Bright Ideas

"We found minor differences in overall intelligence, *but in a timed situation, females have a big advantage."* —STEPHEN CAMARATA

Vaccine may guard against cervical cancer

1. A VACCINE TO PROTECT women against cervical cancer was approved in June by the Food and Drug Administration after a 40-month trial of 4,000 young women at 13 U.S. sites, including Vanderbilt.

The vaccine works by preventing infection by four strains of the human papillomavirus (HPV), the most common sexually transmitted disease. About 20 million people are believed to be infected with HPV, according to the National Institute of Allergy and Infectious Diseases.

The Vanderbilt portion of the study, led by principal investigator Dr. Peter Wright, enrolled 51 young women between the ages of 16 and 26, mostly Vanderbilt undergraduate students. Wright is professor of pediatrics, microbiology and immunology and pathology, and director of the division of pediatric infectious diseases.

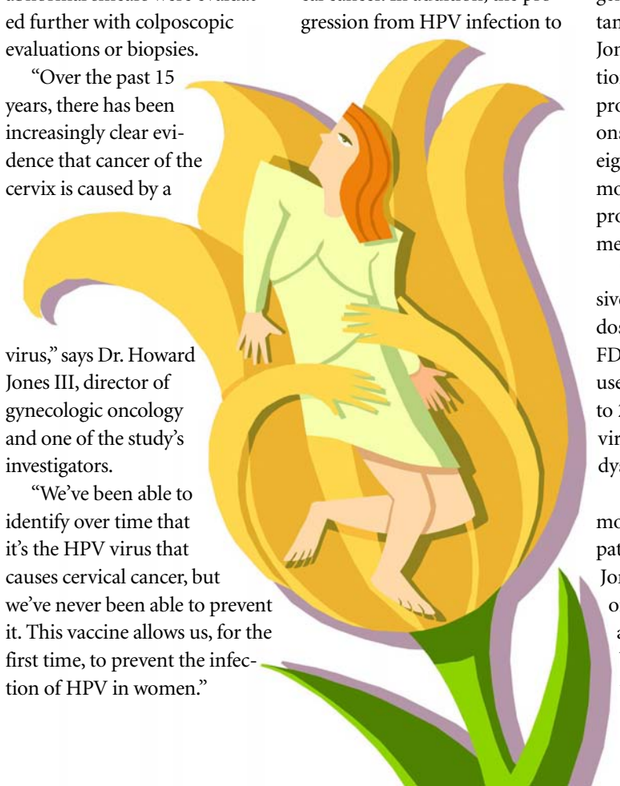
The vaccine, Gardasil, manufactured by Merck & Co. Inc., protects against the two types of HPV responsible for about 70 percent of cases of cervical cancer cases. Although many women are infected with HPV, their normal immune defense mechanisms get rid of the virus, and most women never go on to have an abnormal Pap smear or cervical cancer. The vaccine boosts this natural immunity, completely preventing the viral infection. The vaccine also blocks infection of two other strains of HPV responsible for 90 percent of genital warts cases.

The women who participated in this trial had not been exposed to HPV. Half were vaccinated with the HPV vaccine and half with a placebo. They were followed up in six-month intervals with clinic visits and Pap smears, and those with abnormal smears were evaluated further with colposcopic evaluations or biopsies.

"Over the past 15 years, there has been increasingly clear evidence that cancer of the cervix is caused by a virus," says Dr. Howard Jones III, director of gynecologic oncology and one of the study's investigators.

"We've been able to identify over time that it's the HPV virus that causes cervical cancer, but we've never been able to prevent it. This vaccine allows us, for the first time, to prevent the infection of HPV in women."

The next step is to see if the vaccine works in the general population, and to make sure there are no side effects and that it's effective in larger groups of people, Jones says. "But it is still important that women continue to get their regular Pap smear screening. Even if everyone is being vaccinated 15 years from now, we still might have 30 percent of the current number of women with cervical cancer because the current vaccine is directed against only the two most common types of HPV, which cause 70 percent of cervical cancer. In addition, the progression from HPV infection to cervical cancer is slow, and women may already be infected but not develop an abnormal Pap smear for several years."



GETTY IMAGES

There are 9,500 new cases of cervical cancer each year in the United States, and almost 50,000 cases a year of cervical dysplasia. Cervical cancer kills about 240,000 women in the world each year, and about 3,500 in the United States alone.

Although the vaccine will most likely be marketed as a cancer vaccine, rather than a sexually transmitted disease vaccine, its effectiveness against genital warts may be an important advantage to patients, Jones says. "The onset of infection with virus to cancer is probably five to 10 years. The onset of genital warts is six to eight weeks. That's a much more prompt and visible process, and warts affect men, too."

