Getting to the Heart of the Matter

A common gene mutation that regulates cholesterol levels may raise the risk of heart disease. 9
As summer temperatures peaked this August, pharmacies were already advertising the influenza vaccine. But if you thought that was too early to be getting a flu shot — you were right.

“When adults get the vaccine in September, the peak effect wears off by late December. But flu season peaks in January and February,” warns Laura Haynes, an immunologist and gerontologist at UConn Health. October or November is a much better time to get the vaccine. That way, you’re still protected when virus season is at its worst.

This is especially important for the elderly, who are at particular risk from flu. People over 65 are much more likely than younger adults to have serious complications or even die from a bout with the virus.

One way to better stimulate the immune response is to administer a high-dose vaccine, which contains four times as much flu antigen as the regular version. But the high-dose vaccine has stronger side effects, is more expensive, and may not be best for everyone.

Haynes and her colleagues at UConn Health, funded by a Program Project Grant from the National Institute on Aging, are running two studies to better understand older people’s responses to the regular flu vaccine and the high-dose version. The studies will look at how the immune system reacts to the flu vaccine, as well as how to identify patients who would benefit from the high-dose version.

“When adults get the vaccine in September, the peak effect wears off by late December. But flu season peaks in January and February.”

— Laura Haynes, immunologist and gerontologist at UConn Health
Researchers at UConn Health and Beth Israel Deaconess Medical Center have found that a blood test could make it easier to identify patients at risk for delirium, the sudden, acute state of confusion that most often affects older adults and leads to $6.9 billion in medical costs each year in the U.S. The study, published online in *The Journal of Gerontology: Medical Sciences*, reports that elevated blood levels of specific proteins called cytokines can hint that a patient will develop delirium during a hospital stay.

Dr. George Kuchel, director of the UConn Center on Aging and one of the authors of the study, says the suspected blood signature for delirium shows two cytokines at higher-than-normal levels in patients who develop delirium. Both cytokines are associated with inflammation.

Researchers don’t yet know exactly how inflammation and delirium are linked. The two cytokines the researchers saw in the blood signature, interleukin-6 and interleukin-2, can cause swelling of the membrane around the brain. Chronic stress from low-level illness can also elevate both cytokines and stress hormones such as cortisol, which over the long term can shrink part of the brain and perhaps increase an elderly person’s susceptibility to delirium.

Kuchel and his colleagues worked with patients who participated in the Successful Aging after Elective Surgery (SAGES) study to get a better handle on the relationship between inflammation and delirium. This large study, sponsored by the National Institute on Aging, has been following 566 surgical patients over the age of 70 for the past five years, with the goal of finding new approaches to prevent delirium and its long-term consequences in older adults.

The UConn study found that patients who developed delirium had higher levels of interleukin-2 than non-delirium patients at all times they were tested: before surgery, in the first two days afterward, and one month later.

This is the first study to look at cytokine levels in older surgical patients at several points in time, both before and after surgery. The results need to be replicated in other studies, but if they prove to be generally true, the blood signature could provide a quick way to alert doctors and nurses to seniors at higher risk of delirium. They can then take extra precautions to keep the patients oriented.

“If you do things such as improve a patient’s vision and hearing, reorient them to where they are regularly, promote restful sleep, increase mobility, and stop medications that could be making the delirium worse, all that can help,” says Kuchel.

— Dr. George Kuchel, director of the UConn Center on Aging

Read the full story at [bit.ly/1MsuraP](http://bit.ly/1MsuraP)

The study is published online in *The Journal of Gerontology: Medical Sciences*. View on desktop at [bit.ly/1KWBnFA](http://bit.ly/1KWBnFA)
New Epilepsy Drug May Be Safer, More Effective

A new drug that selectively affects potassium channels in the brain may offer effective treatment for epilepsy and prevent tinnitus, UConn neurophysiologist Anastasios Tzingounis and colleagues reported in a recent issue of The Journal of Neuroscience.

