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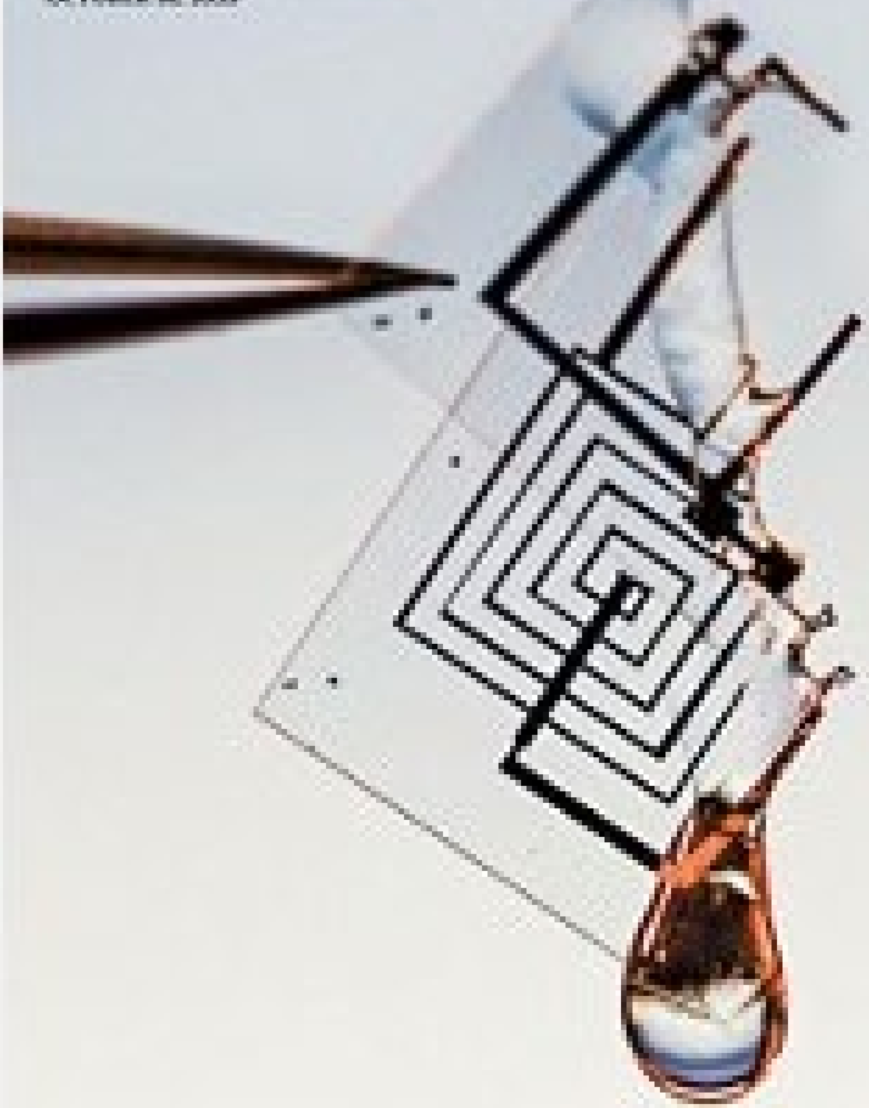

