Lustman Memorial Fund Continues Decade-Long Partnership

Women’s Health Research at Yale is honored to have the renewed support of the Seymour L. Lustman Memorial Fund.

A new grant to our center will allow us to use the funds to support any of our four major initiatives. These are our Pilot Project Program, which provides “seed” funding to initiate studies on women’s health; interdisciplinary research cores, focused on key women’s health concerns; Initiative for Community Wellness, in which we collaborate with the community to translate our findings, and our efforts in training the next generation of women’s health researchers.

The Seymour L. Lustman Memorial Fund was established in memory of Dr. Lustman, who was Professor of Psychiatry on the faculty of the Yale Child Study Center for more than 20 years. In addition to being a gifted clinician, Dr. Lustman was a dedicated researcher who believed in rigorous scientific investigation as the basis for good clinical care.

This latest grant to Women’s Health Research at Yale cements a decade-long partnership with the Seymour L. Lustman Memorial Fund.

“In the past we’ve directed our funds toward educational outreach and the pilot program, but in today’s research funding environment, we felt it was important to provide general support to be used where most needed,” said Susan Lustman Katz, J.D., Chair of the Lustman Fund.

“This continuing commitment to ensure our success is very important to us,” Dr. Carolyn M. Mazure, our Director, said. “Foundation support that we can use to strengthen our major initiatives is essential to our mission, especially at this time of reduced federal funding for research, and we sincerely thank the Seymour L. Lustman Memorial Fund for its repeated generosity.”

Women’s Health Research at Yale generates research findings that transform the scientific community’s understanding of women’s health, answer important questions, and advance knowledge to improve well-being for all.

To learn more please visit our website at:
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or email us at:
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Our Society of Friends ensures the future of Women’s Health Research at Yale. Gifts are welcome at all levels.

To make an online gift visit www.yalewhr.org or mail your gift to Women’s Health Research at Yale P.O. Box 208091 New Haven, CT 06520-8091

Educational and outreach activities are made possible through the generous support of

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Women’s Health Research at Yale was founded in 1998 with initial funding from The Patrick and Catherine Weldon Donaghue Medical Research Foundation.
Understanding and Controlling Obesity in Women

Medical scientists focusing on obesity thought for many years that it was excessive abdominal or “belly” fat that increased the risks for health problems such as diabetes and cardiovascular disease.

This hypothesis was based largely on evidence that men tend to gain weight in the belly and that overweight men were at a higher risk for developing diabetes and cardiovascular disease. Overweight women, according to this hypothesis, were thought to be at a lower risk of cardiovascular disease than overweight men because women tended to gain weight under the skin throughout the body.

However, recognition that cardiovascular disease is the number one killer of women as well as men in the United States, and that the obesity epidemic is growing among both genders, has prompted a new look at the nature of obesity.

Overall, rates of obesity among Americans have grown dramatically over the past 20 years. In every state, at least a fifth of the population is now obese, and in 12 states concentrated in the South the prevalence of obesity is 30 percent or more, according to the U.S. Centers for Disease Control and Prevention. Nationwide, more than a third of adults are obese, CDC figures show.

In addition, 34 percent of adults are overweight—meaning that two-thirds of American adults are either obese or overweight and there appears to be no end in sight to this upward trajectory.

Moreover, health scientists have observed another troubling trend involving excess weight. “It seems to be affecting people at younger ages,” according to Dr. Matthew Rodeheffer, Assistant Professor of Comparative Medicine and of Molecular, Cellular and Developmental Biology.

Recently, in fact, rates of obesity and being overweight have been increasing among American women in the age group between 20 and 34 years old more rapidly than in any other age group for women or men, according to CDC figures. More than a third of children (ages 10 – 17) nationwide are obese or overweight, according to a 2011 report on obesity by the Trust for America’s Health and the Robert Wood Johnson Foundation.

Furthermore, recent analyses of data from population studies of women have indicated that obesity may actually be associated with greater health risks in women than men, said Rodeheffer, who has been studying obesity for nearly a decade. Obese women, in fact, are up to eight times more likely than obese men to develop secondary health conditions including diabetes and cardiovascular disease.

According to Rodeheffer, one of the limitations to understanding what is going on with respect to obesity and related health problems in women is that studies of obesity-related disease have been performed almost exclusively in men or male animals models.

Rodeheffer recently carried out experiments in animal models to determine whether there are differences between females and males in the molecular mechanisms that trigger weight gain due to diet. In these experiments, conducted in the fall of 2010, he wanted to begin to explore a fundamental question: what happens to fat cells at the start of obesity!
“Was it different in females and males, the same, similar? One short experiment told us it’s quite different,” he said in a recent interview in his laboratory.

