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IN THE LAB | April 9, 2012, 6:48 p.m. ET

New View of Depression: An Ailment of the Entire Body

By SHIRLEY S. WANG



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Scientists are increasingly finding that depression and other psychological disorders can be as much diseases of the body as of the mind.

People with long-term psychological stress, depression and post-traumatic stress disorder tend to develop earlier and more serious forms of physical illnesses that usually hit people in older age, such as stroke, dementia, heart disease and diabetes. Recent research points to what might be happening on the cellular level that could account for this.

Shirley Wang on Lunch Break discusses the impact of depression on aging and why people with a history of depression are also known to be at greater risk for cardiovascular disease, diabetes and other aging-related diseases.

Scientists are finding that the same changes to chromosomes that happen as people age can also be found in people experiencing major stress and depression.

The phenomenon, known as "accelerated aging," is beginning to reshape the field's understanding of stress and depression not merely as psychological conditions but as body-wide illnesses in which mood may be just the most obvious symptom.

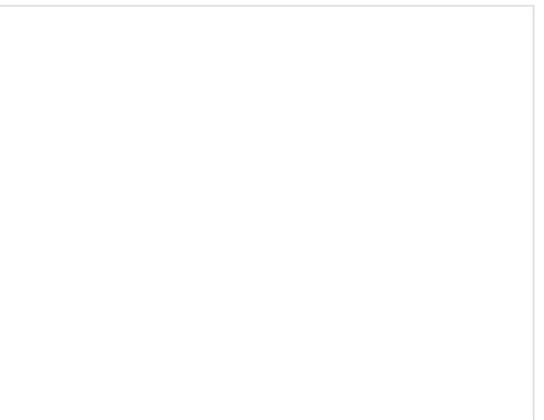
"As we learn more, we will begin to think less of depression as a 'mental illness' or even a 'brain disease,' but as a systemic illness," says Owen Wolkowitz, a psychiatry professor at the University of California, San Francisco, who along with colleagues has conducted research in the field.

Gaining a better understanding of the mechanisms that link physical and mental conditions could someday prove helpful in diagnosing and treating psychological illnesses and improving cognition in people with memory problems, Dr. Wolkowitz says.

What We Lose With Age
As cells divide over time...
Chromosomes shorten, and eventually cell division stops.

In an early look at accelerated aging, researchers at Duke University found about 20 years ago that brain scans of older people with depression showed much faster age-related loss of volume in the brain compared with people without depression. The reasons for the accelerated aging appeared to go beyond unhealthy behaviors, like smoking, diet and lack of exercise, researchers said.

Recent efforts to study what is behind



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accelerated aging on a cellular level have focused on telomeres, a protective covering at the ends of chromosomes that have been recognized as playing an important role in aging. Telomeres get shorter as people age, and shortened telomeres also are related to increased risk of disease and mortality.

In several studies conducted at UCSF, researchers have found shortened telomere length to be associated with depression, childhood trauma and other conditions. A study of 43 adults with chronic post-traumatic stress disorder, whose average age was about 30, and 47 healthy control subjects, found shorter telomere length in the PTSD group that equated to an estimated 4.5 years of accelerated aging, Dr. Wolkowitz says. The study was published last year in *Biological Psychiatry*.

In separate research, scientists in Sweden found similar results. In a study involving 91 patients with major depression and 451 healthy control subjects, researchers from Umeå University concluded that shortened telomere length was associated with depression and greater perceived life stress. The study was published in *Biological Psychiatry* in February.

### Early Aging

People who have major bouts of depression have an increased risk at a younger age of developing conditions typically associated with getting older. This may be because depression makes cells age prematurely, new research suggests.

~Heart disease

~Atherosclerosis

~Hypertension

~Stroke

~Dementia

~Osteoporosis

~Type 2 diabetes

Source: Owen Wolkowitz, UCSF

head of the division of biological psychiatry at Duke University, who isn't involved in telomere work. Such information could help provide clues about how much of age-related disease is due to genetics versus life experience, and whether it can be reversed, he says.

Researchers also want to understand why not all stressed people develop shortened telomeres. Telomere length is thought to be affected by the body's production of certain stress hormones or inflammatory molecules, which are made in greater quantities when people are stressed or depressed. Meanwhile, an enzyme known as telomerase acts to protect against telomere shortening.

Some people appear to have innate biological protective factors, like higher antioxidant level and anti-inflammatory proteins, according to UCSF's Dr. Wolkowitz.

How individuals experience the stress, cope with it and view the world more generally also are thought to relate to telomere length. In 2009, the UCSF researchers found that a personality characteristic, pessimism, correlated with shorter telomeres and increased production of a chemical produced by the immune system related to stress.

In another study, UCSF researchers brought into the lab 50 women and exposed them to standard experimental tasks known to induce stress: giving a speech about their personal strengths and weaknesses and completing a difficult math problem out loud. Some of the women were caregivers for chronically ill children and therefore had presumably more stressful lives. But telomere length didn't seem to depend on whether a woman was one of the caregivers or not. Instead, the telomeres were shorter only in those women who reported greater levels of anxiety about having to perform the experimental tasks—seemingly the ones who tended to get more stressed about life's challenges. The research, led by UCSF postdoctoral fellow Aoife O'Donovan, was published online in March in the journal *Brain, Behavior, and Immunity*.

Researchers believe it takes months, or even years, for stress or depression to affect telomere length. However, the level of activity of the enzyme telomerase may be affected more quickly. In a pilot study involving 24 patients with prostate cancer, Dean Ornish,

Scientists say more work needs to be done to figure out exactly how severe a psychological experience must be to affect telomere length. Some research suggests that as few as two episodes of major depression may be sufficient to affect cell structure. Other studies indicate that the more bouts of depression a person experiences, the more impact there is on telomere length.

The "holy grail" of this area of work is to try to find the molecular mechanisms by which depression or stress take their toll on the body, says P. Murali Doraiswamy,

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In the Lab explores cutting-edge research that holds the promise of answers to some of medicine's biggest and smallest questions. Every other Tuesday, Shirley Wang, a former researcher who has published work in peer-reviewed journals, takes you into the labs of scientists from around the world to understand why the body is the way it is and what advances are to come in health and medicine.

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founder of the Preventive Medicine Research Institute, a nonprofit research group in Sausalito, Calif., demonstrated that telomerase activity in blood cells increased after three months of changes in the patients' lifestyle, including lowering of cholesterol and psychological distress. Although the study didn't measure telomere length, the researchers suggested that increased telomerase activity in the patients could be signaling greater telomere protection at the cellular level. The study, performed together with UCSF researchers, was published in the Lancet Oncology in 2008.

Heightened telomerase levels have been found in some depressed people who are given an antidepressant. These patients also show improvement in clinical measurements of their depression. Other depressed patients, however, who don't show clinical improvements after being given medication, also didn't experience an increase in levels of the enzyme. The findings are from a small study published in February in Molecular Psychiatry.

After finding that some psychological conditions appear to affect telomere length, researchers at UCSF are trying to find out whether information about what is going on in a patient's cells can be used to change the person's psychology. In an ongoing study, researchers are telling patients how their telomere length, which can be detected through a blood sample, compares with that of an average person of the same age. Researchers are then tracking whether the patients, armed with that information, are more motivated to adopt a healthier lifestyle.

Write to Shirley S. Wang at [shirley.wang@wsj.com](mailto:shirley.wang@wsj.com)

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