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UT SOUTHWESTERN RESEARCHERS LINK HOMOCYSTEINE TO METHOTREXATE-INDUCED NEUROTOXICITY

DALLAS — July 31, 1997 — Researchers at UT Southwestern Medical Center at Dallas have been the first to link elevated levels of homocysteine in spinal fluid with increased neurological problems in children receiving the commonly used cancer-fighting drug methotrexate.

The findings could have wide-ranging implications for many patients who take methotrexate, including those with rheumatoid arthritis, psoriasis and lupus.

Homocysteine is an amino acid needed for normal body function. People with genetically high levels of homocysteine — a disease called homocystinuria — have been shown to be at greater risk for vascular disease and stroke. The administration of methotrexate also can cause elevated levels of homocysteine in the body.

"We thought people who take methotrexate might have the same problems as those who have genetically high levels of homocysteine," said Dr. Barton Kamen, professor of pediatrics and pharmacology at UT Southwestern and holder of the Carl B. and Florence E. King Foundation Distinguished Chair in Pediatric Oncology Research. Kamen is also an American Cancer Society Clinical Research Professor.

According to Kamen, as many as 10 percent to 20 percent of patients who receive methotrexate suffer some form of acute neurotoxicity, which can result in headaches, seizures, nausea, drowsiness, vascular damage in vessels leading to the brain and, in the case of children, intellectual dysfunction.

Kamen and colleagues at UT Southwestern report in the August issue of the

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Journal of Clinical Oncology on a study of approximately 40 children who received methotrexate for leukemia over the past three years. The researchers, who included Dr. Charles T. Quinn, chief resident at Children's Medical Center of Dallas, measured the amount of homocysteine in cerebrospinal fluid removed during routine spinal taps. Children with the worst neurotoxic side effects had homocysteine levels up to four times higher than those who did not have side effects.

In addition to associating higher levels of homocysteine with increased neurotoxicity, Kamen and his colleagues also associated high levels of two other chemicals — HCA and CSA — with increased neurotoxicity. These are "excitotoxic" amino acids that are formed from homocysteine and increase toxicity.

"The children who received methotrexate had a remarkable increase in these compounds," Kamen said. "Normally there is only a small, often undetectable, amount of them in the brain."

Now that these compounds have been associated with neurotoxicity, Kamen said the next step is to test treatments that can help overcome this neurotoxicity. One possibility is to give cancer patients the same compound — betaine — that is given to people with homocystinuria. For acute problems, physicians could give dextromethorphan, a cough suppressant that works against the excitotoxic amino acids.

The research is the latest in Kamen's ongoing attempt to better understand and treat the side effects of methotrexate. In a 1995 paper published in the British medical journal, *The Lancet*, he showed that increased levels of adenosine caused by methotrexate — which result in nausea and headaches — can be overcome with doses of aminophylline. Aminophylline is a medication used to treat asthma that is similar to caffeine, a common ingredient in soft drinks. As a result, Kamen's patients who suffer from acute neurotoxicity are sent home with a can of cola, and now maybe a bottle of cough medicine.

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