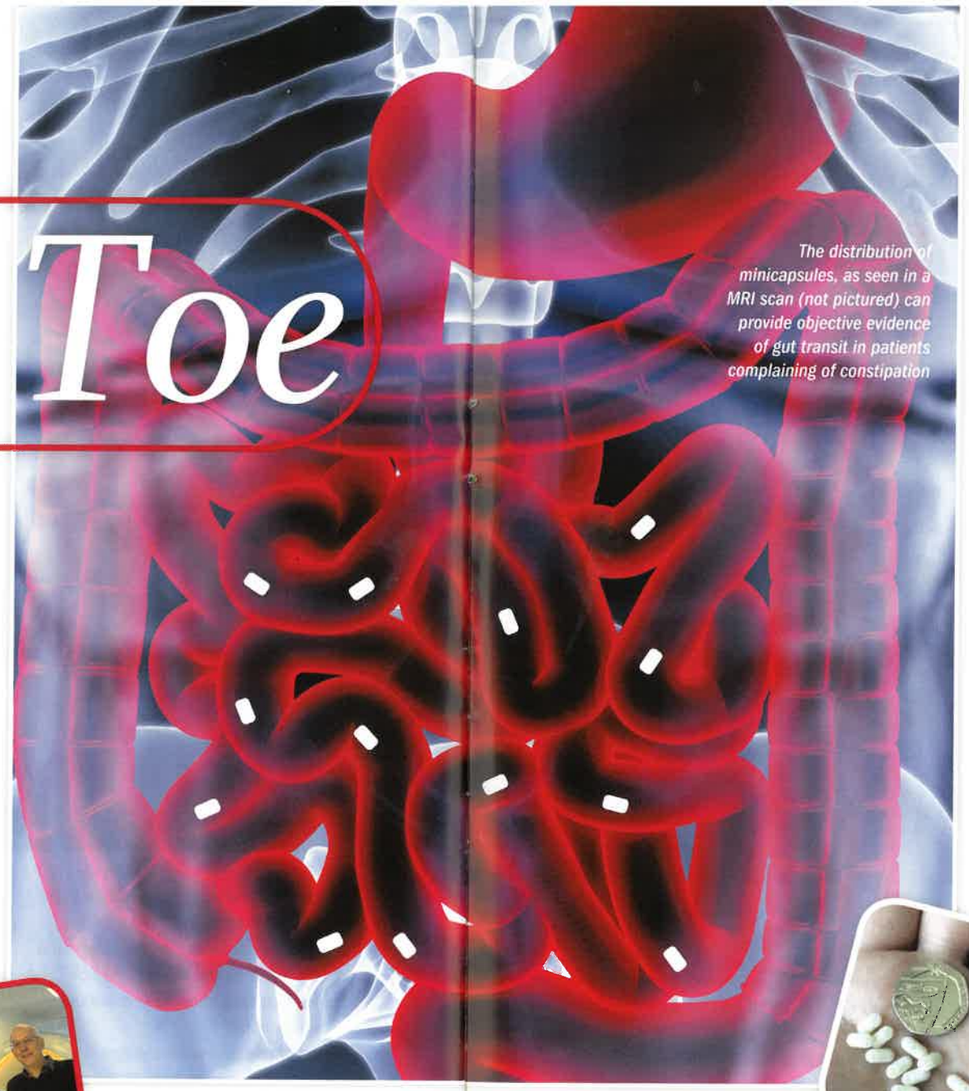
Tic Tac Toe



The distribution of minicapsules, as seen in a MRI scan (not pictured) can provide objective evidence of gut transit in patients complaining of constipation

adobe.stock.com/dimdimich

A new improvement of an old method of diagnosing intestinal problems has relied on a novel manufacturing process to produce a new kind of tracker bead

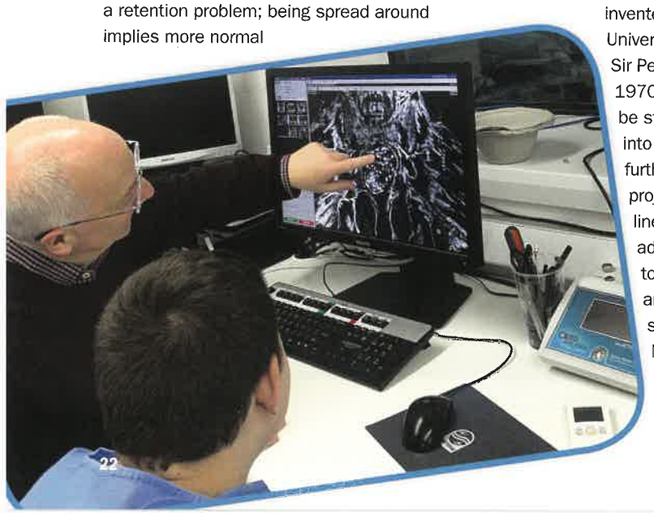
Since the 1980s, people suffering from intestinal complaints such as constipation have sometimes been given a handful of plastic pellets containing barium (radiopaque markers) to help diagnose their problem using X-ray diagnostics, explains Dr Luca Marciani, University of Nottingham associate professor in gastrointestinal MRI (pictured, with patient Jed Randall).

