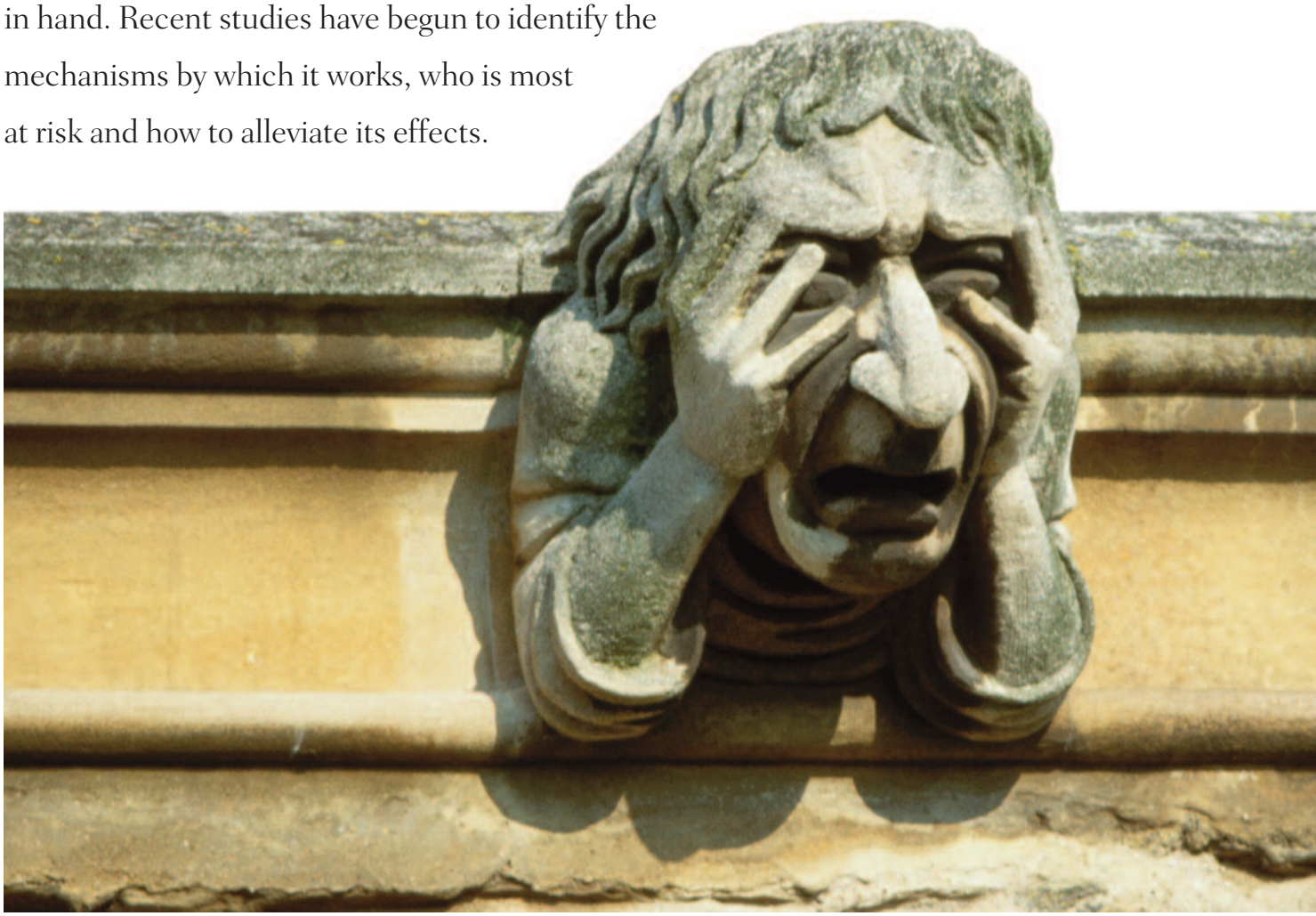
Chemobrain:
delving into possible mechanisms

Eleanor Mayfield

'Chemobrain' is an informal term coined by patients who are – or were – on chemotherapy, to express the feeling of being not quite switched on or able to think clearly and focus on the tasks in hand. Recent studies have begun to identify the mechanisms by which it works, who is most at risk and how to alleviate its effects.



