TIME AND TIME AGAIN, Americans hear the message to eat right and exercise. But a growing obesity epidemic indicates that the message is not stemming the tide. At the same time, mounting scientific evidence indicates that obesity is a major contributor to cancer-related deaths. Cancer Center faculty are on the front lines of examining the complex connection between cancer and obesity and what can be done to reduce the health problems caused by this connection.

“The public recognizes that obesity is a problem, but I don’t think they recognize its seriousness,” says Cancer Center Senior Scientist David Allison, Ph.D., director of the UAB Clinical Nutrition Research Center and head of the Section on Statistical Genetics. Dr. Allison studies the causes, consequences and treatment/prevention of obesity. His research interests include the connection between caloric restriction and obesity and the metabolic pathways involved in weight gain. “Quite simply, as a population we suffer from diseases of over-consumption.”

In recent years, news headlines have spotlighted this issue. A massive study published in The New England Journal of Medicine (2003) demonstrated that obesity plays a larger role in cancer causation than previously believed, accounting for approximately 14% of cancer mortality in men and 20% in women. Obesity raises the risk for most forms of the disease, even those not previously linked to obesity, including cancers of the liver, prostate, cervix, ovary and non-Hodgkin’s lymphoma. In fact, results of this epidemiologic study suggest that an estimated 90,000 Americans die each year of cancer related to obesity and excess weight.

“We have known that there has been an association between obesity and cancer for more than 30 years, particularly in breast cancer. Scientists weren’t really thinking about it; they just supposed it was an epidemiologic finding that didn’t have much validity. It wasn’t until this study was released that we realized the extent of the connection in many cancers,” says Tim Nagy, Ph.D., Cancer Center scientist and Associate Professor in the UAB Department of Nutritional Sciences. His research includes the role of caloric restriction and body fat and where it is located in relation to cancer. It is particularly relevant in the state of Alabama, where more than one out of four individuals are obese.

REVERSING THE TREND: A SCIENTIFIC EXAMINATION

Classifications of “overweight” and “obese” are usually defined by the Body Mass Index (BMI), a common measure expressing the relationship (or ratio) of weight-to-height. It is a mathematical formula in which a person’s body weight in kilograms is divided by the square of his or her height in meters. Individuals with a BMI of 25 to 30 are considered overweight, while individuals with a BMI of 30 or more are considered obese (see chart on page 15). According to the National Institutes of Health (NIH) all adults (aged 18 years or older) who have a BMI of 25 or more are considered at risk for premature death and disability as a consequence of overweight and obesity. These health risks (including cancer, heart disease and diabetes) increase even more as the severity of an individual’s obesity increases.

In 2003, Dr. Allison and his then-Ph.D. student Chenzi Wong, M.D., published a statistical analysis that established a relationship between obesity and years of life lost (Journal of the American Medical Association). Using Centers for Disease Control and Prevention data, including BMI rates, they developed a statistical tool to estimate how weight reduces lifespan among specific populations. “For instance, a 20-year-old white male with a BMI greater than 45 will lose approximately 13 years of his life due to obesity,” Dr. Wang says. “This is statistically and clinically relevant.”

A variety of factors contribute to obesity, including behavior, environment and genetic factors. Ultimately, obesity is a result of a prolonged energy imbalance. In other words, when the amount of calories exceeds the amount of energy expended (physical activity), weight gain can occur. Although some instances of weight gain have a medical connection, a sedentary culture combined with high-calorie foods is the primary culprit. (Slow metabolism, Dr. Nagy points out, is rarely the sole or primary cause.)

Scientists still don’t completely understand why obesity is linked to cancer. Many believe that obesity promotes cancer by raising the body’s levels of hormones — sex hormones like estrogen, or protein hormones like insulin, and insulin-related growth factors. Too much fat around the waist, for instance, can disrupt insulin metabolism and increase the risk for colon cancer, among others. However, until recently, few scientists have closely examined the correlation between a reduction in weight to cancer risk. “We know that body fat produces a large number of hormones and cytokines that in the obese state may influence tumor growth,” Dr. Nagy says.

Significant calorie restriction (reducing 30 to 40% of healthy calorie intake) has been shown to increase life spans in most animals, Dr. Allison says. “We know it prolongs life in rats, mice, fish, guppies, water fleas and spiders — even in protozoa. But does it prolong life in humans?” Conducting a full longevity study in humans, however, is nearly impossible for several reasons: Such a study would take decades, and the subjects would live as long as scientists.
Plus, animal models are kept in strict environments where everything—from temperature to reproductive patterns—are controlled. It is unlikely a human would, or could, submit to such conditions over a lifetime. But, some studies of people who have engaged in voluntary caloric restriction indicate that they develop metabolic profiles suggestive of long life.

In addition, one ongoing NIH-funded study is examining caloric restriction in humans for a short period of time. Even though the study won’t—Dr. Allison says it will—examine longevity, it will examine intermediary biomarkers of aging. “This will give us a sense, at a steep-precipal level, if caloric restriction has benefits in humans,” Dr. Allison says. Ultimately, the future of caloric restriction to reduce obesity may lie in understanding the pathways by which caloric restriction works. “We hope to discover other pathways through which we can intervene to produce the benefits of caloric restriction without having to feel deprived of food,” Dr. Allison says. If scientists could mimic the mechanisms of caloric restriction, they might be able to create a drug to duplicate its effects.

