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## Breathing with Hepatitis

### Does exposure to a liver-inflaming virus prevent asthma?

By Lisa Melton

According to the hygiene hypothesis, the soaring rates of asthma, hay fever, eczema and other allergies in the past two decades have resulted from the overly sanitized conditions of industrial countries. Because children are exposed to fewer bacteria and viruses, the theory goes, their immune systems tend to overreact to otherwise harmless substances such as pollen and dander.

The hypothesis, however, fails to explain why some people are more susceptible than others or why those in dirty environments still develop asthma. But now a genetic study has pointed out a plausible mechanism for allergy development: it suggests that the hepatitis A virus, which thrives in polluted environments, may protect people from asthma.

Recognizing that allergies tend to run in families, a team led by Dale T. Umetsu and Rosemarie DeKruyff at the Stanford University School of Medicine searched for a genetic component. "We knew that finding a susceptibility gene for asthma in humans would be a formidable task, so we decided to simplify the problem and use a mouse model," Umetsu says. Their studies cast up one gene, TIM-1, that predisposed the mice to asthma.

But the researchers got more than they bargained for. "TIM-1 is also the receptor used by the hepatitis A virus to infect human cells," Umetsu explained at a Novartis Foundation symposium in London this past June. This was a crucial discovery, because Paolo Matricardi, now at Bambino Gesù Children's Hospital in Rome, had found that allergies occur much less often in people exposed to the hepatitis A virus. Hepatitis A spreads by exposure to the stool of an infected person and causes jaundice and flulike symptoms; the illness usually clears up on its own.

The Stanford team found that humans carry either a long or a short variant of TIM-1. In a study of 375 people, the researchers saw that those who carried the long version of TIM-1 and who had been infected with the hepatitis A virus were one fourth as likely to suffer from asthma as those with the shorter version. (Overall about 7 to 12 percent of U.S. children develop asthma.) Protection seems to hinge on two crucial factors: inheriting the right version of the TIM-1 gene and succumbing to hepatitis A.

These tantalizing results highlight the importance of genetic interactions with the environment in the development of asthma. In the U.S., because nearly two thirds of whites and blacks and almost half of Asians carry the protective version of TIM-1, a spell of hepatitis A infection might keep allergies at bay. But whereas before the 1970s virtually everyone had been infected with the virus, today's healthier and more sanitized existence means that only 25 to 30 percent of people in developed countries have been exposed.

If hygiene is key, why do children in inner cities suffer from severe asthma? One of the leading theories is that exposure to cockroach feces triggers the problem, which seems to contradict the hepatitis A theory and the hygiene hypothesis. But Matricardi points out that in the 20th century fecal contamination has also declined in depressed areas, just as it has everywhere else in the U.S. "These children are unlucky: they now have the susceptibility to develop allergies and are still exposed to cockroach and mouse allergens, dust mites and cigarette smoke," he remarks.

"Exposure to hepatitis A is one possible mechanism for how the hygiene hypothesis works," says geneticist William Cookson of the Wellcome Trust Center for Human Genetics in Oxford, England. Umetsu's group has produced "interesting work, but the study needs follow-up," Cookson adds. "It would be nice to see it replicated and generalized." Of course, nobody would choose to go back to the bad old days of dubious drainage and rampant infections to fend off asthma. The Stanford team is currently testing whether vaccination will do the trick instead.

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