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DISCOVERY OF MUTATION MAY LEAD TO HELP FOR MALE FERTILITY PROBLEMS

DALLAS – November 24, 1998 – Discovery of a mutation that prevents sperm maturation could lead to treatments for male sterility and development of new male contraceptives, UT Southwestern Medical Center at Dallas scientists reported in today's issue of *Proceedings of the National Academy of Sciences.*

Dubbed morc, or microrchidia, a medical term for abnormally small testes, the mutation in an unidentified gene is expressed only in males during the earliest stages of sperm production, said investigators from the labs of Dr. Mark Watson, assistant professor of pathology, and Dr. Andrew Zinn, assistant professor of internal medicine. The research mice, genetically engineered to have the mutation, are normal at birth and attempt to begin production of sperm at puberty. But their attempts fail, leading researchers to conclude that the morc gene performs a primary regulatory function in male meiosis, the process that produces sperm.

"This uncovers a new point in the regulation of sperm production," said Zinn, who is an investigator in the Eugene McDermott Center for Human Growth and Development. "A difference in this mutation compared with other mouse reproductive mutations is that it is selective for

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spermatogenesis (sperm production) and does not seem to affect oogenesis (egg formation in females).

The researchers began investigating the effects of this mutation when a former member of the team, Dr. Randall Moreadith, was experimenting to produce a mouse with certain genetic features. The first transgenic animal he made was sterile. The scientists launched an investigation to find out why these first rodents could not reproduce.

The researchers found no abnormalities in the mice except that they were infertile; the animals looked and behaved normally, including their mating instincts. Although they formed precursor cells for normal sperm production at birth, by about 10 days old -- puberty in a mouse -- the cells began dying. By the age of six months, all the sperm-producing cells were dead and the testicles were one-third normal size.

"Since a similar appearance is seen in some infertile men, these mice may provide a model for human sterility," Zinn said.

The researchers determined that the cells were dying at a very early stage of spermatogenesis through apoptosis, or programmed cell death. This is a natural process by which cells in the body, including sperm, are regulated for quantity and quality.

"But we don't know if the morc gene normally is involved in preventing apoptosis or whether the apoptosis is just a consequence of the germ cells not developing the way they normally

would," Zinn said. "Because of the nature of this mutation, it should be relatively easy to clone the morc gene, which may reveal a new regulatory molecule involved in male reproduction. In fact, we have already identified a candidate gene.

"This is an important finding because, clinically, 10 percent of couples are faced with infertility. Once we know the pathway which the gene regulates, then biochemically, we may be able to manipulate it to either treat male sterility or to produce a new form of male birth control."

It also is possible that morc could be involved in testicular cancer.

"One theory of human testicular tumors is that germ cells are blocked in sperm production," Zinn said. "This blockage during cell differentiation could cause them to become malignant, a mechanism that is common in leukemia and lymphoma."

The other researchers involved in the study were: Dr. Norimitsu Inoue, a postdoctoral fellow in the Eugene McDermott Center for Human Growth and Development; research assistants Karl Hess and George Albright; and Dr. Clark Duchene, a Southwestern Medical School graduate who is now an orthopaedic surgery resident at Parkland Health & Hospital System.

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