To explore this process, scientists are conducting studies in animals closely related to humans. Two ongoing randomized studies at U.S. institutions are examining the effects of caloric restriction on non-human primates. Dr. Allison and Mark Beasley, Ph.D., Associate Professor of Biostatistics, are the primary statisticians for both studies. In addition, several ongoing studies are examining caloric restriction in mice.

**Caloric or Body Fat: A Cancer Reduction Key?**

Dr. Nagy has a $100,000 grant from the National Cancer Institute (NCI) to examine the relationship between caloric restriction and body fat and longevity of mice. Cancer Center Scientist Ada Elgavish, Ph.D., is co-investigator. “When people refer to caloric restriction, they don’t talk about body fat, and yet if you calorically restrict an animal or human, that animal or human will lose a large amount of body fat,” Dr. Nagy explains. Some scientists assert that the benefits of caloric restriction have nothing to do with body fat, but Dr. Nagy hypothesizes otherwise.

He designed an experiment to give the same amount of food to two groups of animals, but vary the amount of body fat through energy expenditure. Energy expenditure, in this case, is controlled by temperature—one group is kept at a warm temperature, which means they don’t have to increase their metabolic rate to maintain body temperature. Since they don’t have to expend much energy, they get fat. The other group is kept at room temperature, which requires the mouse to spend a fairly high level of energy to keep its body temperature constant. These mice remain very lean.

“If the connection between cancer and obesity is food intake, then the animals that we’re studying should get cancer to the same degree in both groups,” Dr. Nagy says. He has determined that their experimental paradigm works well in producing fat and lean mice. Only one of the study’s two years is complete, but results are promising. “Data are preliminary, but it appears many of the fat mice have developed large tumors, and fewer of the lean animals have experienced comparable tumors. What this suggests is that it’s not the amount of food that’s important, because both of these groups are eating the exact same amount of food.”

Dr. Nagy and Allison recently submitted an NIH grant for a larger study to examine how different types of weight loss could affect longevity. This study would analyze the difference between weight loss and fat loss and if weight loss must be sustained to reduce mortality.

**The Future of Obesity Research at UAB**

Responding to the national problem of obesity, the NCI has allocated substantial funds to examine the cancer connection. In 2003, the NCI announced it would spend $75 million to fund five new research centers to examine nutrition, energy balance and physical activity and the relationship to cancer. These centers will be called Transdisciplinary Research on Energetics and Cancer Centers (TREC’s). UAB will compete for one of the $15-million grants. They will be similar to SPORE grants (Specialized Programs of Research Excellence, of which the Cancer Center holds four). They will fund three to four large projects, supporting cores, pilot studies for young investigators and a cancer development component.

“The role of the TREC’s will be to bring together obesity and cancer researchers to understand how energetics, the flux of energy in living systems, affect cancer in animals and humans,” Dr. Nagy says. The grants will foster interdisciplinary research that will integrate social, behavioral and biological science. This will include a focus on understanding the mechanisms involved with the cancer-obesity link, including causation and prevention. It will bring together researchers from cancer centers, public health schools and academic departments such as molecular biology, genetics and psychology.

“UAB is an ideal place to study this, with our strong obesity and cancer focus,” Dr. Nagy says. Cancer Center Director Albert LoBuglio, M.D., adds that UAB is already engaged in such interdisciplinary research. “The Cancer Center recognizes the importance of the relationship between cancer and obesity,” Dr. LoBuglio says. “We encourage faculty from other UAB departments to work with us on this complex problem.” Other Center faculty involved with cancer-obesity research include Senior Scientists Stephen Barnes, Ph.D., Douglas Heimburger, M.D., and Edward Puttridge, M.D.

Regardless of the grant’s funding status, the Cancer Center is committed to exploring the obesity connection. “Our goal is to conduct human studies and back them up with basic science,” Dr. Nagy says. On the basic science front, researchers will continue to examine the effects of weight gain and weight loss on cancer progression in animal models. Dr. Nagy is currently conducting fat transplants in animals to examine the role of cytokines present in fat on the progression of cancer. In addition, researchers are examining the interaction between cancer and obesity molecules. There are also preliminary plans to examine the connection in humans, including an emphasis on minority populations.

“Cancer and obesity is an emerging field,” Dr. LoBuglio says, “Drawing from our strengths across campus, the Cancer Center intends to grow as a national leader in this area.”

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**CALCULATING YOUR BODY-MASS INDEX**

Individuals with a body-mass index (BMI) of 25 to 30 are considered overweight, while individuals with a BMI of 30 or more are considered obese. To calculate your BMI, visit:

CDC BMI Calculator
http://www.cdc.gov/nccdphp/dnpa/bmi/bmi.htm

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1985 Obesity Map

1985 Obesity Map

2002 Obesity Map

2002 Obesity Map

CDC data illustrate America’s obesity epidemic. In Alabama, more than one out of every four individuals is obese.