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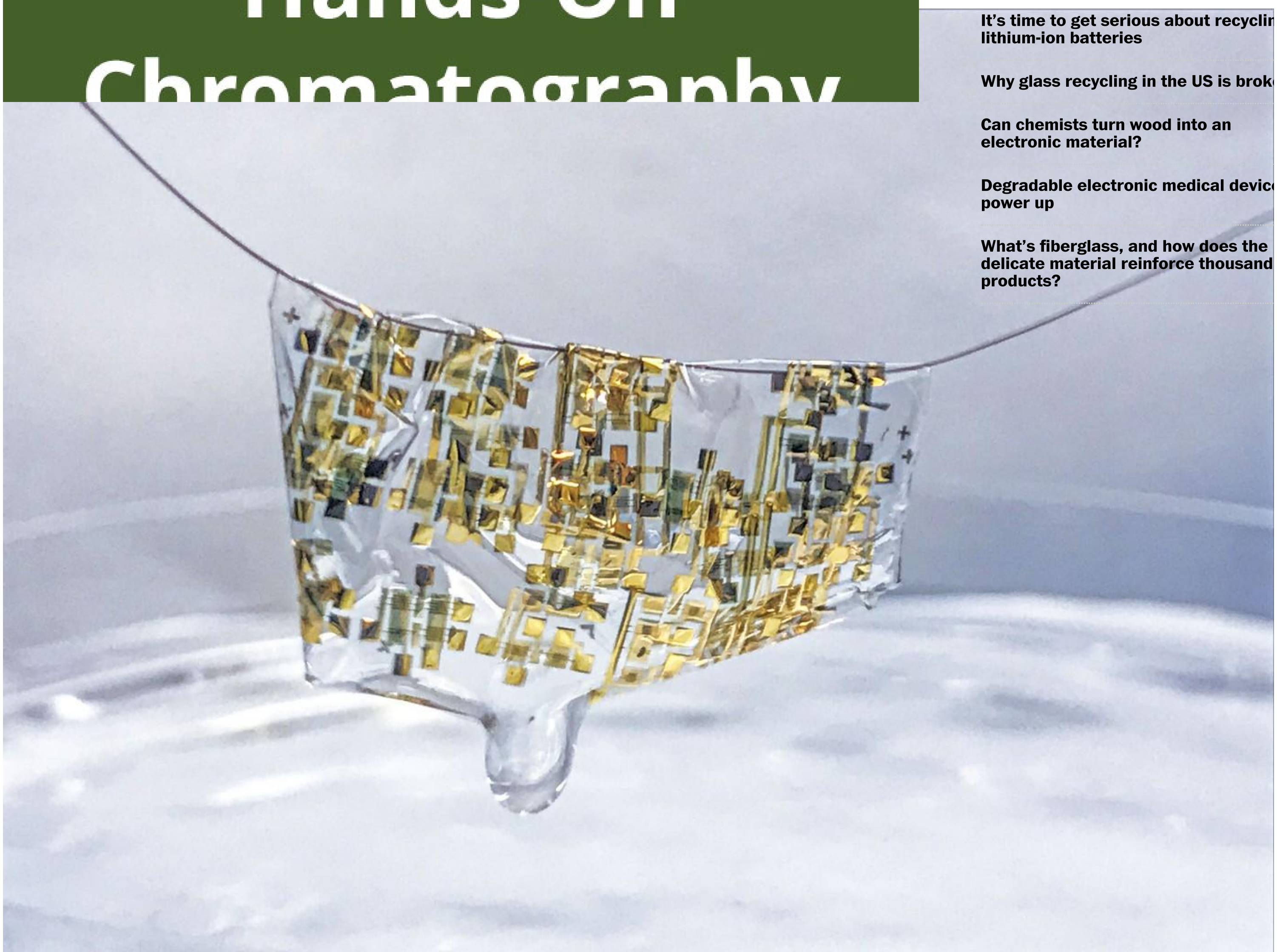

The complications that Armstrong experienced are rare and usually not fatal. But they underscore that with every surgery—even something as routine as removing an implanted device that's no longer needed—comes a degree of risk.

But what if implants could remove themselves? What if all temporary medical devices were made to break down into parts that the body could either use or expel by normal waste processes after the devices have served their purpose, forgoing the need for surgery?

Transient medical devices are far from a new idea. Synthetic **dissolvable sutures have existed since 1962**, years before Armstrong's historic moon landing. And there are many examples of degradable stents, balloons, screws, and other mechanical devices being approved by the US Food and Drug Administration.

But in the past 15 years or so, advances in materials science and engineering have paved the way for electronic devices to become degradable as well. No transient electronic medical devices have made the leap from lab animals to human clinical trials yet, but researchers say that they're primed to do it soon.

