In 1870, James famously declared himself for free will. In a diary entry for April 30, he wrote, "I think that yesterday was a crisis in my life. I finished the first part of Renouvier's [French philosopher Charles Renouvier, 1815-1903] second *Essais* and see no reason why his definition of free will—'the sustaining of a thought *because I choose to* when I might have other thoughts'—need be the definition of an illusion. At any rate, I will assume for the present—until next year—that it is no illusion. My first act of free will shall be to believe in free will."

James identified chance as the source of "ambiguous possibilities" and "alternative futures." "*Chance is not the direct cause of actions,*" writes Doyle. "James makes it clear that it is *his choice* that 'grants consent' to one of them [alternatives]." In an 1884 lecture, "The Dilemma of Determinism," James challenged some Harvard divinity students to ponder his choice of a route home after the talk. "What is meant by saying that my choice of which way to walk home after the lecture is ambiguous and a matter of chance?....It means that both Divinity Avenue and Oxford Street are called but only one, and that one *either* one, shall be chosen. The notion of alternative possibility...is, after all, only a roundabout name for chance."

Chance and randomness, however, are concepts that make many academics uncomfortable. "Philosophers and mathematicians hate probability," says Doyle. "All the great mathematicians—Laplace and Gauss, for example—did not believe chance was real. 'Laws of chance,' as they call probability—are only able to describe events, but there is no *real* chance, because God clearly knows what's going to happen. Most of these thinkers—centuries ago—were very religious. And even today mathematicians like to think someday we'll discover the 'laws of chance'—which makes randomness sound regular and lawful."

In the life sciences, where results depend not only on abstract cerebral processes but data that stream in from nature, chance gets more respect. James was highly conversant with Charles Darwin's work, in which evolutionary theories embraced random mutations of genes. More recently, German neurobiologist and geneticist Martin Heisenberg (son of physicist Werner Heisenberg, winner of the Nobel Prize for his work on the uncertainty principle) published a 2009 *Nature* article on free will (with a letter from Doyle), describing how the bacterium *Escherichia coli* moves in two ways: either tumbling randomly or heading purposefully forward. "This 'random walk' [of tumbling] can be modulated by sensory receptors, enabling the bacterium to find food and the right temperature," Heisenberg writes. Thus, a two-stage process combining chance with choice might even apply at the unicellular level of life.

Quantum physics, by putting physical science on a probabilistic footing, erased any ambitions to remove randomness from its equations. British astrophysicist Arthur Stanley Eddington (1882-1944) even declared, "Now that physics is no longer deterministic—because of quantum physics—the door is open to free will," reports Doyle. "And the philosophers said to him, *'What?* You think a free electron makes *us* free?'" Eddington eventually backed off his position, but subsequent decades of work have only strengthened the claims of the quantum model. "Quantum physics makes predictions to 14 decimal places," Doyle says. "It's the most accurate of all mathematical physical theories." Randomness and even free will, it appears, are fully compatible with some highly precise determinations.

—CRAIG LAMBERT

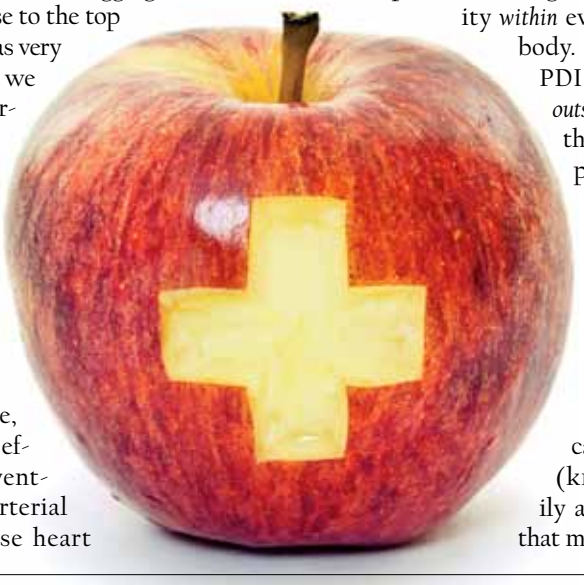
ROBERT O. DOYLE E-MAIL:
rodoyle@fas.harvard.edu
ROBERT O. DOYLE WEBSITE:
http://informationphilosopher.com

MEDICINAL McINTOSH

Curbing Clots

THE OLD ADAGE "An apple a day keeps the doctor away" now has science to back it up: Harvard researchers have found that rutin, a substance contained in that fruit (as well as in onions, buckwheat, and tea), has potent anticlotting powers that could help prevent heart attack and stroke.

