Evolutionary Insights Suggest Novel Treatments for Gout

BY NANCY WALSH
New York Bureau

New York — Replacing the enzyme uricase may offer a new means of treating intractable gout.

Uricase—present in most mammals but lacking in certain primates since the Miocene era, when three mutations in the uricase gene rendered it inoperative—is responsible for breaking down uric acid to the soluble and easily excreted compound allantoin as a final step in the catabolism of purines. Without this enzyme hyperuricemia can, and does, develop in humans, chimpanzees, gorillas, orangutans, and gibbons, Dr. Michael Pillinger of the University of Leeds (England), said he and colleagues have thought that internal signal, said Dr. Pillinger of the University of Massachusetts Medical School (Worcester, Mass.), and researchers from the University of Louisville (Ky.) and the University of Minnesota (Minneapolis) conducted experiments in which they fractionated cytosol from ultraviolet-irradiated mouse fibroblasts. These researchers were able to identify a low-molecular-weight compound secreted in large amounts by dying cells as nucleotides break down—which turned out to be uric acid.

Researchers found that the formation of these crystals and the ensuing host response could have an important role in immune surveillance and the generation of adaptive immunity (Arthritis Rheum. 2004;56:4040-8). This study showed that gout attacks were preceded by an increase in the number of neutrophils, which are the body's first line of defense against infection. The authors suggested that these neutrophils could be involved in the formation of crystals and the release of uric acid into the bloodstream, leading to the development of gout.

Support for the danger signal hypothesis also has been demonstrated in a mouse model, where uric acid levels are elevated during tumor rejection, and rejection was delayed if uric acid was inhibited by the administration of allopurinol or uricase (Cancer Res. 2004;64:1039-62).

An answer to this question, if somewhat speculative, can be found in mutations of the uricase gene that occurred between 10 and 20 million years ago, when many species of primates became extinct. Fossil records suggest that the primate diet at that time, consisting largely of fruit and grasses, was extremely low in salt, at approximately 0.6 g sodium chloride per day. In effect, vegetarian mammals were in a dietary hypertensive crisis that could be most problematic for those who had evolved to stand upright, Dr. Pillinger said.

Texas nephrologist Dr. Richard J. Johnson, who developed this hypothesis, said, "The uric acid may have provided an evolutionary advantage to early hominids by maintaining blood pressure under the low sodium dietary conditions of that period" (Hypertension 2003;41:1183-90).

An association of gout with elevated blood pressure has long been noted, but these new findings suggest a causative role for hyperuricemia in hypertension, Dr. Pillinger said. One study of five adenosine-agonist-sensitive patients found that aggressive treatment with allopurinol normalized their blood pressure. Whether a causal link with uric acid can be found in all patients remains to be seen but is intriguing, he said. A blinded trial investigating this question is currently underway.