Rodeheffer’s experiments showed that when a high-fat diet was introduced the cells that trigger the accumulation of fat – fat precursor cells – increased in the abdominal area in male mice. However, in females the increases in fat precursor cells occurred in both the abdominal area and under the skin throughout the body, with the introduction of a high-fat diet.

Hoping to continue this line of research which seeks to determine fundamental biological differences in how we accumulate fat, Rodeheffer applied for and was awarded a 2011 Pilot Project Program grant from Women’s Health Research at Yale.

One of the main goals in his ongoing study is to identify the cellular mechanisms that control the proliferation of fat (white adipose tissue) at the very outset of diet-induced obesity in female mice. Identifying and understanding these mechanisms is highly relevant to everyone’s health, but particularly important for the health of women because they experience greater obesity-related consequences.

Although there are several factors that contribute to obesity, the basic cause is regular consumption of more calories, in food, than are burned off in daily activities and exercise.

“I think it likely has as much to do with how much we eat as with what we eat. Our diets have changed substantially in the last several decades and the contributions of these dietary changes to the obesity epidemic are unknown,” Rodeheffer said.

“The purpose of our study is to characterize what’s going on in the biology, at the cellular level,” he said. “What we really want to understand are the signals in the body,” which tell fat precursor cells to activate and fat cells to proliferate, resulting in more white adipose tissue mass.

His hypothesis, though novel, is quite simple: the excessive accumulation of all white adipose tissue in women, both in the abdominal area and under the skin throughout the rest of the body, may contribute to the development of obesity-related pathologies such as heart disease and diabetes.

The practical benefit of Rodeheffer’s research lies in the potential for the development of therapeutics for the treatment of obesity, and the prevention and treatment of the related health consequences. Understanding the basics of how fat cell proliferation processes work is expected to enable him to identify molecular and cellular targets “so that we can do very directed drug development to combat obesity,” Rodeheffer said. Just as with other addictions, changing behaviors is key to managing and controlling overeating and poor eating habits, but providing a biological intervention can help many people start the process of gaining control over addictive behaviors and changing their lives.

Rodeheffer already has characterized when, during the onset of obesity, fat cells are induced to produce new fat cells, contributing to increased fat mass. “We are now focused on identifying the signals that cause the precursors to become fat cells,” he said. “Knowing the signals necessary for increased fat cell numbers in obesity will allow us to develop therapeutic strategies that directly target the pathways active in obesity.”

A thorough understanding of the molecular mechanisms that regulate white adipose tissue mass in women also has the potential to change how risk assessment is conducted for obese women, affecting how they are assessed with regard to the likelihood of developing heart disease, diabetes, infertility, cancer and other obesity-associated conditions. Better risk assessments mean more chances for prevention.
Understanding and Controlling Obesity in Women
Q & A with Matthew S. Rodeheffer, Ph.D.

Q: You hypothesize that accumulation of fat under the skin throughout the body and abdominal fat in women may contribute to obesity-related health problems. Can you explain this?

A: We all know that women and men accumulate fat differently, because we can see the difference. Women tend to accumulate more fat under the skin throughout the body than men and this fact was linked to the association of lower levels of heart disease and diabetes in women than men. However, we have recently come to appreciate that women have incredibly high rates of heart disease, and studies have shown that obese women may actually have a greater risk of becoming diabetic than obese men. These findings suggest that fat distribution in women may not protect against the development of these obesity-associated diseases and that it may actually contribute to disease progression.

Q: Why is it important that your study relies on female animal models?

A: Almost all of the mechanistic studies of obesity to date have focused on males. In order to determine why females distribute fat differently than males, it is imperative that we study female models of obesity. In reality, studying the differences between males and females – specifically determining why adipocyte (fat cell) numbers increase in the fat under the skin in females when males do not demonstrate this response – may lead to a better general understanding of the signals that regulate fat mass in obesity.

Q: How will understanding the cellular mechanisms involved in the accumulation of fat help you begin to develop interventions to limit obesity in women?

A: In order to study how something happens you have to know when it happens. Our initial studies have characterized when, during the onset of obesity, fat precursor cells are induced to produce more mature fat cells, leading to increased fat mass. Now that we know when the precursor cells are activated, we can study the activated cells to determine what the signals are that control their activation in obesity.

Once we know the nature of the activating signals, we hope to develop strategies to interfere with the activation of fat precursor cells to potentially mitigate weight gain.

About the Investigator:
Dr. Matthew Rodeheffer

- B.S. University of Washington
- Ph.D. Emory University

A main goal of his laboratory is to determine how white adipose tissue (fat) mass is regulated normally, and how that regulation is altered in obesity. Given the recent appreciation of the obesity epidemic, his study is highly relevant to everyone’s health, but particularly important to women because women suffer greater obesity-related health consequences compared to men.

