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RESEARCHER DEVELOPS MODEL FOR STUDYING PANCREATIC CANCER

DALLAS — August 25, 1993 — Nearly 97 percent of patients with pancreatic cancer die within five years of diagnosis — most within one — because there is no effective therapy and no appropriate animal models have been available on which to test new therapies.

But Dr. Demetrius Kokkinakis, an assistant professor of neurology at The University of Texas Southwestern Medical Center at Dallas, recently has succeeded in defining the initial changes that lead to pancreatic tumors in hamsters that are similar to those in humans.

"The initial lesions and the eventual tumors appear to be the same in both," Kokkinakis said.

Through his research, Kokkinakis hopes to find out how pancreatic tumors develop in humans and how to prevent or diagnose them in the early stages. His research was published in the June 15 issue of *Cancer Research* and the August issue of *Carcinogenesis*.

"Because it has been so difficult to identify the causes of the disease in humans or to develop reliable animal models for laboratory studies, only a few researchers are seriously involved in the study of pancreatic cancer," Kokkinakis said.

The incidence of pancreatic cancer in the United States is low compared to prostate, breast or lung cancers, but pancreatic cancer is deadly and kills quickly. An estimated 27,700 new cases of pancreatic cancer will be diagnosed this year, and 25,000 will die from the disease.

According to Kokkinakis, pancreatic carcinogens do not induce high levels of damage in their target tissue, but even limited damage to pancreatic DNA may be passed along during replication. The exact cause of pancreatic cancer in humans is elusive, Kokkinakis said, but the presence and nature of mutations in a specific gene called **c-K-ras** implicates carcinogens that are capable of damaging DNA, most likely nitrosamines.

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Nitrosamines are a class of important human carcinogens found in the environment, but they are also formed in the stomach when nitric oxide combines with amines present in food. Once the nitrosamines are formed, they are typically metabolized to yield agents that can damage DNA. Even though pancreatic ducts are slow in metabolizing nitrosamines, the pancreatic cells repair DNA damage poorly and are particularly susceptible to damage accumulated by lifelong assaults by the carcinogens.

"In the pancreas, therefore, it is only a matter of time before enough DNA damage occurs to induce malignant transformation," Kokkinakis said.

Exposure to carcinogens and the resulting DNA damage is only one component in the complex process of tumor development in humans, Kokkinakis points out. Mutations alone do not necessarily result in cancer. He said a promoter is needed to maintain tumor growth.

"So far we have identified three promoters for pancreatic tumors," Kokkinakis said, "female sex hormones, orotic acid and diets high in protein and fat."

Female sex hormones increase the incidence and size of tumors in the pancreas of animals, but the mechanism of their action is not completely understood. One theory is that such hormones enable even damaged cells to remain alive, allowing a cell with mutated DNA to survive and contribute to a growing tumor mass. Sex hormones are believed to be the most significant promoter of pancreatic tumors in women.

As for dietary promoters, Kokkinakis has found that high dietary protein and fat have pronounced effects on the frequency and size of tumors induced by nitrosamines. In addition, orotic acid, a component of dairy products, has a similar effect. He said it is too early, however, to recommend dietary and behavioral guidelines for preventing tumors in the pancreas.

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