The vaccine is not inexpensive, costing $360 for the three doses that are required. The FDA has approved the vaccine's use in girls and young women 9 to 26 who test negative for the virus and are without cervical dysplasia.

"We spend an awful lot of money evaluating and treating patients with cervical dysplasia," Jones says. "There's a lot of excitement here, especially among those of us who have been involved in testing this vaccine."

Girls Have Advantage in Timed Tests

2. RESEARCH attempting to shed light on the question of how male and female brains differ has found that timing is everything.

In a study involving more than 8,000 males and females ranging in age from 2 to 90 from across the United States, Vanderbilt researchers Stephen Camarata and Richard Woodcock have discovered that females have a significant advantage over males on timed tests and tasks. The differences were particularly significant among pre-teens and teens.

"We found very minor differences in overall intelligence, but if you look at the ability of someone to perform well in a timed situation, females have a big advantage," Camarata says. "It is very important for teachers to understand this difference in males and females when it comes to assigning work and structuring tests. To truly understand a person's overall ability, it is important also to look at performance in untimed situations. For males, this means presenting them with material that is challenging and interesting but is presented in smaller chunks without strict time limits."

The findings come at a time when parents, educators and the media are paying more attention to the troubling achievement gap between males and females in U.S. schools.

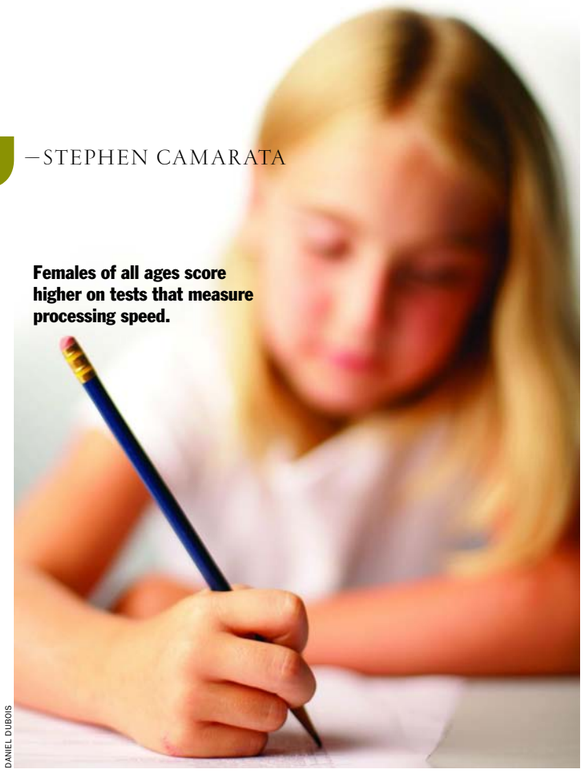
"Consider that many classroom activities, including testing, are directly or indirectly related to processing speed," the researchers wrote. "The higher performance in females may contribute to a classroom culture that favors females, not because of teacher bias but because of inherent differences in processing speed [in males and females]." An additional question is whether this finding is linked to higher high-school dropout rates for males and increased special-education placement for males.

In a new article, Camarata and Woodcock focus on understanding differences in processing speed between males and females.


Camarata


Woodcock

"'Processing speed' doesn't refer to reaction time or the ability to play video games," Camarata says. "It's the ability to effectively, efficiently and accurately complete work that is of moderate difficulty. Though males and females showed similar processing speed in kindergarten and preschool, females became much more efficient than males in elementary, middle and high school."


Females of all ages score higher on tests that measure processing speed.

DANIEL DUBOIS

Males scored lower than females in all age groups in tests measuring processing speed, with the greatest discrepancy among adolescents. But the study also found that males consistently outperformed females in some verbal abilities, such as identifying objects, knowing antonyms and synonyms, and completing verbal analogies, debunking the popular idea that girls develop all communication skills earlier than boys.

The researchers found no significant overall intelligence differences between males and females in any age group.

The research appeared in the May/June 2006 issue of the journal *Intelligence*. Camarata and Woodcock compiled their results through an evaluation of three sets of data collected from 1977 to 2001 as part of the Woodcock-Johnson Series of Cognitive and Achievement Tests.

Camarata and Woodcock plan to conduct further studies to measure brain activity using tools such as functional magnetic resonance imaging and event-related potential tests to better understand which brain areas are playing a role in processing speed and how these areas react differently in males and females.

"We know there are different paths to competence, and we

believe there are fundamental differences in how male and female brains end up getting organized," Camarata says. "Our next studies will give us some insight into where these processing differences are occurring."

Camarata is a deputy director of the Vanderbilt Kennedy Center for Research on Human Development, a professor of hearing and speech sciences, and an associate professor of special education. Woodcock is a member of the Vanderbilt Kennedy Center and a visiting professor of hearing and speech sciences. He also is a research professor at the University of Southern California.