The existing drugs to treat epilepsy don’t always work, and can have serious side effects. One of the more effective, called retigabine, helps open KCNQ potassium channels, which shut down the signaling of overly excited nerves. Unfortunately, retigabine has significant adverse side effects, including sleepiness, dizziness, problems with urination and hearing, and an unnerving tendency to turn people’s skin and eyes blue. Because of this, it’s usually only given to adults who don’t get relief from other epilepsy drugs.

There are five different kinds of KCNQ potassium channels in the body, but only two are important in epilepsy and tinnitus: KCNQ2 and KCNQ3. The problem with retigabine is that it acts on other KCNQ potassium channels as well, and that’s why it has so many unwanted side effects.

Tzingounis’ research has found that a new drug — SF0034, which is chemically identical to retigabine, except with an extra fluorine atom — seems to open only KCNQ2 and KCNQ3 potassium channels, not affecting KCNQ4 or 5. It was more effective than retigabine at preventing seizures in animals, and it was also less toxic.

The drug company that developed SF0034, SciFluor, now plans to start FDA trials to see whether the drug is safe and effective in people. Treating epilepsy is the primary goal, but tinnitus can be similarly debilitating, and sufferers would welcome a decent treatment.

“This drug gives me another tool, and a better tool, to dissect the function of these channels,” Tzingounis says. “We need to find solutions for kids — and adults — with epilepsy. This drug gives me a better tool to dissect the function of [potassium] channels.”

— Anastasios Tzingounis, UConn Health neurophysiologist

CANCER CELLS UNRECEPTIVE TO VITAMIN D

Many human colon cancers may not express receptors for vitamin D, limiting vitamin D’s protective role against colon cancer to the early stages of the disease, Charles Giardina and colleagues at UConn’s Department of Molecular and Cell Biology and Center for Molecular Medicine reported in the April 14 issue of Cancer Prevention Research. The researchers observed that adenomas in the colons of mice tended to repress vitamin D receptors, while having elevated Class I histone deacetylases (HDAC). However, HDAC inhibitors may reactivate the vitamin D receptors. They propose that vitamin D could still be protective against colon cancer, but how its receptors are expressed and inhibited in cancer cells needs more examination.

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FRIENDS ARE UNRELIABLE SOURCES FOR DRINKING STUDIES

In recent years, researchers have turned to friends of people in alcohol studies to verify what the subjects report about their drinking habits. People in the same social situations are sought out, in part, because of the inherent impairment caused by alcohol. But according to a UConn study published in Addictive Behaviors, friends don’t seem to provide any new information. In fact, they typically underreport what their acquaintances consume. The finding supports the so-called “protective effect” of friends described in other research. A growing availability of other information — hair and fingernail samples, for example — may provide a better strategy for corroborating the amount of alcohol subjects consume, says author Michael Fendrich, associate dean of the UConn School of Social Work.

SHE SMELLS HIM, SHE SMELLS HIM NOT

Mice rely on their noses to help them navigate the world. But high levels of progesterone “blind” the receptors in the noses of female mice to male pheromones, UConn Health’s John Peluso and other colleagues, led by Lisa Stowers of The Scripps Research Institute, report in the June 4 issue of Cell. Female mice have high levels of progesterone during the fertile phase of their reproductive cycles, and tend to be indifferent or even aggressive toward males. But during the fertile phase, progesterone levels drop and estrogen rises, and their nasal receptors again respond to male pheromones, the researchers found. Female mice in their fertile phase are friendly and sexually receptive towards males — perhaps because they can smell them.

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THE PULSE UConn Health News
HONOR ROLL

For the second consecutive year, UConn Health has received a Gold Award from Get With The Guidelines, an American College of Cardiology and American Heart Association initiative that recognizes hospitals for providing exceptional care to heart-attack victims according to evidence-based guidelines.

UConn Health psychiatrist Dr. Kristina Zdanys was voted onto the Medical and Scientific Advisory Council for the Connecticut Alzheimer’s Association in June. She will join colleagues Rick Fortinsky and Dr. Lavern Wright, who also sit on the council.

UConn Health welcomes the following new physicians:

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People have unseen scars and they may be reluctant to talk about their stigmatized identity or experience... but if they do choose to talk about it, then they will gain even more benefit from their social interactions than if they remain silent.