Women’s Health Research at Yale’s Pilot Project Program provides funding to Yale researchers to generate feasibility data for innovative scientific studies that can advance medical care. These findings are necessary to apply for and obtain larger external grants so the researchers can continue their investigations.

Dr. Rodeheffer’s study is among our 2011 pilot projects and is funded in part by The Grace J. Fippinger Foundation.
Sex Hormones, the Hormone Cycle and Cognition: Junior Faculty Scholar Studies Influence on Women’s Addictions

Scientific studies of addictions have demonstrated a variety of differences between women and men, in areas that include prevalence rates, clinical presentations, craving for substances, and responses to treatment.

Some researchers have proposed that sex hormones (estrogen, progesterone and testosterone) may influence addictive processes through their impact on the subjective effects of addictive substances, such as the extent of the “high,” cravings and withdrawal.

There has been very little research, however, on whether sex hormones influence addictive processes via their effects on cognition, specifically, impulsivity, or the inclination to act without sufficient pre-planning or without adjustment according to the potential consequences of a situation, according to Elise E. DeVito, Ph.D.

As a key piece of her work in the BIRCWH junior faculty women’s health research training program (see box next page), Dr. DeVito is conducting one of the first studies to thoroughly assess the relationship between sex hormones and impulsivity in cocaine dependent and healthy women and men. As part of this study, she is exploring the role that fluctuating levels of sex hormones across the menstrual cycle may play in addiction for women, and how this might factor into the differences in addiction, among women and between women and men.

Dr. Carolyn M. Mazure, Director of Women’s Health Research at Yale, said DeVito’s research focuses on areas that have not received the attention they deserve.

“Not only do we need to look at gender differences, but it is past time to look at differences among women and differences caused by changes over the course of the monthly reproductive cycle,” Mazure said.

Terminology & Definitions

**Addiction/Addictive Behavior**: Any activity, substance or behavior that has become the exclusive focus of a person’s life and has begun to harm the individual or others. Physical addictions often involve psychological components. Addictions are difficult to break and cessation involves withdrawal. Examples: smoking, substance use (alcohol and drugs), overeating and gambling.

**Impulsivity**: Inclined to act on impulse rather than thought. Persons who are overly impulsive often appear unable to curb immediate reactions.

**Estrogen**: Any of several female sex hormones produced primarily in the ovaries, capable of inducing estrus, and developing and maintaining female sex characteristics. It influences the course of ovulation, lactation after pregnancy, aspects of mood, and the aging process.

**Progesterone**: Female hormone that acts to prepare the uterus for reception and development of a fertilized egg.

**Follicular/Preovulatory Phase**: The two weeks during the monthly menstrual cycle before ovulation. Estrogen levels are elevated during this phase.

**Luteal/Premenstrual Phase**: The two weeks after ovulation. During this phase, progesterone levels are elevated.
DeVito, Associate Research Scientist in Psychiatry at Yale School of Medicine, was selected in 2011 from a highly competitive field to participate in the Building Interdisciplinary Research Careers in Women’s Health, or BIRCWH junior faculty scholar program under a $2.5 million federal grant for which Mazure is Principal Investigator.

This unique research training grant supports promising new scientists in launching careers as interdisciplinary investigators in the areas of women’s health and addictive behaviors.

As Mazure notes, addictive behaviors, whether smoking, overeating, or use of drugs, rank among the most prevalent women’s health concerns, and disorders involving these behaviors are associated with some of the top causes of mortality and preventable disease in women. This grant fills a fundamental need for training new investigators who can bridge many disciplines to fully understand addictive behaviors in women, Mazure said.

DeVito chose to focus on addiction to cocaine (specifically “crack” cocaine, which can be smoked) because it shows a robust pattern of sensitivity to sex hormones. However, her research is relevant to women’s addictions more broadly. Her goal is to understand how the brain works in addictions, and how gender differences in brain functions may contribute to gender differences in addictions. Cocaine addiction is simply a logical starting point.

In her study, 40 non-drug using healthy individuals and 40 cocaine users (half women and half men in each group) will be assessed using measures of cognition and impulsivity, as well as blood samples for endogenous levels of sex hormones. Substance use will be assessed through urine and breath testing, questionnaires and interviews. Other health-related measures known to influence sex hormone levels and cognition, such as sleep, mood, and body mass index (an indicator of body fatness), will also be assessed. A genetics component, involving an additional blood sample, will address secondary hypotheses regarding individual differences in the relationship between sex hormones and addiction in the study volunteers.

Aspects of cognition, including impulsivity, decision-making, attention and memory, will be assessed using computerized tasks. Impulsivity is of interest, DeVito said, because a substantial body of research points to high impulsivity as an important vulnerability factor for addiction, and use of addictive substances can lead to further increases in impulsivity. Risky or otherwise impaired decision-making is also thought to contribute to initiation or persistent use of drugs. Therefore, according to DeVito, understanding the biological mechanisms that contribute to variability in these cognitive functions could shed light on the biological factors that make some individuals more likely to develop addictions.