The research was funded in part by an endowment from the Scottish Rite Foundation of Nashville and by a grant from the National Institute of Child Health and Human Development.

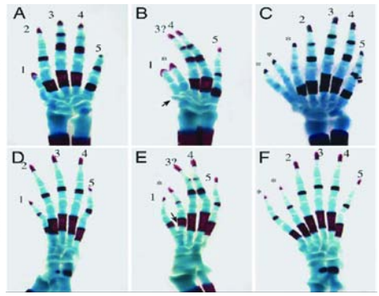
Cholesterol: Thumbs Up for Digit Development

3. Although cholesterol has a bad rap as the sticky, fatty substance responsible for clogging arteries, Vanderbilt researchers have found that the attachment of cholesterol to an important developmental protein controls development of fingers and toes in mice. Without cholesterol, mice developed extra digits, as well as digits in the wrong places.

Their study, published online in the *Proceedings of the National Academy of Sciences (PNAS)* in April, helps to clear up some of the conflicting data about cholesterol's controversial role in limb development, says the senior author on the study, Chin Chiang, associate professor of cell and developmental biology.

The developmental protein at work here, named "Sonic hedgehog" after the video game character, was discovered in the early 1990s and shown to have important roles in patterning the developing embryo, including proper digit patterning. Chiang led early studies showing that mice without Sonic hedgehog developed only a single digit—a thumb on the front paw (or a "big toe" on the back paw).

The Sonic hedgehog protein is produced by a specialized group of cells located at the posterior part of the developing limb bud, which eventually develops into the pinkie finger or toe. At the site of its synthesis, Sonic hedgehog concentrations are high. It then diffuses out across the developing limb bud, and the declining concentrations (or gradient) of the protein dictate the identity of the other digits.

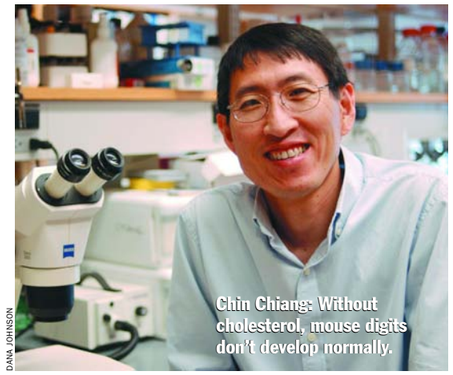


A and D show normal mouse embryo digits. B and E are malformed. C and F have extra, ectopic digits. (Courtesy of Chin Chiang and the *PNAS*.)

"Questions have remained about what regulates the Sonic hedgehog gradient," says Chiang. "And we've been working on that for a number of years."

One clue about this regulation came when other researchers discovered Sonic hedgehog's rather unusual requirement—the protein had to have a cholesterol molecule attached to work properly. "In fact, Sonic hedgehog is the only protein known to be modified by cholesterol," Chiang says.

Because cholesterol is typically found in cell membranes and thought to "tether" proteins to cells, scientists speculated that cholesterol might inhibit the movement of Sonic hedgehog through the developing tissue. This unique modification might explain why concentrations of the protein were high at the site of its production and then tapered off with increasing distance from the synthesis site.


DANA JOHNSON

Chin Chiang: Without cholesterol, mouse digits don't develop normally.

But previous studies in mice suggested that cholesterol promoted the movement of Sonic hedgehog, a counterintuitive proposal given cholesterol's supposed tethering ability. To try and clear up cholesterol's role in digit patterning and the Sonic hedgehog gradient, Chiang and colleagues created mice with an altered form of the Sonic hedgehog protein to which cholesterol cannot attach.

They found that mice lacking cholesterol-modified Sonic hedgehog developed with malformed and ectopic, or out of place, digits. The second, or "index," digits were stunted and misshapen, appearing more similar to a thumb than a normal second digit. The researchers also examined mice in which only half of their Sonic hedgehog proteins could attach to cholesterol. Those mice developed normal digits two through five (index through pinkie), but had duplication of these digits anteriorly.

The findings suggested that Sonic hedgehog without cholesterol traveled further than normal, triggering the abnormal digit duplications. Chiang and colleagues confirmed this microscopically, showing that the protein spread out more evenly across the limb bud in mice lacking cholesterol-modified Sonic hedgehog compared to normal animals.

"We found that, without cholesterol, Sonic hedgehog moves more readily, far from its site of synthesis, all the way to the anterior part of the limb bud where it is normally never detected," Chiang explains.

When Sonic hedgehog travels to tissue where it normally would be absent (as it does when cholesterol is missing), extra digits may form—a condition known as polydactyly. Although the causes of polydactyly in humans are not fully understood, mutations in some part of the Sonic hedgehog signaling pathway are high on the list of suspects. In addition to limb deformities, errors in Sonic hedgehog signaling are involved in a number of other human conditions including cancer and a condition known as holoprosencephaly, a congenital malformation of the forebrain.