— Bradley Weisz, doctoral student in psychology at UConn

‘Talk to Your Mother’ Proves to be Healthy Advice

Bringing out the proverbial “skeleton in the closet” can provide health benefits, but the degree of benefit depends on who you confide in, says a new UConn study.

The study of 400 people, published in the Journal of Health Psychology, found that people who are living with issues such as mental illness, substance abuse, domestic violence, rape, or childhood abuse reap considerable health benefits from discussing those issues.

But they experience more health benefits — both psychological and physical — from disclosing the issue to mom, a romantic partner, or a close friend, says Diane Quinn, UConn psychology professor and study author.

“It seems that people expect their mothers to love them unconditionally, and they just assume that she will handle letting the rest of the family — including the father — know about a problem,” says Quinn.

Researchers studied a group of people who averaged 32 years old and who had at least one past experience that they kept hidden from others.

Participants were asked to rate their social networks according to differing degrees of support. Those ranged from a basic level of support, such as an offer to go to lunch, to more substantial support, such as an offer of a place to stay during an emergency. They were also asked to rate their own physical health, both in terms of actual symptoms of illness and how they perceived their health in general. Finally, they were asked to quantify how “out” they were about their issue within their social network.

Results showed that people who characterized themselves as being the most “out” derived the greatest health benefits, especially when their confidantes included mom, a romantic partner, or a close friend.

“People have unseen scars and they may be reluctant to talk about their stigmatized identity or experience,” says co-author Bradley Weisz, a doctoral student in psychology, “but if they do choose to talk about it, then they will gain even more benefit from their social interactions than if they remain silent.”

But while being “out” about a stigmatized identity or a traumatic experience can be helpful in the long run, Quinn says that not everyone has to follow the same path. “It’s a matter of your personal comfort zone,” she says.

Funded by the National Institutes of Health (NIH), the study was also co-authored by UConn psychology professor Michelle Williams.

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THE PULSE

UConn Health News
By Kim Krieger

Why do some patients with high ‘good’ cholesterol also show signs of heart disease? UConn research has found the common gene mutation that may be to blame.

Guidelines about cholesterol used to be straightforward: high-density lipoprotein (HDL) cholesterol is healthy, and low-density lipoprotein (LDL) cholesterol is not. Relatively high levels of HDL were no cause for concern, as long as LDL was low.

But recent discoveries show that may be an oversimplification. A common variant in a gene that regulates cholesterol levels may raise the risk of heart disease in carriers with high HDL, according to a new UConn Health study.

Researchers examined a variant called missense rs4238001, which alters the type of protein made by the gene SCARB1. The variant form of SCARB1 changes a liver receptor protein from a glycine to a serine. The change
The risk of heart disease among those with the variant was up to 49 percent greater than in the general population. They can offer counseling about heart risk prevention.

UConn Health endocrinologist Dr. Carl Malchoff (See sidebar for more on Malchoff) uses the test to help patients who aren’t sure whether or how they should treat their high cholesterol. For example, Malchoff had one patient with high HDL and a family history of longevity. But she had suffered a stroke at a young age, and wanted more information before deciding on a treatment.

This particular patient tested negative for the variant. But those who test positive would be advised to use a more aggressive type and dose of cholesterol medication. Patients with the variant could also inform their children that they might also have it.

“Usually if patients don’t have the variant, we assume their high HDL is protective,” Malchoff says.

Sometimes, however, a treatment decision might be more ambiguous, and could require further information before the best therapy is chosen. Another patient of Malchoff’s had high levels of both HDL and LDL cholesterol. She was taking a statin to lower her cholesterol, but was experiencing terrible muscle pain as a side effect. She wondered if there was a way to tell whether her high HDL protected her from the heart disease risk associated with high LDL. If so, could she stop taking the statin?

This patient could be tested for the same variant. If her test was negative, she could assume that her high HDL cholesterol was helping protect her against heart attack, even with high levels of LDL cholesterol. If the test was positive, she would know that her high HDL cholesterol would not protect her. She could then take another type of cholesterol-lowering medication, just not one classified as a statin.