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After undergoing surgery, chemotherapy and radiation therapy for stage II breast cancer, Lori (who asked to be identified only by her first name) was looking forward to getting back to her normal, busy life as a working mother of two.

But within weeks of returning full-time to her job as a city planner, she knew something was wrong. "I couldn't work, I couldn't think," she said. Before, multitasking had been second nature, but now it exhausted her. At home, she found that trying to do things like plan dinner for her family was more than she could cope with.

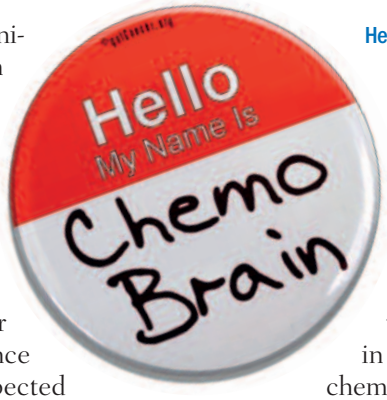
"My brain feels so heavy and tired... I can feel everything slowing down, getting cloudy," she said.

Lori has the classic symptoms of chemobrain: cognitive changes associated with cancer or cancer treatment, most often experienced as difficulties with concentration, memory, multitasking and planning ability. These changes usually first become apparent during chemotherapy (hence the name) and, in around 20% of survivors, persist well after treatment has ended.

A MORE COMPLICATED EXPLANATION

Although chemobrain was first identified and named by breast cancer survivors, research now suggests that the same constellation of symptoms also affects survivors of other cancers. Early studies of patients' cognitive functioning after chemotherapy estimated that the number of survivors with chemotherapy-associated cognitive changes ranged from 17% to 75%.

When researchers began to measure cancer patients' cognitive functioning, both before and after chemotherapy, however, they were surprised to find that, before undergoing chemotherapy, 20%–30% of patients had lower cognitive performance than would be expected based on their age and education. Subsequent studies have consistently shown similar findings.



Health warning. Badges like this one have become popular among US cancer survivors as a humorous way to signal that, while they may look perfectly healthy, they are still not functioning as well as they should be

"This suggests that aspects of cancer biology may influence cognitive functioning, or that there are as-yet-unidentified shared risk factors for mild cognitive changes and the development of cancer," said Tim Ahles, who studies chemobrain at Memorial Sloan-Kettering Cancer Center [New York].

"It's more complicated than chemotherapy," added Ahles. "Almost no one who is treated for cancer receives only chemotherapy. Other aspects of treatment may be equally important to understanding changes in cognitive functioning."

INCREASED VULNERABILITY

Evidence from animal and imaging studies suggests, for example, that the drug tamoxifen, widely used to treat hormone-receptor-positive breast cancer, may disrupt cognitive and other brain functions. In addition, some studies have found that hormonal agents such as goserelin and leuprolide may cause adverse cognitive effects in men who have prostate cancer.

Studies using functional magnetic resonance imaging have identified structural brain abnormalities in patients treated with chemotherapy. In a study using positron emission tomography imaging, breast cancer survivors who had received chemotherapy in the previous 5–10 years used more of their brains to perform a short-term memory task than control subjects who had never received chemotherapy – a sign that their brains are having to work harder to complete the task.

Findings from a preliminary study by Ahles and his colleagues at Dartmouth Medical School [Hanover, New Hampshire, USA] suggest that a form, or allele, of the APOE gene called ε4, which is associated with increased risk for Alzheimer's disease, may be a genetic marker for increased vulnerability to chemobrain. In this study of 80 long-term survivors of breast cancer and lymphoma, participants with at least one ε4 allele had significantly lower scores on standard tests of visual memory and spatial ability and a tendency toward lower scores on psychomotor functioning than subjects who did not carry this allele.

