

A new factor in bladder cancer risk

People who use glucocorticoid drugs for a prolonged period of time may be at increased risk of developing bladder cancer, according to a new study by DMS researchers.

Glucocorticoids help suppress the immune system and are often prescribed to treat inflammatory conditions, such as rheumatoid arthritis and irritable bowel disease. Earlier research has identified links between bladder cancer and treatment with glucocorticoids, along with other drugs, following an organ transplant, as well as between glucocorticoids and other types of cancer. In 2001, for example, epidemiologist Margaret Karagas, Ph.D., and several colleagues reported an increased risk of certain skin cancers among patients who took glucocorticoids.

Prompted: More recently, Karagas led a population-based case-control study that examined the use of glucocorticoids among two groups of subjects—786 people with bladder cancer and 1,083 controls without bladder cancer. Karagas says the research was prompted by previous findings which had hinted at a possible connection between an impaired immune system and a susceptibility to being diagnosed with bladder cancer.

The researchers found that taking glucocorticoids orally was related to an increased risk of bladder cancer. In the general population, the overall risk of developing bladder cancer is about 1 in 27 for men and 1 in 84 for women. Those who had taken the drugs had an estimated 85% increase in risk of developing bladder cancer, and, among those with bladder cancer, patients who had taken glucocorticoids were more likely to have aggressive tumors.

Glucocorticoids may suppress the immune system, says Karagas.

Karagas says that these findings, which were published in the *British Journal of Cancer*, could reflect the possibility that glucocorticoids suppress the immune system, thereby allowing the development of tumors that would otherwise be caught and destroyed by the immune system. It's plausible, she says, that the drugs "may weaken the body's immunosurveillance mechanism against bladder tumors."

Prolonged: The paper's first author, Karl Dietrich, conducted the study while he was a student in Dartmouth's M.P.H. program. Now a first-year medical student at DMS, he says that "the most important finding in this study is the association with long-term use of glucocorticoids. Patients are commonly put on prolonged therapies, and it is important to be aware of other significant risks that could be associated with this treatment."

Both Dietrich and Karagas caution that the findings need to be replicated in other studies before they influence clinical practice. But, Karagas adds, "if glucocorticoids are found to increase risk of bladder cancer, it might indicate the need for closer monitoring of individuals who regularly take oral, systemic glucocorticoids." AMOS ESTY



Kasper, rear, and Ochoa-Repáraz study a mouse model of multiple sclerosis.

Intestinal flora may intensify MS

A team of DMS researchers has found that using antibiotics to reduce bacteria levels in the intestines of mice relieved symptoms associated with multiple sclerosis.

The interdisciplinary group, led by Lloyd Kasper, M.D., studies experimental autoimmune encephalomyelitis (EAE). This condition, which can be induced in mice, is widely regarded as the best experimental model of human multiple sclerosis (MS), an autoimmune condition that can cause a number of physical and cognitive problems. In MS, as in other autoimmune diseases, the immune system attacks its own tissues, either by producing antibodies that attack those tissues or by releasing molecules that cause inflammation and tissue damage. This can result in the loss of myelin, a fatty tissue that protects nerve fibers. In people with MS, patches of myelin and the underlying nerve fibers in the eyes, brain, and spinal cord are damaged or destroyed. About 400,000 Americans have MS, and about 2.5 million people worldwide suffer from the disease.

Role: Javier Ochoa-Repáraz, Ph.D., a research associate in Kasper's lab, used antibiotics to deplete the abundant bacteria that make their home in the intestines of mice—and humans. It is well established that the mucosal surfaces in the intestines play an important role in the immune system, but little is known about the role of all the bacteria in the intestines on the function of the immune system.

Ochoa-Repáraz gave mice with EAE a cocktail of antibiotics by mouth—thereby reducing the amount of bacteria in the intestines—and found that the treatment suppressed the development of EAE. When he gave the mice the same mix of antibiotics through an injection, there was no effect. So reducing the amount of bacteria in the intestines through the oral treatment promoted immune tolerance and hindered the development of this model of MS.

The causes of the effect are still not entirely clear, but the finding may represent an exciting new paradigm in the treatment of MS, and perhaps other autoimmune conditions, too. ROGER P. SMITH, PH.D.