Malchoff and his colleagues at UConn Health are working with Rodriguez-Oquendo to determine when testing for the variant is most helpful.

“My approach to patient care in an academic center is that we should look for things our colleagues in practice can’t do and do those things, so we can help them and be their partners,” Malchoff says of his role in the research.

Now that the UConn study has made the connection between the mutation in SCARB1 and heart disease, the researchers want to figure out a way to fix it.

“We want to go deep in the cell, and figure out how to repair it,” Rodriguez-Oquendo says. The researchers don’t know exactly why changing the protein in a liver receptor from a glycine to a serine makes it more fragile. “We’re really interested in understanding more about how this protein gets chewed up and degraded faster.”

The answers may impact the current standard of care for heart disease prevention and treatment for patients who are carriers of this genetic variant. That could happen through indirect means, such as adjusting hormone levels to alter cholesterol metabolism, or in the future through direct means such as genetic therapy.
A woman who won’t drive long distances because she has panic attacks in the car. A man who has contamination fears so intense he cannot bring himself to use public bathrooms. A woman who can’t go to church because she fears enclosed spaces. All of these people have two things in common: they have an anxiety disorder, and they happen to be parents.

These parents sought help because they struggle with anxiety, and want to prevent their children from suffering the same way. Anxiety tends to run in families, with 30 to 50 percent of children of anxious parents growing up to be anxious themselves. But that does not have to be the case, according to new research by UConn Health child psychologist Golda S. Ginsburg.

Ginsburg and colleagues at Johns Hopkins University tested a one-year therapy intervention as part of a study of 136 families where at least one parent had anxiety and at least one child was between the ages of 6 and 12.

The study, published in the December issue of The American Journal of Psychiatry, found that therapy-based intervention works. Only 9 percent of children who participated in a therapist-directed intervention developed anxiety after one year, compared to 21 percent in a group that received written instruction, and 31 percent in the group that did not receive any therapy or written instruction.

Both inborn temperament and life experiences play a role in whether an adult has anxiety. The more negative experiences a person has growing up, the greater the likelihood he or she will struggle with anxiety as an adult. But there is also a component of anxiety that is learned, taught inadvertently by parents who model the behavior. It’s these learned behaviors and thought patterns that interventions can help change, according to Ginsburg.

“Children of anxious parents have up to a 50 percent chance of growing up to be anxious themselves. But that does not have to be the case. The finding underscores the vulnerability of offspring of anxious parents who can protect their kids from becoming anxious adults.”
anxious parents,” says Ginsburg. She wants to do something about that vulnerability. “If we can identify kids at risk, let’s try and prevent this.”

Most of the adults who participated in the study struggled in school and didn’t tell anyone. They didn’t raise their hands, or they got sick before exams. They might not have had any friends. As adults their anxiety still limits their activities and sometimes those of their family members, and they are very motivated to help their children avoid the same.

Physicians can often identify children at risk before they develop an anxiety disorder. Such kids are often hyper-aware of aches and other bodily sensations, and are frequent flyers at the doctor’s office and emergency room. For example, such a child might think “my heart is racing — I’m having a heart attack!” when a less anxious individual would think “my heart is racing because I just ran up a hill.”

Other signs of children at risk for anxiety include avoidance of school, parties, and other social situations, as well as unusual worries. “Anxiety and fear are protective and adaptive,” says Ginsburg. “But in anxious kids they may not be, because these children have thoughts about danger and threat when there really isn’t one.”

For such a child, meeting a new peer for the first time can be paralyzing. Trying an unfamiliar food might summon worries of being poisoned. To cope with this kind of debilitating anxiety, children start avoiding whatever provokes the anxious feelings. If they’re afraid of the dark, they might insist on sleeping with all the lights on. If they’re afraid of failing, they won’t try new things. In extreme cases, they may refuse even to leave the house.

One of the ways to reduce anxiety is to do a reality check. It’s a way to recognize when a fear is healthy and worth paying attention to (a growling dog) or unhealthy (a possibly poisoned birthday cake).

