Target tissues as trigger for DES

Chemical causes of cancer often involve an unkind quirk of biochemistry. Body enzymes can turn an innocuous compound into a carcinogen. Most examples so far studied by scientists primarily involve the body's detoxification center, the liver. There chemical changes make molecules more water soluble for easier excretion. But the same reactions may also create a reactive compound that can bind to proteins and nucleic acids, destroying the normal controls on cell growth.

Such "toxification" did not seem to be involved in the ability of natural and synthetic estrogen hormones to increase human cancer rates. "Most endocrinologists would say estrogens cause cancer because of their ability to stimulate growth," says John A. McLachlan of the National Institute of Environmental Health Sciences.

Recent research by Manfred Metzler of the University of Würzburg in West Germany and McLachlan offers a new and novel perspective on the hormones. The scientists find that the synthetic estrogen DES (diethylstilbestrol) is chemically transformed in certain body tissues and thus may become a compound carcinogenic in the traditional sense.

Since 1971 physicians have reported an association between women taking DES during pregnancy (it was once believed to prevent miscarriage) and vaginal cancer in their daughters, and genital tract abnormalities in their sons. McLachlan discovered similar effects in mice and found that DES administered to a pregnant mouse accumulates in the reproductive tracts of its fetuses. The levels there become much higher than in the blood or in the gut.

Metzler discovered in 1975 that, contrary to previous expectation, the DES in mice does not stay in the form administered. It is altered by enzymes along several pathways. In six species, including humans, Metzler and McLachlan have discovered oxidative metabolism. This metabolism occurs largely in the genital tract and other hormone-sensitive tissues, McLachlan told an NIH science writers' seminar.

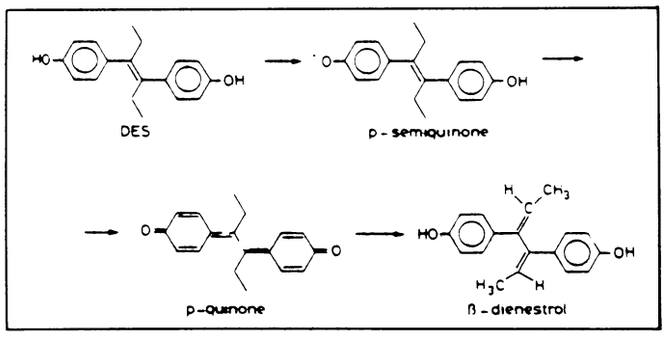
The metabolism of DES is specific to the DES "target organs," because the synthetic hormone itself triggers the metabolism mechanism. When DES enters a uterine cell, it binds to a receptor and interacts with the cell's DNA. That interaction turns on production of an enzyme, peroxidase, which converts DES to a related compound, dienestrol. The intermediates in that reaction, which include semiquinone and quinone, are able to bind to DNA and protein. "Thus they meet the criteria for classical carcinogens," McLachlan says.

Natural estrogen, as well as DES, turns on production of peroxidase in uterine cells and is metabolized to a variety of compounds. McLachlan is now analyzing metabolites of natural and synthetic estrogens. Some act like estrogens, some inhibit estrogens and some have no estrogenic activity at all.

Fetuses may be more sensitive to DES than to natural estrogen because of characteristic blood proteins, in addition to the differences in metabolism. McLachlan reports that alpha-fetoprotein, which appears in the blood of fetuses, pregnant females and newborns, binds natural estrogen but does not recognize DES. McLachlan says biological evolution apparently did not anticipate DES being synthesized in 1938.

McLachlan is concerned about the effects of DES and other estrogen-like compounds on human health. Although DES is no longer prescribed to pregnant women, livestock producers use more than 27,000 kilograms annually. McLachlan says little is known about what happens to the hormone and its metabolites in the environment. Most of the metabolites are not destroyed by bacteria, but rather kill bacteria. (Thus the Ames test for mutagenesis in bacteria is of no use in predicting which metabolites may cause human cancer.)

In addition to synthetic hormones, a wide variety of chemicals of quite different structures act weakly like estrogens in the body. Compounds that bind to estrogen receptors and that promote growth of the uterus include kepone, DDT, a hormone from clover, a fungal product, a polycyclic aromatic hydrocarbon and possibly tetrahydrocannabinol, marijuana's active ingredient. McLachlan says those environmental chemicals may reach the same target organs as DES and increase a person's estrogenic burden. □



DES is converted to reactive intermediates by an enzyme in reproductive tract tissue. The semiquinone and quinone seem to bind DNA and protein and may cause abnormalities in fetuses.

Metzler and McLachlan, BBRC

Nerve regeneration not duplicated

Three years ago, Soviet scientists Levon A. Matinian and A. S. Andreasian reported that injections of specific enzymes into the spinal cords of paralyzed rats regenerated nerves in the cords and thus allowed the rats to walk again. If Matinian and Andreasian's findings could be confirmed in animals and then applied clinically, it would be a tremendous feat and a start toward successfully treating millions of people with damaged central nervous systems — people for whom there is currently no cure (SN: 7/17/76, p. 42).

Matinian and Andreasian's spectacular results have, alas, failed to be duplicated by a group of U.S. scientists who tried to confirm them. The researchers are Lloyd Guth, Edson X. Albuquerque, Sharad S. Deshpande, Charles P. Barrett and Edward J. Donati of the University of Maryland School of Medicine in Baltimore. They reported their important, although disappointing, results at the recent annual meeting of the American Association of Neurological Surgeons in Los Angeles.

In the 1950s, Matinian, a researcher with the Academy of Science in Yerevan, Armenia, cut the spinal cords of rats to test whether some chemical might block the formation of scar tissue around the severed nerves and thus allow them to regrow axons. He worked doggedly and systematically toward this goal for 20 years. Finally, in 1973, he and colleague A. S. Andreasian hit upon trypsin and several other enzymes that seemed to do the trick. What's more, 40 percent of their 350 rats also recovered from their paralysis and walked. In 1974, one of the scientists who had given Matinian the idea for such research in the first place — William F. Windle of the University of Pennsylvania School of Medicine — visited Matinian's lab and concluded that his work was authentic. In 1976 Matinian and Andreasian visited the United States and discussed their experiments with U.S. researchers.

The authenticity of any experimental results, of course, can be verified only through duplication by other scientists, and such duplication is especially critical when research results are so unexpected. So after Matinian and Andreasian visited the United States, Guth and his co-workers set out to replicate their experiments as precisely as possible.

They duplicated Matinian and Andreasian's operative procedure in their initial experiments. The spinal cords of eight rats were visualized, then cut across with a fine blade, the scientists making as certain as possible that the transection was complete. Even before enzyme therapy was given, though, six of the eight animals started to walk, so naturally Guth and his colleagues wanted to know why. They soon found the answer after examining