Ahles and his team are currently analysing the data from a larger study, looking at the role of genetic polymorphisms in the development of cancer-related cognitive changes. They are also investigating the hypothesis that patients

"Other aspects of treatment may be equally important to understanding changes in cognitive functioning"

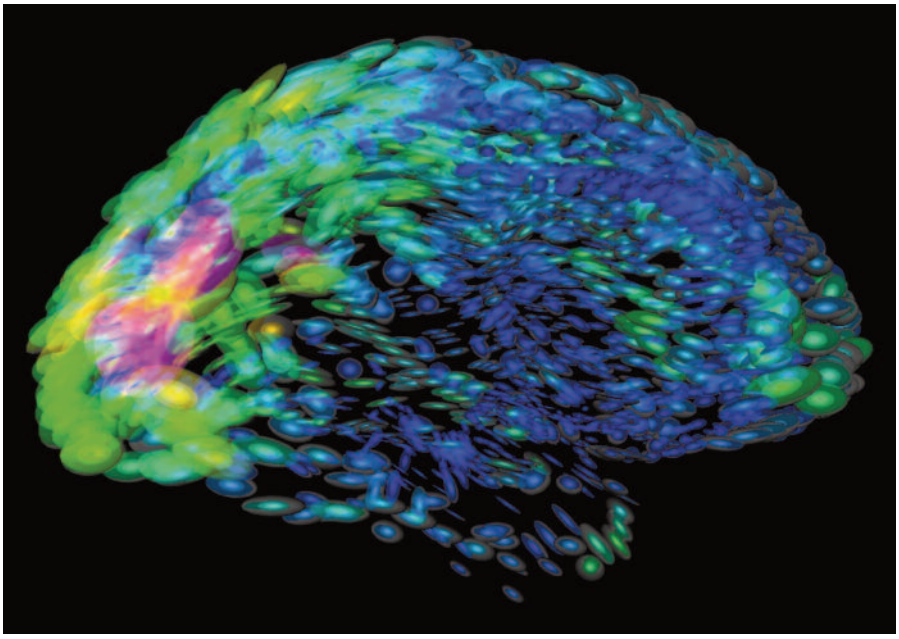
whose cells have a reduced ability to repair the DNA damage caused by chemotherapy are at higher risk for chemobrain.

Patricia Ganz and her colleagues, at the Jonsson Comprehensive Cancer Center at the University of California, Los Angeles [UCLA], suspect that uncontrolled inflammation may be a cause of chemobrain. "Many of the patients in our breast cancer survivorship programme who have cognitive complaints also have fatigue, sleep disturbance or depression," she said. "Our hypothesis is that polymorphisms in genes that regulate the immune system render some patients more vulnerable to this constellation of symptoms."

Many cancer treatments, including surgery, radiation, chemotherapy and immunotherapy, can increase inflammation, Ganz added, which may not resolve after treatment ends. "We have found that post-treatment fatigue is associated with specific single-nucleotide polymorphisms in genes that code for interleukin-1 and interleukin-6, two cell-signalling molecules associated with both inflammation and cancer-related fatigue," she explained. "Our research is examining whether disruption in immune regulation is also involved in the development of cognitive complaints."

Treatment studies

Research on treatments for chemobrain is still in its very early stages. Ganz is beginning a pilot study of rehabilitation strategies for affected breast cancer survivors. Some evidence suggests that medications that stimulate the central nervous system may moderate adverse cognitive effects.



Comparing brains. This image of the human brain shows neurological differences between two people – the green blurred areas indicating greatest variation, the areas of blue oval shapes indicating the least. Studies have shown that people who have undergone chemotherapy in the previous 5–10 years use more of their brains to perform a short-term memory task than control subjects who had never received chemotherapy (image courtesy of Arthur Toga, University of California, Los Angeles)

Lori has obtained some improvement by taking the stimulant Adderall (dextroamphetamine and amphetamine). She also finds that exercise and getting a good night's sleep help her feel more clear headed.

The most challenging aspect of chemobrain, she said, is its invisibility. "I look fine, so people think I'm well. But my brain still isn't well."

Julia Rowland, who directs the American NCI's Office of Cancer Survivorship, is encouraged that this new body of research is bringing needed attention to, and better scientific understanding of, the cognitive problems that affect many survivors during and after treatment. "The very real challenges caused by cancer-related difficulties with memory and thinking have been poorly understood and are often dismissed when reported by survivors," said Rowland. "Findings from these studies should empower survivors to ask their medical providers what can be done to help them improve their cognitive health, especially after treatment ends."

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