In the study, some of the families participated in eight, hour-long sessions with a trained therapist over a period of two months. Others were just given a pamphlet that contained general information about anxiety disorders and treatments. Still others received nothing at all.

The families who participated in therapy were taught to identify the signs of anxiety and how to reduce it. They practiced problem-solving skills, and exercised safe exposures to whatever made their child anxious.

“We taught the kids how to identify scary thoughts, and how to change them,” Ginsburg says.

For example, if a child is afraid of cats and encounters one in the street, the child can first identify the scary thought: ‘That cat is going to hurt me.’ Then the child can test that thought: ‘Is it likely that cat will hurt me? No, the cat doesn’t look angry. It isn’t baring its teeth or hissing, it’s just sitting there. Okay, I can walk past that cat and it won’t do anything.’

In general, children who participated in the intervention had lower anxiety overall than children who did not participate in the intervention with their families.

Now the researchers have funding from the National Institutes of Health for a follow-up to see whether the effects are maintained over time. Ginsburg wonders whether there would be value in providing regular checkups for families on mental health issues. She is considering approaching insurers about offering this kind of service to families at risk, to see if it lowers their healthcare costs overall.

“I’d say we need to change our model of mental health to a checkup method. Like going to the dentist every six months.”

— Golda Ginsburg, Psychologist, UConn Health
How Does the Supreme Court’s Latest ACA Decision Impact Physicians?
Q&A With UConn Law Professor John A. Cogan Jr.

In June, the U.S. Supreme Court turned away yet another challenge to the Affordable Care Act (ACA), commonly referred to as Obamacare. The Court, in King v. Burwell, ruled 6-3 that the government could continue to provide premium subsidies nationwide to middle- and low-income Americans who purchase their health insurance directly from insurers on health insurance exchanges.

The subsidies are a crucial component of the ACA, which requires all Americans to have health insurance. Had the Court ruled against the government, the individual health insurance market would have been thrown into chaos, says insurance law expert John A. Cogan Jr., an associate professor at UConn Law. Unsubsidized, healthier consumers would be driven out of markets, and premium costs would spike.

While the Supreme Court’s ruling brought certainty and stability to the individuals who purchase insurance on the health insurance exchanges, there is still uncertainty for another group — physicians. Recent mega-mergers in the health insurance industry may leave doctors with less bargaining power in the future, possibly affecting reimbursement rates, says Cogan, who has written extensively about health law and policy.

What was the immediate effect of the Supreme Court’s ruling in King v. Burwell?

The major effect was to cement the federal government’s implementation of the law. The case dealt with a very specific issue: the subsidies offered to low- and moderate-income people. Unlike the previous ACA case, King v. Burwell wasn’t a constitutional challenge, it was based purely on a question of statutory interpretation: Could the government give out subsidies? The Supreme Court said yes. Since the constitutional and major statutory challenges have failed, we may see opponents attempt to chip away at portions of the ACA they do not like, but I think it’s safe to say we won’t see any more major cases attempting to unravel the whole law.

In the wake of the decision, we saw announcements by insurer Aetna that it intended to buy competitor Humana, and then that Anthem would buy Cigna. That would bring the number of major health insurers in the U.S. from five to three, with UnitedHealth the third. How will these mergers benefit the insurance companies, and how will they affect healthcare providers?

The post-merger companies will each have a larger share of the market, thereby consolidating their power. Consolidation allows insurers to increase profits through efficiency gains. But these larger insurers will also gain bargaining power with healthcare providers. This is important because providers are paid directly by insurers. If you have doctors and hospitals negotiating with several different insurers, they have the ability to walk away from any one of those insurers, giving providers some leverage. But if there are only two insurers, that leverage is diminished. Major hospital systems and large physician groups will still have some bargaining power because of their size, but individual physicians will see their bargaining power diminish further.

Will the effect of the mergers be in line with the intent of the law?

The ACA’s express intent was to expand coverage, and it worked. There’s nothing in the ACA regarding industry consolidation. Nevertheless, the fallout of the ACA’s expansion of coverage — efforts by insurers to consolidate market share — was foreseeable. Now that the ACA is here to stay, federal and state regulators will have to wrestle with consolidation issues.
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