



Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress David Geffen School of Medicine at UCLA

From the Desk of Emeran A. Mayer, MD Center Director



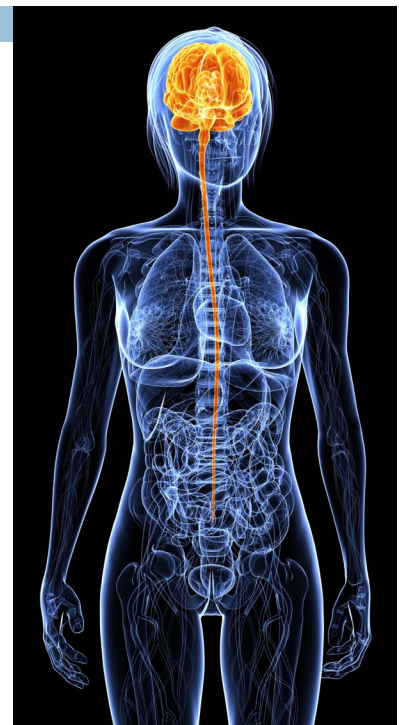
Our quarterly Center newsletter highlights important news and updates from the various Programs within our Center (for more details on these programs, please visit uclacns.org). In this edition, we are highlighting some exciting news from the Pain Program which deals with novel approaches to understanding and treating chronic pain. It also draws attention to the important topic of early adverse life events and their impact on adult health and disease vulnerability. The article on food, gut microbiota and

the brain comes from the Enteric Neuroscience Program as well as the story about a serious, yet often undiagnosed disturbance of the brain-gut axis. We would like to express our gratitude to all the individuals who have generously contributed to our Center’s ongoing success.

Novel Approaches to Understand and Treat Chronic Pain

The Magnitude of the Problem. Chronic pain affects about 100 million American adults—more than the total number of people affected by heart disease, cancer, and diabetes combined. Chronic pain also costs the nation up to \$635 billion each year in medical treatment and lost productivity. Patients with chronic abdominal and pelvic pain make up a significant portion of the chronic pain population, including syndromes ranging from chronic pancreatitis, irritable bowel syndrome (IBS), chronic abdominal pain syndrome, interstitial cystitis/painful bladder syndrome and vulvodynia. Women are disproportionately affected, and alterations in mood or affect (in the form of symptoms of anxiety and/or depression) are common. Like the majority of chronic pain patients, those suffering from chronic abdominal or pelvic pain typically undergo multiple, often unnecessary, diagnostic evaluations and therapeutic interventions, without getting satisfactory care for their primary symptoms. Besides the tremendous impact on patients’ lives, the unnecessary diagnostic and therapeutic procedures create a staggering burden on the healthcare system.

Continued on page 2



Inside

Novel Approaches to Understand and Treat Chronic Pain .....1
You Are What You Eat ...3
Adult Onset Cyclic Vomiting Syndrome .....4
Did You Have a Happy Childhood? Implications For Adult Health .....4

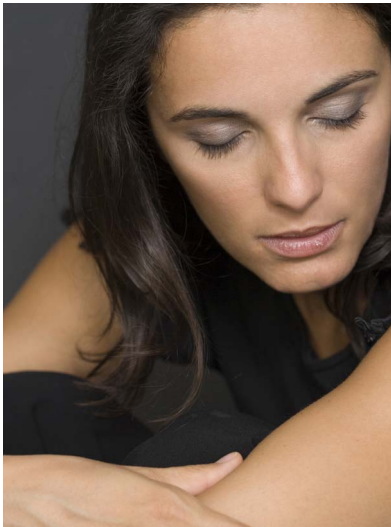
CHS 42-210
10833 Le Conte Avenue
Los Angeles, CA 90095-7378
(310) 206-0192
uclacns.org
painrepository.org



## Novel Approaches to Understand and Treat Chronic Pain

*Continued from cover*

**Clinical Expertise at UCLA.** Several members of the Center are internationally renowned clinical experts in the diagnosis and treatment of these abdominal/pelvic conditions, presenting as gastrointestinal (L Chang, K Tillisch, EA Mayer), urological (L Rodriguez), gynecological (A Rapkin) and pediatric (L Zeltzer) pain problems. The majority of patients seen in these specialty clinics have already undergone extensive evaluations before coming to UCLA, only to be told that there is nothing physically wrong with them and that they must learn to live with their symptoms. These UCLA physicians are not only experts at making definitive diagnoses, but also in recommending a cutting edge holistic approach to treatment, combining pharmacological with integrative medicine, including various relaxation and stress management strategies, hypnosis, meditation and yoga.