These tests can provide some objective evidence, as opposed to the patient reporting their toilet stops – or a parent doing it for the child. "There are various facets of this, from the more normal gut transit with symptoms of pain to slow-transit constipation, to retention and obstruction," Marciani points out. In X-rays, the heavy element barium shows up as opaque in an X-ray scan, so the pellets' progress or lack of progress in the bowel can indicate what factors might be causing the problem. Bunching at the top of the bowel indicates severely slow transit; piling up at the bottom suggests a retention problem; being spread around implies more normal function. A missing group of pellets suggests a bowel movement has occurred.

But the test is not ideal for children. First, it involves exposing them to ionizing radiation, large doses of which are bad for developing organs and can cause problems in later life. Second, the X-ray image itself is difficult to interpret, as internal organs tend to come out fuzzy, and the bowel curls around the abdominal cavity in complex way, he adds.

Still, a test was needed to help clinicians diagnose the causes of childhood constipation, to find the right treatment. The condition peaks in school-age children, some 14% of whom suffer from it at some point. And as many as 30,000 in England per year end up in hospital as a result, according to government figures.

Much better results – without the health risks – are to be found from more recent technology, particularly the MRI, magnetic resonance imaging, technologies of which were invented by Nottingham University physicist Prof Sir Peter Mansfield in the 1970s. MRI scans can be stitched together into 3D images. (A further goal of the project, down the line, is to develop add-on software to automatically analyse the images; specialist firm Motilent designed an initial analysis software module).



The way in which MRI acquires images of the body differs from the way that X-rays do, so the two technologies' images look very different. In particular, plastic pellets don't stand out; but oil-water emulsions do.

So the idea was a capsule containing a medically-safe fat emulsion. Drug capsules are a great way to carry material into the body, but they are designed to disintegrate; the gastrointestinal transit test process requires something hard enough to resist stomach acid and bowel water for a few days of transit. Also, the size of the capsule would need to be adapted to suit children, whose smaller throats make it difficult to swallow full-sized tablets.

His vision of the way the test would work is to provide a patient with 24 minicapsules a day for three days (72 in total), and then ask them to come in for an MRI scan on the fourth day.

"The challenge was to produce something small, workable, fillable, and safe to use," states Marciani. He tasked design consultancy Renfrew to find a solution.

PRODUCTION TECHNOLOGY

Renfrew design development director Michael Phillips recalls that it could find no technology to make capsules of that small size (8mm by 4mm, about the size of a Tic Tac breath mint), so it considered novel small-capsule filling methods, and explored other ways of containing the imaging medium, such as encapsulating the emulsion within a polymer gel.

The innovative idea that the Renfrew team ultimately chose was to fill a medical-grade tube with the emulsion, and then use a welding process to cut and seal the filled tube using heat and novel tooling. It developed tools and iterated the process with a number of materials and tube bore and diameters. Experimentation helped reduce the flashing and get a smoother edge radius. The team patented the method. It also developed a semi-automatic injection moulding production method.

As it is not a manufacturer, Renfrew passed the design to JEB Technologies, a diversified manufacturing subcontractor and design engineering company based in Suffolk that originally met Marciani at the Med-Tech exhibition.

"The work that had been done was very good," recalls JEB business development manager Sean Licence, himself a qualified toolmaker. "And what we had to do was use that as a springboard to develop reliable volume manufacturing."

Although Licence credits the Renfrew team with a 'superb' idea for the minicapsules, it had trouble using the process to produce the capsules at a sufficient level of quality. And there were time pressures; it had only three months to set up production, validate it and include it in the technical documentation to send to the UK medical council for clinical trial permissions.

Instead, JEB came up with an alternative production concept "in an afternoon, out of a flash of inspiration". Licence recalls working the heat-sealing jig by hand, with another engineer. After one particular run, he recalls: "We looked at each other, and said, 'that's going to work'". Starting with tube, they closed one end, injected the emulsion into the other, and then sealed it thermally. After making some prototype tooling, they sent samples to Marciani for approval. His okay led them to develop low-volume, manual, single-cavity tooling, producing about 1,000 capsules per day using a revised design that uses plastic injection-moulded blank rather than tube.

The manufacturing process, however, was only part of the work required for medical sign-off. Process validation included materials investigation to make sure it would not put patients at risk, as well as sterilization validation, packaging validation, shelf-life testing and transport.

The team in Nottingham carried out a first feasibility clinical study, which was successful. It involved giving each of 42 test subjects a 72-microcapsule dose, all of which were produced by JEB.

In July, Nottingham hospital started gearing up for a second clinical investigation to prove the capsule's safety and performance, following a £1.2m funding award from NIHR. This will be a larger trial of 436 children and teenagers in clinics. After that, the team is possibly going for the NHS's Accelerated Adoption Programme, which short-circuits the years-long process of testing new treatments in special cases.

Having produced the initial batch, JEB's next focus is on CE marking. Research results, clinically evaluated, are added to the technical file and to be submitted. Licence hopes to achieve that next year.

Part of that resubmission involved up-scaling the manufacturing process by automating parts of the operation. That is a step toward the ultimate production capacity of up to 500 parts/minute that Licence estimates will be needed once worldwide demand ramps up. This is because JEB's ultimate stake in the project was not a share of the project cost, but the contract to manufacture and distribute the goods, worldwide, a model that proved very successful for the firm in a recent defence contract. Its hope for future income is what supports its £320,000 investment that Licence estimates that JEB has spent on its minicapsule development work so far. Pentland Medical is lined up as the UK distributor.

Concludes Licence: "It's an amazing project. We are so proud of this device, and we know it's going to change people's lives because of what it will be able to do, once it's approved for use. That's a great feeling."