Tamoxifen's maker publishes cancer data

The developer of tamoxifen — a drug widely used to treat women with breast cancer — has just published data on the synthetic hormone's ability to cause liver cancer in rats. The incidence of these cancers was higher than expected at all doses used during the two-year study.

Moreover, says John Topham, a toxicologist involved in the study, the lowest dose studied produced in the rats' blood a range of tamoxifen concentrations that overlapped those measured in women now taking the drug.

Word of this study began circulating in the medical literature as early as 1986, notes Joachim G. Liehr, a chemist at the University of Texas Medical Branch in Galveston. However, he notes, the Sept. 1 CANCER RESEARCH paper by Peter Greaves, Topham, and co-workers at ZENECA Pharmaceuticals in Alderley Park, England, represents the first formal publication of the study and its findings.

Like many other toxicologists studying tamoxifen, Liehr has been anxiously awaiting access to these data — especially since new studies by him and others over the past 18 months have begun turning up additional signs that the drug might pose a cancer risk, especially to the liver (SN: 4/25/92, p.266).

Further fueling interest in these data, the National Cancer Institute (NCI) in Bethesda, Md., launched an experimental trial last year to treat with tamoxifen several thousand healthy women at high risk of developing breast cancer (SN: 5/9/92, p.309). The new toxicity data have spawned considerable controversy over whether the federal government's cancer-prevention trial might actually jeopardize some women's overall health (SN: 11/28/92, p.378).

The ZENECA study found that, compared to rats given no drug, the group receiving just 5 milligrams of tamoxifen per kilogram of body weight daily developed 20 to 35 times more liver tumors — many of them highly invasive. They observed even higher rates of liver cancer among animals in the two highest-dose groups. Indeed, compared to untreated rats, animals in these high-dose groups had significantly elevated death rates.

Though liver cancers also killed some rats in the group receiving the lowest tamoxifen dose, "overall survival in this group was better than [that of untreated animals]," the researchers note, largely because of reductions in kidney disease and pituitary cancers. (They attribute these reductions to the reduced food consumption seen in animals treated with tamoxifen.)

Greaves' team concludes that "tamoxifen must be regarded as a hepatic carcinogen in rats." But the mechanism by which the drug fosters cancer remains unclear, they maintain. At issue, Topham says, is whether the cancer results from damage to DNA or from severe hormonal perturbations wrought by this compound, which can produce both estrogen and anti-estrogen effects.

Asked to comment on the Greaves liver-cancer report, tamoxifen expert Susan G. Nayfield of NCI said, "We are concerned about this." But she says the liver cancer is probably "species-specific," adding that NCI is "very carefully" monitoring tamoxifen patients, including those in the prevention trial, for liver problems.

Others remain less sanguine. Liehr and Gary M. Williams of the American Health Foundation in Valhalla, N.Y., have both observed tamoxifen's ability to generate adducts — a type of DNA alteration believed necessary to initiate many cancers. This suggests that tamoxifen's carcinogenicity traces to DNA damage, they say. And tamoxifen's ability to cause DNA changes in mice, rats, and hamsters "suggests that for adducts, there is no species specificity," says Williams.

During the 24 years tamoxifen has been used to treat breast cancer patients, only two human liver cancers have been reported. Concludes Williams, "Either it means it hasn't been looked for well enough or something is protecting humans [from this cancer]." — *J. Raloff*

Visual skills show two-pronged development

A new study suggests that there's more to some visual feats than meets the eye, not to mention the brain.

Improvement in performing rapidly presented visual tasks peaks within minutes of practicing these skills and stays stable for at least eight hours after training ends. At that point, performance of the tasks gets an unexpected boost from apparently permanent brain changes sparked by the initial learning, assert two neuroscientists in the Sept. 16 NATURE.

"It's surprising that there's such a high level of plasticity in the adult brain for what we think of as hard-wired visual processes," says Avi Karni of the National Institute of Mental Health in Bethesda, Md. "The learning of many sensory and motor skills may proceed in two stages separated by a latent period of at least several hours."

Karni conducted the research with Dov Sagi of the Weizmann Institute of Science in Rehovot, Israel.

In test sessions, each of nine adults watched a computer screen on which flashed a square-shaped "test" image of several hundred dashes encasing three horizontally or vertically oriented lines. A "mask" pattern then flashed on the screen, composed of randomly oriented V-shaped characters intended to interfere with visual processing of the first image. Presentation of each test and mask image took less than a second.

Participants identified the orientation of the angled lines following each presentation. Over a series of 800 to 1,200 trials per person, the researchers gradually narrowed the fleeting gap between the appearance of test images and mask patterns. Accuracy at the task rose sharply over the first several hundred trials and then leveled off.

Yet about a half day later, in the absence of intensive practice, volunteers displayed further large improvements in performing the visual task. Moreover, they retained these gains over a two- to three-year follow-up period.

The initial learning of some perceptual skills apparently sparks several hours of cerebral "consolidation," assert Karni and Sagi. During this period, small groups of brain cells undergo as yet poorly understood changes that boost an individual's sensitivity to the sensory task at hand and promote long-lasting memory for the skill, they contend.

Their conclusion contradicts a long-standing scientific assumption that practice produces improvement on various perceptual skills in a direct way, with no delayed effects. However, the new data coincide with an emerging view that the brain contains a plethora of cell groupings devoted to different tasks, rather than a general mechanism that orchestrates all sorts of learning.

"Some types of perceptual experience trigger permanent neural changes in early processing stages of the adult visual system," Karni and Sagi propose. "These may take many hours to become functional."

The scientists cannot explain how particular groups of brain cells produce two phases of learning separated by several hours of silent consolidation. A chemical messenger in the brain, acetylcholine, may play an important role in facilitating consolidation after initial learning, Karni contends.

In another study recently completed by the same researchers, volunteers practiced similar rapidly presented visual tasks in the evening and performed the tasks again about eight to 12 hours later, after waking up in the morning. Disruption of rapid eye movement (REM) sleep in some participants blocked their delayed improvement on the task and erased previous gains from training. Acetylcholine levels rise significantly during REM sleep, Karni says. Disturbing sleep at other times did not interfere with consolidation.

"Consolidation is an active neural process that can be stopped," Karni holds. — *B. Bower*