Credit: *Science*

By immersing a prototype bioresorbable pacemaker in saline solution at 95 °C, researchers can accelerate and study its degradation process.

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"There's a whole series of existing implantable electronic devices that would be greatly improved and transformed by bioresorbable electronic materials," says **John Rogers**, director of the **Querrey Simpson Institute for Bioelectronics** at Northwestern University. Rogers is also one of the cofounders of **NuSera Biosystems**, a start-up working to commercialize a degradable **temporary pacemaker**.

THE TEMPORARY TOOLBOX

The foundation of any device, whether degradable or permanent, electrical or mechanical, is **the stuff it's made of**. "Nothing would exist without the materials. That's really the distinguishing characteristic of the technology," Rogers says.

Related: Vertical organic transistors topple performance records

Every component of an electronic device can be boiled down to a combination of three types of materials—insulators, conductors, and semiconductors. The fundamental pursuit in research on transient devices is finding examples of each type of material that controllably degrade to benign products on a useful timescale without sacrificing their electrical properties.

The insulators are, in some ways, the easy part. There's a sizable library of biocompatible and biodegradable materials that do not conduct electricity and can be used as substrates and encapsulation layers. The FDA has recognized many of them as safe for other applications. So it's relatively straightforward to repurpose them for something new, says **Christopher Bettinger**, a biomedical engineer who works on degradable and ingestible electronics at Carnegie Mellon University.

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> — ***John Rogers**, director, Querrey Simpson Institute for Bioelectronics, Northwestern University*

Biodegradable insulators can be naturally derived proteins such as silk fibroin, or they can be polysaccharides such as cellulose, starch, chitosan, or gelatin. They can also be synthetic materials; some of the most commonly used are polylactic acid, polyvinyl alcohol, and poly(lactic-*co*-glycolic acid). These polymers break down through hydrolysis or enzymatic degradation into soluble monomers. In many cases, scientists can tune the degradation rate by tweaking the copolymer ratio or molecular weight.

Dielectrics are a subset of insulators that can be polarized by an electric field. They're essential for components such as capacitors, resonators, and transistors. The list of degradable dielectrics includes some natural and synthetic polymers and several inorganic compounds, such as magnesium oxide, silicon dioxide, and silicon nitride.

Finding degradable electrical conductors for interconnection points and electrodes isn't terribly difficult either. Several metals, including zinc, magnesium, iron, and molybdenum, oxidize relatively quickly to soluble oxide and hydroxide by-products. And the human body knows how to process these elements; many of them are ingredients of daily multivitamins. But these metals have limitations—they're not as high performing as the gold and silver used in typical electronics, says **Ravinder Dahiya**, an electrical engineering researcher at Northeastern University.

The most crucial and challenging material in any electronic device is the semiconductor, without which it is impossible to make advanced components such as transistors and diodes. "It's kind of the workhorse material in any electronic system," Rogers says. So it's important to use a semiconductor that performs its job well. "There's no shortage of lousy semiconductors out there," he says. "But what are you going to do with them?"

Until a little more than a decade ago, research on degradable semiconductors was in its infancy. What little research existed in the field was largely devoted to polymers. In 2010, Bettinger, then working as a postdoctoral scholar with **Zhenan Bao** at Stanford University, published one of the first studies describing degradable organic field-effect transistors. The devices featured a semiconductor inspired by the structure of melanin and a dielectric made of a cross-linked polyvinyl alcohol. The device dissolved in about 2 months in citrate buffer at 37 °C (*Adv. Mater.* 2010, DOI: **10.1002/adma.200902322**). A group at Johannes Kepler University Linz published a paper describing a similar concept in another journal several months later (*Adv. Funct. Mater.* 2010, DOI: **10.1002/adfm.201001031**).