Chiang is now examining the role of cholesterol-modified Sonic hedgehog in the developing brain and spinal cord. "We are finding some surprises," Chiang says, "suggesting that the function of cholesterol is different in these different tissues." The continued study of the wide-ranging actions of Sonic hedgehog promises to expose the incredible secrets of the developing embryo and could provide clues for preventing devastating birth defects.

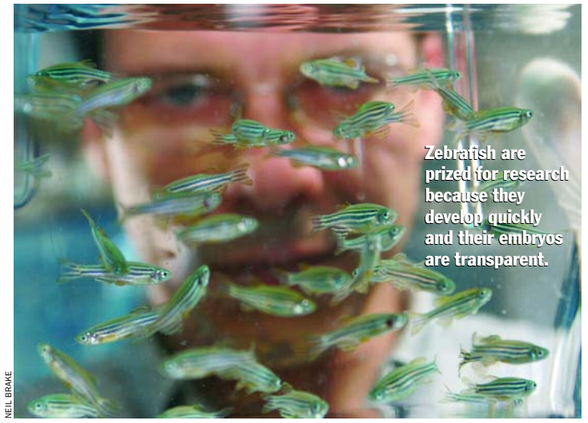
Yina Li, Huimin Zhang and Ying Litingtung were co-authors on the paper. The research was supported by grants from the National Institutes of Health and the March of Dimes Foundation.

Symmetry May Be in the Genes

4. From the outside, human beings look symmetric—our left and right sides mirror each other. But inside, it's another story. The heart is on the left, as are the stomach, pancreas and spleen. The liver and gall bladder are on the right. Even the left and right hemispheres of the brain have subtle but important physical differences.

This left-right asymmetry results from an intricate developmental process that scientists are just beginning to decipher at the molecular level. Vanderbilt investigators have discovered a new player in this developmental routine: one of the genes involved in regulating left-right organ placement in zebrafish. Researchers predict that the gene will play a similar role in all vertebrates, including humans.

About one in 10,000 individuals in the U.S. suffers from laterality defects, meaning their organs are not in the normal positions. And the heart, which depends upon coordinated left-right signaling for its complex looping and connection to the vasculature during development, may be particularly prone to defects in left-right asymmetry. Some researchers have speculated that certain congenital heart defects may result from mutations in left-right patterning genes.


NEIL BRAKE

Zebrafish are prized for research because they develop quickly and their embryos are transparent.

Vanderbilt investigators didn't set out to find a left-right asymmetry signaling pathway, say leaders Susan R.Wente, professor and chair of cell and developmental biology, and Bruce H. Appel, associate professor of biological sciences.

Wente and Appel may never have worked together had it not been for their common roots in rural Iowa. "We grew up 12 miles from each other, but we went to different schools and never met," recalls Wente, who joined the Vanderbilt faculty in 2002.

When Wente's group attended its first Vanderbilt Program in Developmental Biology scientific retreat, Appel, aware of the Iowa connection, made it a priority to speak with Wente's postdoctoral fellows and students, and a collaboration was born.

One of the areas of interest in the Wente laboratory is a family of signaling molecules called inositol polyphosphates. This series of small molecules is generated by actions of enzymes called inositol kinases and phosphatases. Disturbances in inositol signaling can result in diseases including cancer of the brain, prostate and skin, and neurological disorders.

PHOTOS BY DANA JOHNSON

Wente and collaborators, working in yeast, a simple single-celled organism, discovered several inositol kinases in 1999 and 2000. They were interested in the roles they might play in disease and development, and intended to move to mammalian cell culture and mouse-model systems to find out.

Appel and Wente do not expect their findings to lead to therapies for correcting laterality defects in human beings. But since the inositol polyphospate signaling cascade plays multiple roles in human disease and could offer targets for therapeutic intervention, it's important to understand all its many roles, they say.

Wente says it is especially gratifying that a discovery her laboratory made in a very simple model organism—budding yeast—is now offering insights to development in a multicellular vertebrate organism. The inositol kinases that she and her collaborators found in yeast had been sought for many years in mammalian systems, she says.

"It really reinforces the power of using simple-model organisms to get a handle on some of these molecules before moving to more complicated multicellular systems."

Wente and Appel credit the Zebrafish Initiative funded by Vanderbilt's Academic Venture Capital Fund with making their collaborative studies possible. The investigators are also grateful to Christopher V.E. Wright, professor of cell and developmental biology and director of the Program in Developmental Biology, and David W. Piston, professor of molecular physiology and biophysics and director of the W.M. Keck Free-Electron Laser Center, for their insight and technical assistance over the course of the project.