Housecleaning cells may become assassins

Four years ago, scientists reported that in rats, large doses of vitamin A transform minimally toxic doses of carbon tetrachloride into a potent liver poison. Because the vitamin by itself exhibited no adverse liver effects, the researchers began investigating to find the agent behind vitamin A's lethal action.

Last week, they unmasked the villain. And in classic murder-mystery fashion, they show that Kupffer — the "butler" — did it.

Named for 19th century anatomist Karl W. von Kupffer, these liver residents form an integral part of the immune system. Like other macrophages, Kupffer cells remove unwanted visitors — such as bacteria and parasites — by engulfing and chemically destroying them. They also rid their domicile of foreign debris.

Like any good butler, they wait quietly until called upon. Only when summoned to action do they show force. It now appears that the pent-up chemical fury they harbor can, once unleashed, compound the liver injury they had been mobilized to prevent, notes I. Glenn Sipes of the University of Arizona in Tucson.

Three reports of vitamin A's potentiation of liver toxicity by his team appear in the April TOXICOLOGY AND APPLIED PHARMACOLOGY. Two other reports in the journal also characterize this Jekyll-to-Hyde transformation by Kupffer cells.

Rats exposed to a single minimally toxic dose of carbon tetrachloride (0.15 milliliter per kilogram of body weight) exhibit a small amount of damage in key cells in the liver, known as hepatocytes. Sipes and his co-workers compared that damage to what they saw in animals who received up to 250,000 international units of vitamin A (retinol) per kilogram of body weight daily.

In animals pretreated with vitamin A for one day to five weeks prior to carbon-tetrachloride exposure, Sipes says, "the previously minimal injury has exploded to look like we've given a huge dose of carbon tetrachloride." Vitamin pretreatment did not affect the type of cell affected or region of injury, only the magnitude of damage.

In similar tests, rats received toxicants — acetaminophen, allyl alcohol, and a poison produced by *E. coli* bacteria — which caused very different patterns of liver damage. Again, pretreatment with vitamin A exaggerated the specific pattern of damage characteristic of each agent.

Sipes recalls being puzzled about why systemic delivery of the vitamin should foster selective damage only to those cells targeted by another toxic chemical. Eventually, members of his team spotted structural changes in Kupffer cells from vitamin-A-treated rats. The changes signaled the Kupffers were primed to release biologically damaging free radicals.

So Sipes' team performed their experiments again. But this time they added one of three different chemicals to shut down Kupffer-cell activation. And each time vitamin A's exaggeration of carbon tetrachloride's toxicity disappeared. Concludes Sipes, "Small amounts of carbon tetrachloride somehow triggered primed Kupffer cells to over-respond" in their production of cell-killing free radicals.

"We got into these studies because large doses of [vitamin-A-like] retinoids are being used in cancer therapy," Sipes says. Future studies will explore whether lowering doses of both the vitamin (to levels more commonly consumed by humans) and a toxic chemical also causes damage.

But the biggest take-home message, Sipes says, is the value of animals in studying potentially toxic mixtures. Popular *in vitro* tests using only one type of cell would miss this new effect, he says, since the toxicity depends on the interaction of different cell types.

Though such research into the effects of chemical mixtures "is really at an embryonic stage," it is essential for teasing out risks people face from exposures to a complex cocktail of agents in the real world, points out Raymond S.H. Yang of Colorado State University in Fort Collins.

— J. Raloff

Pediatric exam foreshadows vision problems

Eye doctors may soon be able to predict an infant's risk of developing nearsightedness later in life, thanks to the unexpected results of a long-term study of visual development. The study raises the hope that an eye exam soon after birth will enable ophthalmologists to prevent myopia and other visual problems.

Eighteen years ago, researchers at the Massachusetts Institute of Technology began recruiting newborns for a study of how normal vision develops. The group used a retinoscope to detect visual defects, including myopia. People with myopia can see objects close at hand, but distant objects appear blurry. To the investigators' surprise, many of the infants were myopic.

Those findings prompted the team to keep track of the infants, says Jane Gwiazda, a psychologist at MIT and one of the researchers. They have since taken nearly 8,000 vision measurements from more than 400 children.

The team discovered that nearsightedness improves dramatically during the first five years of life. That finding fits with the observation that very few children in kindergarten have vision problems.

However, the MIT data reveal that some children start showing signs of myopia between age 6 and 12. More significant, the children who had myopia as infants also had the highest risk of developing this problem later, Gwiazda says. She presented the results of the study at the Science Writers Seminar in Ophthalmology held this week in Universal City, Calif.

The findings suggest that a child's first eye exam ought to take place at least six months after birth but before age 1. The standard recommendation to have an eye exam at school age is unlikely to yield useful information about a child's future risk of myopia, she says.

Children with myopic parents have a greater chance of developing this visual problem, the study shows. When both parents were myopic, 42 percent of their children became nearsighted; if only one parent was nearsighted, the incidence of myopia in offspring dropped to 22.5 percent; and if neither parent suffered myopia, only 8 percent of their children were nearsighted, Gwiazda says.

Many researchers postulate that close-distance work, such as reading and writing, which increases when children enter school, may trigger symptoms of myopia. In fact, some ophthalmologists believe that society's reliance on computers and its penchant for television viewing have also contributed to the disorder. The link between close-distance work and myopia remains controversial, however, Gwiazda notes.

The study's findings raise the question of whether physicians can prevent nearsightedness in children at risk. Current efforts start well after school age, but the new results suggest that preventive measures could begin much earlier, perhaps in infancy.

In a related report, ophthalmologist Joseph M. Miller of the University of Arizona in Tucson stressed the need for early detection of amblyopia, another visual defect in children. A child with amblyopia, or lazy eye, has one eye that is misaligned. To prevent double vision, the brain ignores the image from the skewed eye. The result is that vision in the affected eye deteriorates, often to the point of legal blindness. At the seminar, Miller reported on a computerized method of image analysis that detects amblyopia in very young children.

Right now, there is no way to stave off nearsightedness, even if at-risk infants are identified, Gwiazda admits. She hopes that research into the cause of myopia will lead to preventive treatments for this common visual problem. By contrast, early diagnosis of amblyopia could lead to more timely treatment, Miller says. Prompt treatment, usually with an eye patch, can restore perfect or near-perfect vision in an affected child, he says.

— K.A. Fackelmann