Rogers was also looking into degradable organic semiconductors at the time. That began to change when one of his postdocs discovered that the thin silicon nanowires that the team was working on for a different biosensor project were soluble in a buffer solution—something few scientists had thought was possible, Rogers says. Silicon dissolves to silicic acid very slowly, losing around only 5 nm from the surface per day at body temperature. For typical crystalline silicon wafers, that's of practically no consequence. But if the silicon is only several dozen nanometers thick, as the nanomaterials Rogers's group was studying then were, it disappears in about 2 weeks.

The researchers made a **field-effect transistor using silicon nanomembranes**, magnesium electrodes, and magnesium oxide dielectrics. They fashioned the device on a silk substrate and used crystallized silk and magnesium oxide as encapsulating layers (*Science* 2012, DOI: **10.1126/science.1226325**). The charge-carrier mobility, a key measure of semiconductor performance, was about 10,000 times as high as those of the earlier organic semiconductor devices. Bao says that organic semiconductors have improved by an order of magnitude in recent years and are now nearly on par with amorphous silicon.

The discovery of soluble silicon opened up a viable path to sophisticated biodegradable electronic devices and sparked much of the field's growth in the past decade, according to Rogers.

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MAKING THINGS THAT BREAK DOWN

Designing a degradable device can be a bit of a paradoxical exercise. It must work as reliably as a permanent device and yet be undergoing a constant, gradual disintegration so that it's gone as soon as possible after it's no longer needed. "Any residence time after it's done functioning is just kind of silly and pointless," Bettinger says.

The device's lifetime is often set by an encapsulation layer, which protects the guts of the device from breaking down before they're meant to—even as the protective layer itself slowly dissolves. That role means it must be made of something that undergoes a predictable surface erosion process at a steady and well-defined rate but is otherwise impermeable to biofluid. "It's a tricky business in terms of the materials chemistry," Rogers says.

Fabricating biodegradable electronics comes with some unique challenges as well. The materials are all sensitive to water to some degree, so device makers must carefully consider wet processing steps that could ruin what they're trying to make. In addition, traditional silicon patterning methods aren't compatible with polymer substrates, which would melt or burn at standard processing temperatures that can exceed 1,000 °C, Dahiya says.

There are several techniques to get around these limitations, such as laser ablation, inkjet printing, and transfer printing. But these methods can sacrifice resolution and thus lead to worse performance, Dahiya says. The ideal approach would be to directly print everything at or near room temperature, which is something his lab is working on for silicon. For now, he says, organic semiconductors are far easier to fabricate than silicon and other inorganic materials and could be a good option if the lengths that the charges must travel are short enough to counter the slower mobility.

Gaurav Balakrishnan, a graduate student in Bettinger's lab, says the next big hurdle is reducing trade-offs between processability and performance to make advanced biodegradable circuits that can be manufactured on a large scale. Today, these devices are usually made by hand in small quantities by the researchers studying them.

Related: Temporary pacemaker can fully dissolve in animal models

"Getting to that point with degradable materials where we have a library of high-performance electronics is going to take some time, but I think we're in good shape to move towards it," Balakrishnan says.

WHAT DEGRADABLE DEVICES CAN DO

As the selection of degradable materials has expanded in recent years, researchers have been able to create proof-of-concept devices with a wide array of functions—some diagnostic, others therapeutic. "The inner brains of these devices are very different. But the core structural elements are largely similar," Bettinger says.

> **"The inner brains of these devices are very different. But the core structural elements are largely similar.**
>
> — ***Christopher Bettinger***, *biomedical engineer, Carnegie Mellon University*

Sensors for physical measurements such as pressure and strain are the simplest type of implantable electronics and therefore the easiest to make degradable. The sensors typically work using piezocapacitance or piezoresistance, converting physical deformation or temperature change to easily measured changes in capacitance or conductivity.

Researchers have designed physical sensors **aimed at postsurgical monitoring** in places such as tendons, blood vessels, and **the brain**. Such sensors could help people and their doctors monitor symptoms such as inflammation in the days or weeks after a procedure. Surgical monitoring is an ideal application for a degradable sensor because no additional surgery is needed to put in the device or take it out, Bettinger says. "You're already in the implantable space."