In addition to their clinical expertise, the UCLA team is made up of national leaders in research efforts aimed at a better understanding of the mechanisms underlying chronic abdominal and pelvic pain, as well as in the development of novel, cost-effective strategies for treatment. Funded by grants from the National Institutes of Health (NIH), Center investigators are studying biological mechanisms underlying symptoms in these pain conditions. There is a growing consensus in the chronic pain field that in contrast to *acute* pain conditions which are largely a consequence of easily identifiable organ injury, inflammation or obstructions, symptoms in *chronic* pain (regardless of detectable changes in the body) are, to a large degree, maintained and worsened by changes in the nervous system (including cognitive and emotional factors) and that these factors can be identified as structural and functional “signatures” in the brain. Some of the most exciting questions asked by Center investigators in these studies include: Are there brain signatures that are specific for a particular chronic pain disorder? What are the molecular mecha-

nisms underlying these brain signatures? Are there subgroups of patients with chronic abdominal or pelvic pain with different brain signatures, requiring custom-tailored, individualized therapies?

**Innovative Research.** To better characterize the fingerprints of chronic pain in the brain, Center investigators have recently obtained funding from the National Institute on Drug Abuse (NIDA) and National Center for Complementary and Alternative Medicine (NCCAM) to build the first international repository for standardized brain images from patients with various chronic pain conditions (Pain and Interoception Imaging Network [PAIN], [painrepository.org](http://painrepository.org)). Currently, 15 institutions from North America and Europe will contribute brain images and associated clinical and biological data, which aims to grow to a size of 1,000 brains in 2 years. The repository will provide an unprecedented opportunity to probe structural and functional brain alterations associated with various forms of chronic pain, identify differences between male and female patients, correlate these brain changes with environmental and genetic factors, and identify commonalities and differences between different pain syndromes.

**Innovative Treatment Program.** Another innovative and exciting research area Center investigators are involved in is the development of an interactive web-based cognitive behavioral treatment (CBT) program. With the extensive experience of Drs. M Craske and B Naliboff, who have successfully developed and evaluated CBT for IBS, mental health and primary care, we aim to build a platform that can be adapted to different pain and chronic diseases, including IBS, inflammatory bowel diseases and migraines. Web-based treatment programs for chronic diseases have already been successfully implemented in several European countries. Such approaches can provide patients with user friendly access to highly effective mind-based treatment programs which can enhance traditional treatment approaches.

## You Are What You Eat

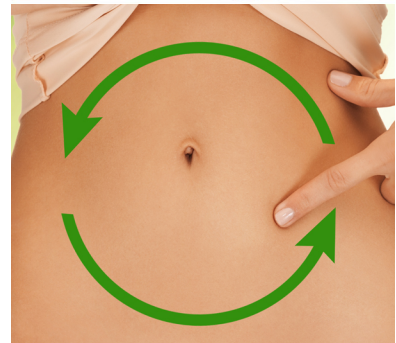
It's often been said that "you are what you eat," generally meaning that eating poor quality food can lead to poor health. However, we now know that it is not only the nutritional value of food that is important for us, but also the components of food that can influence many of our organs including the brain. Many of these information containing food components first need to be broken down ("metabolized") by the trillions of microbes that live in our intestine.

The patterns of these microbes that live in our intestines ("enterotypes") and their metabolites vary with our diets. For example, people consuming a typical Western diet high in animal fat and protein, have a different composition of gut microbes than those consuming a so-called agrarian diet, high in vegetables and fiber. Most of these microbes have a symbiotic relationship with us in that we provide them a home and food and they provide us by helping digestion and generating molecules that affect our health. Some of these microbes are considered probiotics, or organisms which are beneficial to our health.

In addition to the probiotics that reside in our gut, we commonly ingest probiotics in yogurts which contain species of *Lactobacillus*, *Streptococcus*, and *Bifidobacterium*. Other food products containing probiotics include miso, tempeh, kombucha drinks, the Korean cabbage dish called kimchi, sauerkraut and other fermented vegetables, though not all pickles are fermented. Almost every culinary tradition contains fermented foods, though often we don't even realize we are eating them, and rarely do we realize how important they are for our wellbeing.

