Obesity — is there hope for the future?

BY ALEIXO MUISE

Obesity.

It is one of the leading health risks in the western world and it is strongly linked to adult-onset diabetes, hypertension, heart diseases, and certain cancers.

Society's obsession, both physical and psychological, with controlling weight is evident by the price we are willing to pay. This lucrative market is made up of a billion dollar fitness industry and multi-billion dollar low-fat (health) food industry (see *Middle Kingdom*, Aug. 3, 1995). Unfortunately, our ultimate failure to master our weight leads to major health concerns for the over six million Canadians considered to be obese. With an aging population becoming more susceptible to the diseases associated with obesity, the burden on our already-strained health care system continues to grow.

So why are some people obese while others, on similar diets,are slim and healthy? There are no easy answers, but in recent years, adipose (fat) tissue has been in the spotlight. Researchers in Canada and around the world have shed some light on the basic mechanisms that control it. Once considered a dormant entity only capable of storing fat, adipose tissue is now hailed as a vital organ (like the heart, liver, or brain) with the potential to control metabolism, influence energy balance, and dictate our appetite.

Throughout history (with the exception of the past hundred years in western civilization), easily available food has been scarce. We have survived by storing energy as fat during bountiful times and then utilizing these stores during times of need. These systems developed over tens of thousands of years, and gave a competitive advantage to those who were more efficient at storing energy when food was available. In today's fast-food culture, there is a failure to maintain a healthy balance between nutritional intake and exercise. For this reason, our rich diets have caused us to become a society prone to obesity and its associated crippling diseases.

The media has given fat a bad rap. In reality, fats are essential — they supply the basic building blocks for the components of biological membranes; they act as intermediates in cell signalling pathways; and, of course, they provide an accessible reservoir of energy. This energy is stored in a specialized type of fat cell called an adipocyte.

Adipocytes are the major components of adipose tissue, and an adult may have as many as 600 billion of these cells, all capable of storing fat. Adipocytes have an enzyme called lipoprotein lipase on the cell surface. This enzyme cuts up the fat molecule, enabling it to enter the cell. Once in the cell, the fat is reformed to produce a droplet that can fill almost the entire volume of the cell. In extremely obese individuals, adipose tissue can make up 70% of the total body weight. If all your adipocytes somehow get filled (approximately 30 kg of fat), there is a pool of precursor fat cells known as preadipocytes that are capable of developing into new adipocytes. Thus, there appears to be an endless supply of cells capable of storing all the excess fat you can provide.

Studying obesity in humans is difficult, so researchers have relied on a number of obese rodent models which differ from their peers by the possession of a single gene mutation. These mutations have been given names that correspond with their phenotypes; for example, *obese, diabetes, fat, fatty, tubby, adipose,* and *yellow*. These model systems allow researchers to cross-breed mice with different characteristics to determine the varying degrees of obesity associated with each mutation. This also allows the mutations to be genetically mapped.

This year, scientists discovered the mutations that cause two of the mouse phenotypes: *fat* and *obese* (as reported in the *Globe and Mail*, Dec. 1, 1994). The mutations in different genes cause different defects in very different systems, but both result in obese mice. Jurgen Naggart and colleagues (*Nature Genetics*, June 5, 1995) identified a single mutation that may result in the *fat* phenotype. Mice with the *fat* mutation developed obesity at a slower rate than either the *obese* or *diabetes* animals, but eventually swelled up to 3 to 4 times larger than their non-fat litter mates. The researchers determined that these mice had a defective enzyme needed for insulin production in the pancreas. The enzyme, carboxypeptidase E, is required for processing proinsulin (an inactive form of insulin). Also, it regulates hormone production from other sources, such as the pituitary gland and brain. Obesity in these *fat* mice may be caused by widespread defects in processes which produce mature hormones that play vital roles throughout the body.

Recently, the *Globe and Mail* (July 27, 1995) reported that a fat-melting hormone was ready for human tests. The results cited in this article were astonishing: obese mice lost 20-30% of body fat after one month of treatment. The pending patent was bought for an unprecedented $20 million by Amgen Inc. This *ob* gene, discovered by Jeffrey Friedman and coworkers at Rockefeller University, is expressed only in adipocytes and produces a protein termed leptin (derived from the Greek *leptos*, meaning thin). Originally, Friedman found that a mutation in the *ob* gene caused the phenotype *obese* . Mice with mutations of both copies of the *ob* gene (all animals have two copies of every gene) were extremely obese and were victims of adult-onset diabetes. Mice with only one copy of the mutated *ob* gene were better suited to survive when nutritionally deprived over long periods of time. These animals appeared to have a selective advantage during periods of famine.

Friedman's group determined that leptin protein that may send a signal to the hypothalamus to control appetite and increase metabolism. Leptin may also inform the brain when enough fat is stored in the adipocytes. But could leptin reduce obesity in *obese* mice?

Three independent laboratories (*Science*, July 28, 1995), including Friedman's group, tested the effects of daily injections of leptin into obese mice carrying two mutated copies of the *ob* gene and normal mice with two good copies of the *ob* gene. The results were astounding — the obese mice (that were twice as large as the normal mice) lost 40% of their fat in one month, ate less, and their metabolism increased. Normal mice that received low doses of leptin ate less, and when injected with high doses of the protein, lost 12% of their body weight and practically all their body fat.

So what does this mean to your average overweight Canadian, or someone afflicted with adult-onset diabetes or heart disease? Well, it's too early to tell.

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