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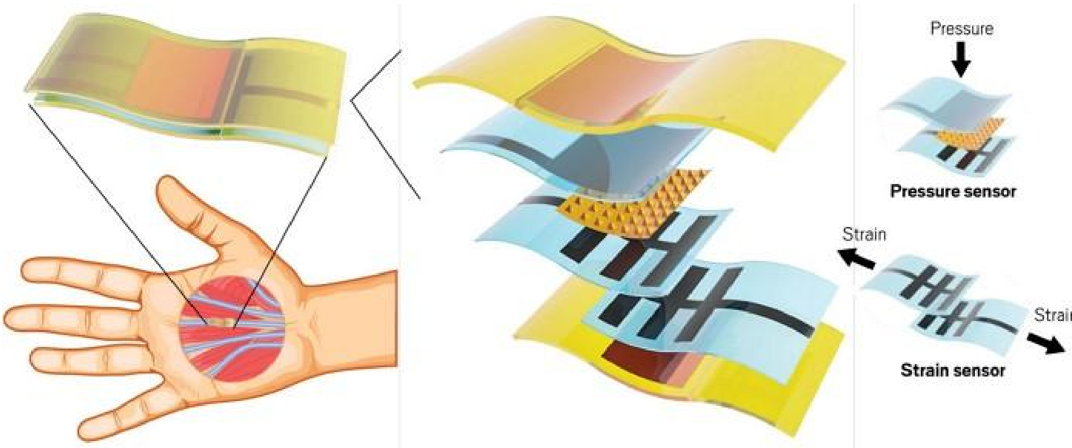
SHORT-TERM SENSING

Made of multiple layers, this biodegradable sensor is designed to monitor mechanical forces on tendons after surgery. The sensor detects pressure and strain by measuring changes in capacitance and dissolves slowly over several weeks after surgery. The electrodes (black) are magnesium metal evaporated on top of a polylactic acid substrate (blue). The encapsulation layers (yellow) are poly(octamethylene maleate (anhydride) citrate), and the dielectric (orange) in the pressure sensor is poly(glycerol sebacate).



Credit: Adapted from *Nat. Electron.*/Yang H. Ku/C&EN/Shutterstock

Several research groups are also working on more complex sensors for measuring electrical activity in the brain or chemical information such as pH or levels of neurotransmitters or glucose. But here, again, the devices have paradoxical design requirements that make recording data a challenge. Chemical sensors must directly interface with and measure the very same environment that is actively eating away at them, which means the signal drifts over time more than it ordinarily would.

Much of Rogers's focus in recent years, when it comes to degradable electronics, has been in the realm of therapeutic devices. In addition to working on pacemakers, his group has collaborated on devices to heal nerve damage, block pain signals, and deliver drugs. Many of these devices rely on a radio-frequency antenna to receive signals saying when and how to deliver a targeted electric pulse to the tissue in which they're implanted. They dissolve in a couple of months under physiological conditions.

Colin Franz, a physician-scientist at Shirley Ryan AbilityLab who is collaborating with Rogers on implantable electrical stimulation devices for nerve regeneration, says that transient implants could be a good way to bridge the gap between acute and long-term treatment. If it's unclear how a person with nerve or spinal cord damage will recover, they could receive a temporary device to support and monitor the healing process. If all goes well, the device will disappear as the injury does, he says. But if short-term therapy isn't enough, "we can still put in a permanent implant."

TRANSIENT TRANSLATION

In theory, a degradable implant should be safer than something that has to be removed surgically or remains in the body permanently, Rogers says. But that doesn't mean it will be an easy road from the lab to clinical approval.

"There's an inherent lag to getting from a new material or new device to being able to do a clinical trial," Franz says. And the last steps in the technology translation process are by far the most expensive and riskiest, usually requiring commercial funds or philanthropic grants.

