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.

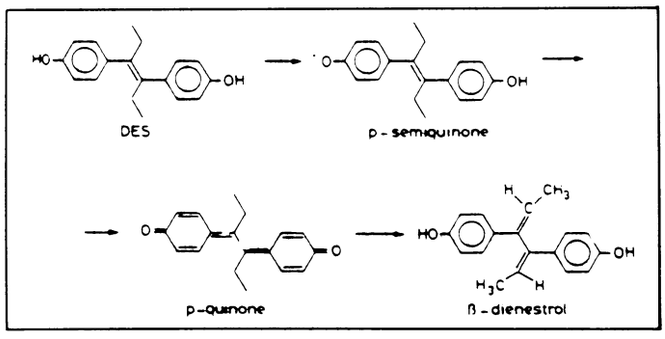
The metabolism of DES is specific to the DES "target organs," because the synthetic hormone itself triggers the metabolism mechanism. When DES enters a uterine cell, it binds to a receptor and interacts with the cell's DNA. That interaction turns on production of an enzyme, peroxidase, which converts 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

their operative sites under a microscope: A small number of nerve fibers in each rat's spinal cord had not been severed and thus kept the rats from being totally paralyzed by spinal cord transection.

Guth and his co-workers then adopted an operative procedure somewhat different from that of Matinian and Andreasian to achieve greater assurance that they were severing rats' spinal cords. A fine wire probe was passed beneath each rat's spinal cord, each cord was cut down to the probe, and the probe was then lifted through the incision, thus ensuring that the cord had been completely transected. Ninety-two rats operated on in this manner were then injected with enzymes according to Matinian and Andreasian's protocols.

All 92 rats, Guth and his team report, remained totally paralyzed for the four- to six-month duration of the experiments, and autopsies gave no evidence that any of the enzyme treatments reduced scar formation, facilitated nerve regeneration or permitted recovery from paralysis. "The functional recovery reported by Matinian and Andreasian," they conclude, "probably resulted from incomplete transection of the spinal cord rather than from enzyme therapy." □

Mental health bill introduced

Imagine more local mental health centers, especially for persons in rural and inner city areas, more chronically mentally ill persons being reintegrated into the community through halfway houses, more preventive measures for mental health, a better guarding of the civil rights of mentally ill patients....

These are some of the improvements in the nation's mental health care system envisioned in President Carter's Mental Health Systems Act. The President and First Lady Rosalynn Carter unveiled the proposed legislation at a press conference this week, and the President subsequently submitted it to Congress. It is based on the findings of the President's Commission on Mental Health (SN: 5/6/78, p. 293), of which Rosalynn Carter is honorary chairperson. This is the first time that a President has proposed major changes in the United States' mental health care system since President Kennedy's Community Mental Health Centers Act in 1963.

Actually many of the findings by President Carter's Commission on mental Health were upbeat — during the past 30 years the mentally ill in the United States have enjoyed a dramatic improvement in care, particularly in being removed from large state mental hospitals to community-based services. The mentally disturbed, however, still experience serious unmet needs, and it is these needs that the President's proposed act seeks to meet.

For instance, while the community mental health center concept started under President Kennedy has brought 700 such centers to three million mentally ill patients annually, many areas of the United States have been unable to meet the stringent qualifications of a CMHC and thus have little or no outpatient treatment available. President Carter's legislation would make the qualifications for community centers more flexible so that more communities could implement them. The proposed legislation would also give patients leaving mental hospitals places to live. Currently, half the patients released from large state mental hospitals are readmitted within a year of discharge because they receive no supportive services and have no place to reside.

Another innovation under the proposed act would be to have states and localities award grants to develop preventive mental health programs, such as training parents, teachers and the police in how to deal with the chronically mentally ill. To promote protection of the rights of the mentally ill, the bill would fund demonstration projects to deliver advocacy services to them and to study existing advocacy programs to determine the appropriate role for the federal government in this area.

"I am very pleased that today we have a good bill," Rosalynn Carter announced at the press conference. "It is sound, it is durable." Whether it will be passed by Congress in this year of tight budgets is questionable, though, since it would cost around $99 million the first year, and possibly more later. □

Weird world on the bottom of the sea

A miniaturized, solid-state television camera has focused in on the unusual animals thriving under 9,000 feet of sea in the Galapagos Rift. The photographic equipment included a videotape unit inside the research submarine *Alvin* and bright lights and a remote camera outside. The scientists inside *Alvin* followed the camera's view on a small television screen, which showed the surroundings more clearly than did the submarine's viewports. The camera's small size, 4 inches in diameter, allowed it to be placed on a movable arm. The scientists could bring the camera's lens to within 4 inches of the subject. Previously the only way to move the camera was to move the submarine.

The new setup also removed severe restrictions on the amount of underwater picture-taking. The scientists could load film from inside *Alvin,* instead of being limited to the film in the exterior camera.

Marine geologist Robert D. Ballard said the scientists were startled by the bright colors of the marine life and the clarity of the pictures they obtained. The submarine was equipped with quartz iodide lights to illuminate the ocean depths where no sunlight penetrates. "It was like taking a TV studio to the bottom of the sea," says Emory Kristof of the National Geographic Society. The scientists obtained close-ups of giant tubeworms (SN: 4/7/79, p. 231), fish, crabs, foot-long clams and sea spiders. □

Al Giddings/NGS

Close-up of giant tube worms, which live inside flexible tubes they build as they grow. See entire colony (lower right) and sea spider that spans about a foot.

Al Giddings/NGS

Emory Kristof/NGS