Cancer drugs shown to cause mutations in mice offspring

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(Medical Xpress) -- For many years, most of the studies done to see what effects cancer treatment has on the offspring of survivors, has involved radiation. This is because radiation is known to cause mutations in cells. Not so well studied have been the generational effects of chemicals used to treat cancer. Now, research by Colin Glen and Yuri Dubrova at the University of Leicester in the UK, shows that male rats given chemotherapy drugs sire pups that have twice as many mutations in a part of their DNA as do their fathers. They have published their results in the *Proceedings of the National Academy of Sciences*.

Lead researcher Dubrova, a geneticist, has been studying the effects of cancer therapies on animals for the past decade, mostly focused on the aftereffects of radiation treatment. Recently however, he began looking into the possible genetic effects chemicals might be having on offspring, or even subsequent generations. Such drugs are given systemically whereas body parts not being treated by radiation are covered, potentially making the outcome worse for chemotherapy. To find out, he and his colleague subjected male mice to three of the most common types of chemotherapy drugs at dosages relative to their size. They then studied a section of the mouse genome in the male offspring produced after mating with non-treated females and found twice as many mutations as in either parent.

The authors suggest their findings should not be cause for alarm however, as most cancer patients are too old to conceive children, or become sterile as a result of treatment, leaving children who receive

treatment as the one group at possible risk. But they say, their results need to be taken in proper context. The mice used in the study only live for a couple of years, thus they reproduce much sooner after receiving the chemicals than children would as they take much longer to reach child bearing age. To find out if a time lag might allow for repair of the damaged genes before reproducing, more research will need to be done with animals that live much longer.

Another interesting find in the research was that DNA in the offspring that was contributed by the mother, who was not given any of the drugs, was affected in much the say way as that from the treated fathers, a result that they say has been seen before in other studies, but is still not understood.

More information: Exposure to anticancer drugs can result in transgenerational genomic instability in mice, *PNAS*, Published online before print January 30, 2012, doi: 10.1073/pnas.1119396109

Abstract
The genetic effects of human exposure to anticancer drugs remain poorly understood. To establish whether exposure to anticancer drugs can result not only in mutation induction in the germ line of treated animals, but also in altered mutation rates in their offspring, we evaluated mutation rates in the offspring of male mice treated with three commonly used chemotherapeutic agents: cyclophosphamide, mitomycin C, and procarbazine. The doses of paternal exposure were approximately equivalent to those used clinically. Using single-molecule PCR, the frequency of mutation at the mouse expanded simple tandem repeat locus Ms6-hm was established in DNA samples extracted from sperm and bone marrow of the offspring of treated males. After paternal exposure to any one of these three drugs, expanded simple tandem repeat mutation frequencies were significantly elevated in the germ line (sperm) and bone marrow of their offspring. This observed

transgenerational instability was attributed to elevated mutation rates at the alleles derived from both the exposed fathers and from the nonexposed mothers, thus implying a genome-wide destabilization. Our results suggest that paternal exposure to a wide variety of mutagens can result in transgenerational instability manifesting in their offspring. Our data also raise important issues concerning delayed transgenerational effects in the children of survivors of anticancer therapy.