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For degradable electronics specifically, “there are all kinds of potentially confounding issues that the FDA hasn’t worked through in the past, because it’s totally new technology,” Rogers points out. Academic research may reward pushing boundaries and devising new, complex functions, but clinical translation requires simplicity, safety, commercial viability, and a clear benefit for patients.

For any new device that’s designed to come into direct contact with body tissue, inventors have to show the FDA data proving that it is at least as safe and effective as what’s already on the market. That means assessing all the materials used in the device, how the device is manufactured, where in the body it will be used, and for how long. And for transient devices, researchers must take into account what the degradation products are and what happens to them.

While **the FDA’s rules for device evaluation** say that the agency looks at whole devices rather than individual materials, using materials that the agency already recognizes as safe generally makes the process easier, Franz says. But if there aren’t any materials already out there that do what you need them to do, “then that’s worth pushing the boundaries on, even if it’s going to take longer,” he says.

Likewise, Rogers says, it’s smart from a regulatory and commercial standpoint to start with a device function that already exists—so there’s already a demonstrated market—and then use degradable elements to improve and expand a device’s usefulness. “It’s not a technology push as much as it is a solution to technical clinical problems and unmet needs,” he says.

The degradable pacemaker is one of a few technologies that Rogers and his collaborators **Igor Efimov** and **Roozbeh Ghaffari** are working on commercializing through NuSera, which they started in 2020. Currently, Efimov says, their research is funded by the US National Institutes of Health and philanthropic grants, but they’re also pitching their ideas to investors.

In the latest version of the company’s pacemaker, the implantable part is small enough to be inserted via syringe, and it’s powered by a tiny dissolvable galvanic cell that uses biofluid as the electrolyte. The fact that it’s a life-supporting device raises the bar for approval, but Rogers says he’s optimistic about it. “I think there’s a good combination of a clinical need and technology superiority over the standard of care,” he says. The team is testing the device in rodents, pigs, and dogs to get the data they need to start clinical trials.

WHERE DO WE GO FROM HERE?

The field of degradable electronics is in a good place today, Rogers says. It matured enough over the past decade that there are around a half-dozen potentially commercializable applications that are attainable with existing materials and methods. But there’s still much more to be explored on a fundamental level, so academic research opportunities remain abundant.

Helen Tran at the University of Toronto is one of the people working on pushing the boundaries of degradable organic semiconductors, building on her **postdoctoral work with Bao**. Introducing easily breakable bonds, such as esters, tends to interrupt the conjugation needed for charges to move through the polymer, which makes it challenging to get high electron mobility.

But the goal, according to Tran, isn't to replace silicon-based electronics with organics. Instead, she aims to take advantage of organic molecules' synthetic adjustability to design materials with new properties. For some applications, it might be OK to take a hit on charge mobility to build in softness or stretchiness. For other devices—for example, ones requiring complex circuitry—that might not be an option.

Trying to design molecules and materials with new combinations of properties is a complex puzzle, but "that's why it's fun," she says.

Related: Zhenan Bao makes stretchable electronics for artificial skin

Tran and her students take inspiration from conjugated molecules in nature, such as melanin, indigo, and β-carotene, to make semiconducting polymers with imine links. Those links maintain conjugation along the polymer backbone but can be broken in an acidic environment. She and her group published a paper earlier this year on carotenoid-based polyazomethines (*J. Am. Chem. Soc*. 2023, DOI: **10.1021/jacs.2c12668**) and two preprints—articles published before peer review—related to degradable conjugated polymers (ChemRxiv 2023, DOI: **10.26434/chemrxiv-2023-xdglp** and **10.26434/chemrxiv-2023-rgm98**).

For his part, Bettinger sees a lot of promise in ingestible electronic devices, which would perhaps be easier to get regulatory approval for than something surgically implanted. There's precedent for ingestible electronic devices earning approval: in 2017, the **FDA approved Abilify Mycite**, a "smart pill" with an ingestible sensor meant to help people with schizophrenia and bipolar I disorder track their treatment regimens. But the company that made the sensor, Proteus Digital Health, **filed for bankruptcy in 2020**.