Researchers discovered rutin's antithrombotic property when they screened a set of 5,000 compounds for their ability to block the action of a key protein involved in the formation of vessel-clogging blood clots. When rutin rose to the top of the list, "It was very surprising, and we still don't understand exactly why it is so potent," says associate professor of medicine Robert Flaumenhaft, the study's senior author.



What's more, rutin could be effective at preventing both the arterial clots that cause heart attacks and strokes and the venous clots that cause deep-vein thrombosis and pulmonary embolism, even though the two types form by somewhat different mechanisms. Existing anticlotting drugs (aspirin, Plavix, Coumadin/warfarin) target one clotting mechanism or the other.

Indeed, if scientists had tried to design a clot-preventing molecule, they could scarcely have created one more perfect than rutin. The protein it blocks—PDI (protein disulfide isomerase)—is essential for protein folding, a critical activity *within* every cell of the body. Rutin inhibits PDI activity only *outside* cells, where the protein's clot-promoting activity takes place.

Health-conscious consumers may be familiar with rutin: it is one of a class of substances called flavonoids (known primarily as antioxidants that may help prevent

JAMES MCQUILLAN/ISTOCK IMAGES

cancer and slow aging), and is already sold as a nutritional supplement. Because the Food and Drug Administration has already granted it "generally recognized as safe" status, fewer regulatory hurdles apply to the clinical trial Flaumenhaft and his colleagues are beginning to conduct.

Research in humans has not yet compared rutin directly with widely used antithrombotic medications, but one thing is already clear: those medications are not effective enough on their own. People who have one heart attack or stroke are usually prescribed one of them, yet each year there are 400,000 recurrences—a subsequent heart attack or stroke in a patient who's already had one—in the United States. "Thrombotic disease kills more Americans than cancer, than HIV, than anything else," says Flaumenhaft. "If you have a drug that improves upon existing options by even 2 or 3 percent, that would still be many thousands of lives saved."

—ELIZABETH GUDRAIS

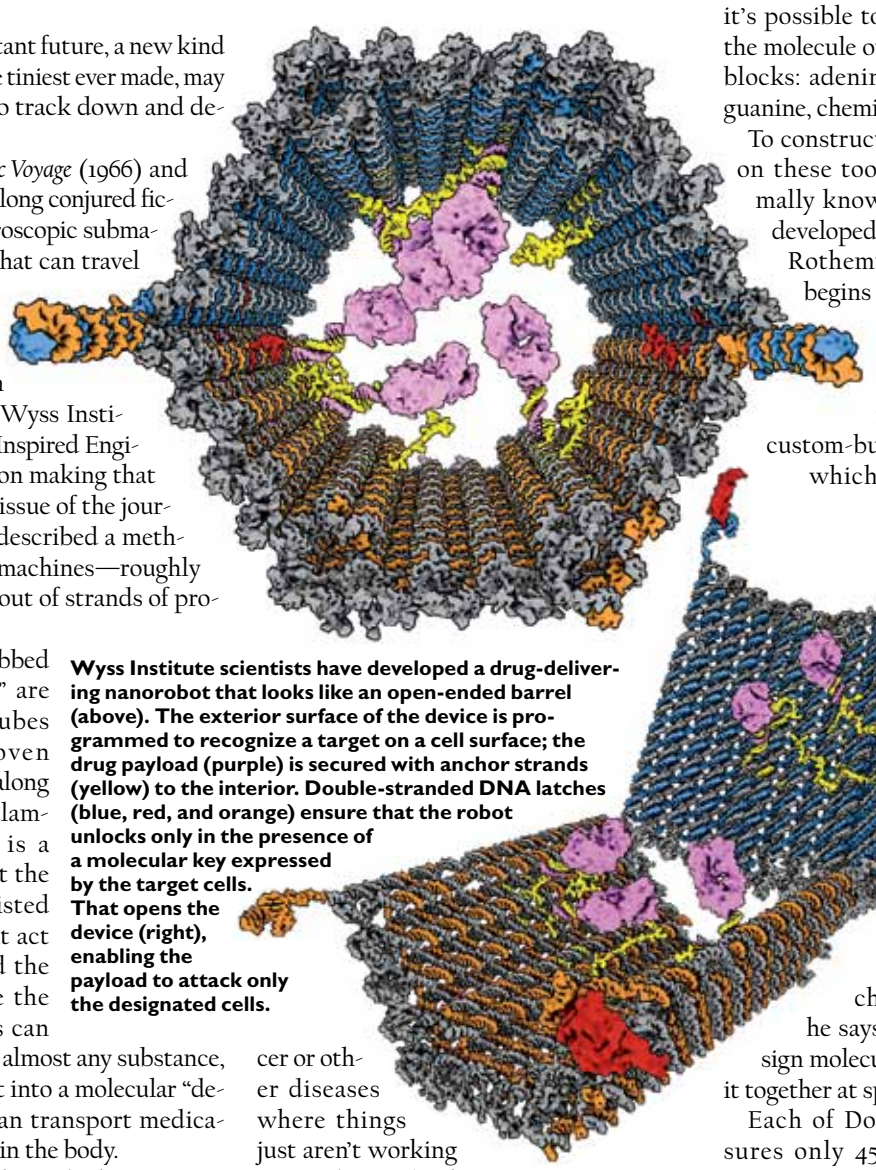
ROBERT FLAUMENHAFT E-MAIL:
rflaumen@bidmc.harvard.edu

