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Cachexia: The Last Illness

Researchers are gaining insight into the causes of a devastating form of muscle wasting that is often the final stage of cancer and other diseases

By Corie Lok, Nature magazine on December 10, 2015

As a palliative-care researcher, Susan McClement has talked to many people dying of cancer and their families—and some of their stories are burned into her brain. One man was so concerned by the sight of his emaciated wife, whose body had been ravaged by metastatic breast cancer, that he resorted to force feeding her—pinching her nose and slipping in a spoonful of food when she opened her mouth. Convinced that food would give her the energy to fight the cancer, his daily visits became protracted battles. She died a few weeks later.

McClement, who works at the University of Manitoba in Winnipeg, Canada, says that nutritional conflicts can become a source of regret for relatives. "They said, 'You know, if I could do it over again, I would have spent much less time fighting about tapioca pudding and much more time telling my wife that I loved her.'"

The woman in this case had **cachexia, a metabolic disorder** that affects some 9 million people worldwide, including *as many as 80% of people with advanced cancer*. It typically involves extreme weight- and muscle-loss, makes routine activities difficult and increases the risk of deadly complications such as infections. Adding calories doesn't reverse cachexia, and McClement says that the disorder sometimes provokes extreme reactions from family members because it serves as visual confirmation of their worst fears. "It's a constant reminder that the person is sick and is not going to get better," says McClement.

Cachexia is seen in the late stages of almost every major chronic illness, affecting 16–42% of people with heart failure, 30% of those with chronic obstructive pulmonary disease and up to 60% of people with kidney disease. But for many years it was

overlooked, as physicians and researchers focused their attention on the primary illness instead.

Now, scientists are **increasingly viewing cachexia as a distinct, treatable condition.** Basic research has revealed how it is driven by inflammation and metabolic imbalances, and has generated drug targets, says Stefan Anker, a cardiologist and cachexia specialist at the University Medical Center Göttingen in Germany. "Now we have quite a number of powerful options to test," he says. This has spurred investment from drug developers who aim to reduce suffering, and possibly give patients the strength to withstand chemotherapy or surgery.

But some high-profile clinical trials in the past two years have produced disappointing results, prompting much self-reflection in the young field. "I'm a little bit worried that if we don't see a successful clinical trial in the next five years, the dollars from the pharmaceutical industry to develop a treatment will go somewhere else," says Jose Garcia, a clinical researcher focused on wasting disorders at the Michael E. DeBakey Veterans Affairs Medical Center in Houston, Texas. "In my view, that would be a missed opportunity."

Wasted energy

The term cachexia is derived from the Greek *kakos* and *hexis*, meaning 'bad condition'. It is thought that **Hippocrates recognized the syndrome**—but it took until 2006 for the cachexia field to start working up a formal definition, which includes a loss of 5% or more of body weight over 12 months, and reduced muscle strength. In the clinic, it remains under-recognized by oncologists, says Egidio Del Fabbro, a palliative-care physician and researcher at Virginia Commonwealth University in Richmond. There are no standard guidelines for treatment.

In the past decade, researchers have made strides in learning about the causes of cachexia, thanks to funding from the US National Cancer Institute and some advocacy groups. New international conferences (including one that wrapped up this week in Paris) and the launch of a research journal—the *Journal of Cachexia, Sarcopenia and Muscle*—have also drummed up interest in the field.

It is now clear that a **key mechanism underlying cachexia is the increased breakdown of muscle protein, along with dampened protein synthesis, which leads to overall muscle loss.** Studies in 2001 helped to jump-start the field when they identified genes that were more active in atrophying rodent muscles than in normal ones. These genes encode enzymes called E3 ubiquitin ligases, which tag proteins for destruction in the cell. Mice without these enzymes were resistant to muscle loss.

Muscle cells seem to make more of these ligases when hit with certain inflammatory signals from tumours or from immune cells responding to cancer or other illness. Abnormalities in apoptosis (programmed cell death) and in the muscle cell's energy-producing organelles, mitochondria, have also been implicated.