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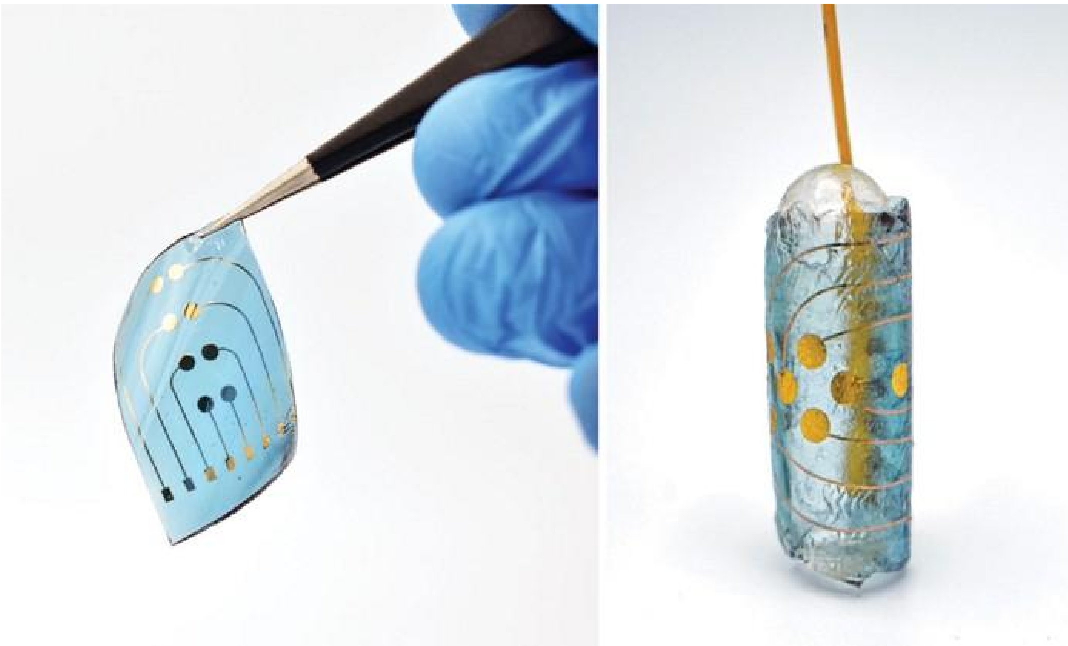

Credit: Gaurav Balakrishnan

This ingestible sensor, which is printed flat and then rolled into a capsule, is designed to monitor gastrointestinal inflammation by electrochemical impedance. The gelatin substrate dissolves so that the electronic components can safely pass through the digestive tract.

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Bettinger and Balakrishnan recently coauthored a paper on a partly degradable ingestible device for monitoring inflammation in the gastrointestinal tract (*Adv. Mater.* 2023, DOI: **10.1002/adma.202211581**). The gelatin substrate breaks down so that the active components can easily pass through the digestive tract. Ingestible devices don't have to break down completely to remove themselves from a person's system. That gives researchers more leeway to explore new applications that aren't yet possible with the current library of degradable materials and techniques, Balakrishnan says.

Besides sensors, Bettinger's group is also working on ingestible electronics for therapeutic purposes. Now that science knows more about how the gut and brain communicate with each other and the microbiome, "we're kind of realizing there's a therapeutic dimension to the gut," Bettinger says. Electrical stimulation could help drugs cross the intestinal walls or even signal the vagus nerve to tell the brain that the stomach is full.

Rogers anticipates that basic and translational research will drive each other forward to achieve things that nobody has yet thought of. "I think in the future we'll see devices that go beyond anything that exists today in clinical medicine," he says.

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ISSN 0009-2347

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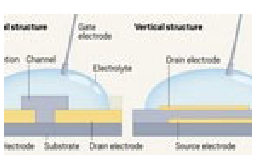

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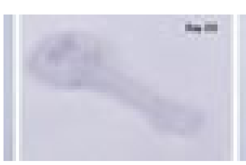

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