Recently it has been discovered in animal studies that changes in the composition of microbes in the gut can change the animal's level of anxious behaviors, gut inflammation, and even their weight! A recent study done at the Center has shown that eating a specific yogurt for 4 weeks leads to a decrease in the brain's response to pictures of angry and fearful faces, suggesting that someday we may find that yogurt decreases our response to stress. Some researchers have gone so far as to coin the terms "melancholic microbes" or "psychotropic microbes" and suggest that in the future probiotics may be used as treatments for a variety of diseases from anxiety, depression, autism and obesity.

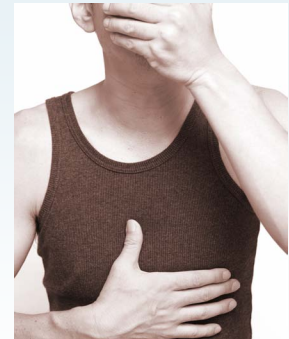
Ongoing research to study these concepts is vital as the translation of concepts learned in animal studies doesn't always translate to humans. At the Center we pursue exciting research to understand the effects that gut microbes may have on our brains, if altered microbe to brain signaling contributes to common diseases such as anxiety, depression or chronic abdominal pain and discomfort, and if therapeutic interventions such as diet, probiotics or other therapies can normalize this disturbed gut to brain communication. In these studies, we collect gut microbiota samples along with brain images, genetic tests, weight and body fat assessments, diet histories, and questionnaires about stress, life events, and mood to help determine how our gastrointestinal microbes help make us who we are.





## Adult Onset Cyclic Vomiting Syndrome – One of the Most Devastating but Easiest to Diagnose and Treat Gastrointestinal Disorders

John is a 25 year old student who has suffered from recurrent episodes of prolonged nausea and vomiting for the past 7 years and has ended up in the emergency room many times for medications to stop his incapacitating attacks. Nobody has been able to diagnose or treat his problem, and emergency physicians often accuse him of drug seeking behavior. He has been unable to maintain his college courses and is desperate for help. His mother learned about a possible diagnosis that would fit his symptoms on the internet.



John suffers from a disorder called adult cyclic vomiting syndrome, a diagnosis that can easily be made based on the stereotypic, cyclic nature of the attacks. Scientists at the Center have studied the underlying mechanisms of this syndrome which is triggered by an abnormal release of a stress hormone within the brain. Center physicians are well familiar with the syndrome and have extensive experience in designing individualized treatment regimens. For more information about the syndrome, visit the Cyclic Vomiting Syndrome Association's website, [cvsaonline.org](http://cvsaonline.org).

## Did You Have a Happy Childhood? - Implications for Adult Health

Julie is a 22 year old college student who suffers from chronically recurring severe abdominal pain episodes which are so severe that they keep her from studying or socializing and she is concerned she may not be able to finish her semester in college. She is a highly successful member on the swim team, and has been accepted into law school. The frequency of the episodes has increased during the past 4 months. Even though she has seen many doctors for her problem, she has never been asked a simple question about her childhood – until now. “Did you have a happy childhood?” asks the physician during her recent visit at the UCLA Digestive Health and Nutrition Clinic.

This question aims to identify a history of early adverse life events, which include death/chronic illness of the primary caregiver, discordant marital relationship between parents and verbal, physical (and rarely sexual) abuse to name a few. Many studies have shown that if such adverse life events occurred during the time when the human brain is developing (prior to age 18) they greatly increase the likelihood of an individual to develop a range of chronic medical and psychiatric conditions later in life, including, but not limited to, chronic gastrointestinal problems (such as chronic abdominal pain, irritable bowel syndrome, cyclic vomiting syndrome), heart disease and obesity.

While everybody agrees that such early life experiences are not beneficial for the development of a child, a remarkable body of research has revealed the molecular mechanisms which underlie this relationship between the quality and stability of early environment and long-term health outcomes. In a NIH funded study, investigators at the UCLA Center are exploring the molecular (“epigenetic”) mechanisms by which early adversity can lead to lifelong modifications of genes that program the responsiveness of the stress response system, and how such changes can influence the clinical course of patients.

Patients like Julie greatly benefit from the extensive knowledge that Center physicians translate from their basic research directly into the clinic. Many patients appreciate learning about the connections between some aspects of their personal history which they have never paid much attention to, with the symptoms they are suffering from today. Treatment recommendations are often based on learning strategies to counteract the epigenetic changes that have developed early in life.

