If a single word could describe the diverse disorders collectively known as cancer, it might be unpredictable. Trying to judge the course and prognosis of this meandering, unforgiving, and frequently fatal disease is almost impossible. But Thomas Deisboeck, as director of a pioneering project to "engineer" different kinds of tumors, is trying to make cancer more predictable—and hence, more treatable. His Center for the Development of a Virtual Tumor (CViT) doesn't grow cells in a lab or study cancer in mice. Instead, it serves as a "virtual laboratory," using computers rather than test tubes, and three-dimensional images instead of lab animals, to foster collaboration among researchers from around the world. "At CViT, we extract data from experiments and the scientific literature, and build models with it," explains Deisboeck, an assistant professor of radiology at Harvard Medical School. "Basing our computational models on a cell's interaction with its environment, we can simulate everything from a single cell to an organ, and make predictions from what we observe."

The digraph table helped evaluate those guesses. "For instance, the letter pair 'vj' is impossible in English, so that excludes any alignment that creates that digraph," Smithline wrote. "Alternatively, the letter pair 'qu' is rare, but when there is a 'q,' it must line up with a 'u.' When 'q' and 'u' do line up, that is strong evidence in favor of that alignment." Lastly, he applied dynamic programming—a technique used today in computational biology to find, for example, similar regions in two DNA base sequences—to statistically identify top-scoring guesses on section size, row pairs, and extra letters. (The dynamic program works despite significant errors in transcribing the handwritten cipher to typed characters.) Certain constraints in Patterson's cipher, Smithline wrote, reduced the overall computational load to fewer than 100,000 simple sums—tedious in the nineteenth century, but doable.

This analysis allowed Smithline to decrypt the challenge cipher that had held its message inviolate for more than two centuries. Had Jefferson cracked the code, he quite likely would have divined the entire message from its first few words: "In Congress, July Fourth,..."—the preamble to the Declaration of Independence, from Jefferson's own hand.

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**Cancer's New Reality**

**Virtual Tumors**

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Headquartered at Massachusetts General Hospital and part of the National Cancer Institute’s (NCI) Integrative Cancer Biology Program, CViT “funds multidisciplinary research teams that take a ‘holistic’ approach toward cancer,” explains Dan Gallahan, who as deputy director of NCI’s division of cancer biology has worked closely with Deisboeck. Harvard’s contribution to the CViT project includes high-performance-computer access through the School of Engineering and Applied Sci-
ences, and a uniquely cross-disciplinary research environment that Gallahen says provides “a critical mass of researchers across a broad spectrum of knowledge.”

Such cross-disciplinary teamwork, computing power, data availability, and better imaging have been the greatest drivers of scientific modeling, a field that has seen its most high-profile use to date in meteorology and weather forecasting. When applied to cancer research, a computer-generated model might simplify a complex metabolic pathway, revealing how millions of individual cells signal and communicate with one another: “Okay, we’ve grown enough for now,” or “We need a bit more of that hormone over here.” Carcinogens encourage tumor growth by interfering with intercellular communications, and models can show precisely how and where the interference occurs.

Deisboeck’s cancer research builds on earlier work he did as director of the Harvard-MIT Complex Biosystems Modeling Laboratory: most notably, a headline-making 2003 paper in which he asked a simple but intriguing question: Does tumor growth follow a “universal” law? In his answer, developed with a team from Italy, Deisboeck proposed not only that a mathematical law governs cancer growth, but that it’s the same law—described in 2001 by a team of physicists and biologists in the journal *Nature*—that normal tissues obey. The discovery is important, he says, because it could allow physicians a better way to measure the right amount of anti-cancer therapy a patient needs at the most opportune time in the course of the disease.

The discovery suggested that tumor modeling could work, boosting the fortunes of his nascent CViT project. The latest CViT development is a Web-based digital model repository that came online in May and provides “instant access to a variety of predictive models to scien-

Traditional light-microscopy, such as this image of human brain-tumor cells in culture (far left), still has a place in cancer research. But to aid in the study and treatment of the disease, scientists and clinicians are turning increasingly to tools such as this three-dimensional brain-tumor simulation (left) that shows the evolution of a population of cancer cells. (The colors indicate different clones of cancer cells.)
The diagnosis of depression rests entirely on symptoms: extreme self-criticism and suicidal thoughts, loss of interest in activities that were once fun and satisfying, changes in sleep patterns and appetite. If these symptoms disappear, a patient is considered fully recovered (although susceptible to relapse). But in a recent study, professor of psychology Jill Hooley found that the brains of recovered patients still show distinctive activity patterns—even though the subjects reported feeling normal.

Hooley specifically sought to examine the way subjects’ brains processed criticism. Using the relatively new technology of functional magnetic resonance imaging, she aimed to update an earlier finding from her own 1976 study, which established that patients who’d recovered from depression were more likely to relapse when living in a highly critical family environment. She and colleagues therefore imaged the brains of subjects listening to criticism from their own mothers in the form of 30-second recorded messages. (Each of the study sub-