Several drug-makers have homed in on the protein myostatin, which blocks muscle growth. In a 2010 paper that got many people excited about a possible cachexia drug, researchers from biotechnology company Amgen in Thousand Oaks, California, showed that they could reverse muscle loss and extend the lives of mice with tumours and cachexia by blocking signalling through the myostatin pathway.

Research since then suggests that cachexia is more than a muscle disease. Studies have identified problems in the brain's regulation of appetite and feeding, and even ways in which the liver might be contributing to the energy imbalance that sees the body burn its own tissue to sustain itself. Others have looked at fat tissue, which can also waste away in cachexia. They showed that inflammation and molecules made by tumours cause white fat cells to turn into brown fat cells, which burn more energy to generate heat than white fat cells. The question that researchers are now tackling is how tissues and organs—muscle, brain, fat, even bone—are communicating with one another. A paper published last week suggests that fat signalling could be involved in muscle atrophy.

All this research has brought more representatives of biotechnology and pharmaceutical companies to cachexia meetings in recent years, says Denis Guttridge, a cell biologist at the Ohio State University in Columbus, who organizes one such conference. "That's exciting for a basic scientist like myself," he says. "I can see the increase in the translational pipeline."

Drug disappointment

Despite the excitement in labs, clinical research has so far proved disappointing. In 2011, biotech firm GTx of Memphis, Tennessee, launched two late-stage clinical trials of enobosarm, a molecule that binds to the same receptor as testosterone but only in muscle and bone, mimicking the hormone's ability to stimulate muscle build-up but without its undesirable side effects. Results from earlier, smaller trials looked promising: people taking the drug had increased lean body mass and improved physical function, as measured by their speed at climbing stairs. But in the larger tests of the drug, on people with advanced lung cancer, the benefits in function disappeared. The firm has since abandoned muscle wasting, and is instead testing larger doses of enobosarm to treat breast cancer.

A pair of unpublished studies on people with lung cancer and cachexia tested a compound called anamorelin, which mimics ghrelin, an appetite-stimulating peptide hormone produced mainly by the stomach. The trials were sponsored by pharmaceutical company Helsinn in Lugano, Switzerland, which reported that participants in the treatment group put on weight and muscle mass compared with those taking a placebo, but showed no difference in hand grip strength. Still, the company announced last week that the European Medicines Agency is reviewing its drug for approval.

There is a lot of debate about why the trials failed to show functional improvements. Some researchers say that the teams did not use the most clinically relevant measures of muscle function. "We don't really know what is the best test for this," says Garcia. "If

you can climb up a set of stairs one second faster, what does that mean?" This confusion about trial design is a problem for the field, says Anker. "We need to reach consensus on endpoints and what to aim for in our treatments."

Another **problem** is that animal data on cachexia may not translate into humans. Some work has tried to make a case that the mechanisms found in rodents might be similar to those in humans, by looking at human tissue samples, says Vickie Baracos, a clinical translational researcher in muscle wasting at the University of Alberta in Edmonton, Canada. "But held up to scrutiny, this clinical evidence is often rather sketchy."

Researchers in the field lament the dearth of human data and clinical samples. Baracos says that studies are needed that follow people with cachexia over time, collecting blood and muscle samples along the way. "A cachexia data repository with a biobank would sure be a great thing," she says.

Perhaps the **biggest challenge** is that the field has to compete for funding and recognition with research into other major diseases, says Anker. "Cachexia is competing for internal resources within big companies, fighting with cancer, cardiology," he says. Few companies have dedicated cachexia groups or departments. GTx stopped its work on muscle wasting in part because insurers did not seem interested in covering a medication that was only going to target cachexia and not cancer, says Mary Ann Johnston, the company's vice-president for clinical development. "There's a lack of interest in supportive care."

But an effective treatment would be transformative, says Garcia. It might spur physicians to talk more to patients and their families about the troubling symptoms of cachexia. Without the tools to treat the syndrome, many doctors don't address it, he says. And that vacuum of information can be distressing.

McClement, for her part, has been interviewing more families of people with cachexia. She hopes to find ways to better inform them about the condition and help them to cope. Given the absence of pharmacological interventions, such psychosocial ones are important, she says. "That's all we've got."

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