NANO TRANSPORT

Cancer-fighting Robots

IN THE not-so-distant future, a new kind of robot, one of the tiniest ever made, may have the ability to track down and destroy cancer cells.

Films like *Fantastic Voyage* (1966) and *Innerspace* (1987) have long conjured fictional images of microscopic submarines or machinery that can travel inside the human body to cure ailments. Now Shawn Douglas, a research fellow at Harvard's Wyss Institute for Biologically Inspired Engineering, is working on making that a reality. In a recent issue of the journal *Science*, Douglas described a method for creating tiny machines—roughly the size of a virus—out of strands of protein and DNA.



Wyss Institute scientists have developed a drug-delivering nanorobot that looks like an open-ended barrel (above). The exterior surface of the device is programmed to recognize a target on a cell surface; the drug payload (purple) is secured with anchor strands (yellow) to the interior. Double-stranded DNA latches (blue, red, and orange) ensure that the robot unlocks only in the presence of a molecular key expressed by the target cells. That opens the device (right), enabling the payload to attack only the designated cells.

These devices, dubbed "DNA nanorobots," are short hexagonal tubes made of interwoven DNA that can open along their length like a clamshell. At one end is a DNA "hinge," and at the other, a pair of twisted DNA fragments that act as "latches" to hold the device shut. Inside the nanorobot, Douglas can enclose molecules of almost any substance, essentially turning it into a molecular "delivery truck" that can transport medication to specific cells in the body.

"Our goal is to make tools that can zero in on malfunctioning cells," he says. "We want to be able to fix things when they break—when cells go haywire due to cancer or other diseases where things just aren't working correctly. To do that, I think it makes sense to master this kind of nanoscale construction."

As it turns out, says Douglas, DNA is an ideal material for building at the nanoscale level. Well-developed tools are already in place to understand, manipulate, and even manufacture it. Using computers and special machines called DNA synthesizers, it's possible to create custom lengths of the molecule out of its four basic building blocks: adenine, cytosine, thymine, and guanine, chemicals known as nucleotides.

To construct his devices, Douglas calls on these tools and a technique informally known as "DNA origami," first developed by Caltech researcher Paul Rothemund in 2006. The process begins with a single long strand of DNA that Douglas uses as a backbone or "scaffold" for a structure. That strand is mixed with short chunks of custom-built DNA he calls "staples," which are designed to bind to specific sections of the scaffold, bending and twisting it into pre-determined shapes.

Douglas chose to use the DNA of a virus called M13 (which is harmless to humans) as his scaffold, but notes that almost any long DNA molecule will work. "As long as you know the sequence [of those chemical building blocks]," he says, "it's pretty simple to design molecular 'staples' that will pinch it together at specific spots."

Each of Douglas's nanorobots measures only 45 nanometers long by 35 nanometers wide—minuscule compared to the 75,000-nanometer width of an average human hair. The advantage of a machine this small, he says, is that it can

Images courtesy of Shawn M. Douglas / Wyss Institute for Biologically Inspired Engineering