the major complications of capsule endoscopy. It occurs when the patient is unable to expel the capsule within 14 days.
In half of the cases, surgery is required to remove it; in 26% of cases, it is possible through an endoscopic procedure. Today, cases of retention have greatly reduced because the risk factors have been identified, including diabetes with neuropathy, Crohn's disease, diverticulosis, and use of anti-inflammatories. To verify the feasibility of the test, a "patent capsule" is used today: it is as large as the endoscopic capsule, and can be located with x-rays; if it encounters an obstacle, it dissolves within 30 hours.