The men will be assessed once and the women will be assessed on two occasions — once in the luteal or premenstrual phase of the monthly cycle and once in the follicular or pre-ovulatory phase of the monthly cycle. Estrogen levels are higher during the pre-ovulatory phase, while progesterone levels are higher in the premenstrual phase.

Training the Next Generation

Building Interdisciplinary Research Careers in Women’s Health (BIRCWH) Scholar Program

A key part of Women’s Health Research at Yale’s mission is to teach students, fellows and junior faculty who want to pursue research in women’s health and gender differences. Our $2.5 million grant from the National Institutes of Health’s Office of Research on Women’s Health, the National Institute on Drug Abuse, and the National Institute on Alcohol Abuse trains and mentors junior faculty scholars to conduct interdisciplinary research on addictive behaviors in women. The five-year program began in 2011 and annually supports four scholars.

The accompanying article, featuring the work of Dr. Elise DeVito, is the second of four BIRCWH Scholar profiles that will appear in our newsletter.
Although the scientific literature is limited in this area, studies have shown that sex hormones and monthly cycle phases modulate aspects of cognition and behavior. Treatment with estradiol, the predominant estrogen during reproductive years, improves spatial working memory performance, for example, in healthy young women and in healthy young men, while high endogenous levels of estradiol are associated with better visual memory performance, DeVito said. During the early premenstrual phase of the monthly cycle, when levels of progesterone are elevated, healthy women perform better on measures of sustained attention, when compared to their performance at other times in the cycle, according to DeVito.

Such modulations of cognition related to hormones and cycle phases, DeVito hypothesizes, may contribute to the start of addictive behaviors, their maintenance, and the ability to stop the behaviors and resist relapse. These processes may contribute to clinical differences in addiction between men and women. With this study, she wants to determine whether the relationships between sex hormones and aspects of cognition differ between women and men, whether they differ within women across their cycles, and whether these relationships are disrupted in individuals who use addictive substances – in this case cocaine, DeVito said.

“I remember being interested in how biology influences behavior,” DeVito said of her evolving interest leading to her current BIRCWH project.

She earned her Ph.D. in cognitive neuroscience at Cambridge University, in England, and began utilizing the latest brain-imaging technologies in her work. DeVito arrived at Yale as a post-doctoral fellow in 2009 and soon became interested in addictions and women's health.

“I realized that there are variables that differ, by gender or by sex, that are related to these aspects of cognition and behavior that we think are relevant to addiction and other psychiatric disorders,” she said. “It was more of a realization over time of how much of an understudied but central issue it really is,” in so many areas of health research, DeVito recalled.

She finds the junior faculty training program’s emphasis on mentoring a very welcome feature. “It’s going to help scientific progress in general,” she said, “if we make effective mentoring an important and valued part of everyone’s job.”

Naturally, DeVito hopes to become a mentor herself someday.

The practical benefit of her research is that a better understanding of these relationships and gender differences related to hormones and cognition may lead to improved prevention and treatment strategies for addictive behaviors in women, she said.

DeVito has long been interested in science and the biology at work in the functioning of the brain. Her curiosity was first sparked in middle school when she went to a university library to read as much as she could for a paper on schizophrenia. By the time she was studying biology in an advanced placement high school course, she knew she wanted a career as a researcher in neuroscience.
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Women’s health has become a central topic in our nation’s discourse. It seems everyone is talking about it.

In my view – and I’ve seen and heard a lot as an advocate for women’s health – one of the best ways to play a positive role in this ongoing discussion is to support the discovery of new scientific information that can be translated into improved health for women.

This has been the laser-like focus of our center since its inception in 1998. Now as never before, your contribution to Women’s Health Research at Yale can make a statement in favor of new knowledge to propel gender-specific medicine forward.

Given the monumental challenges our health care system is facing, it is imperative that we take advantage of what we know – and what we can learn – by initiating and continuing studies on the many gender differences that exist in health and disease.

This will benefit everyone’s health.

With your help, we will surpass the most ambitious Annual Appeal goal in Women’s Health Research at Yale’s history by the time the fiscal year ends June 30th. Private contributions large and small are essential to our continued success.

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In the News

Council News...

Dinny Wakerley Joins Council

Diana S. Wakerley, who recently retired from PricewaterhouseCoopers after a distinguished career in accounting and training tax professionals, is the newest member of our advisory Council. Dinny, as she is known to friends and family, served on the Executive Committee for our Women of Vision Award event in 2005 which honored Gloria Steinem and founding Council member Roslyn Milstein Meyer. Dinny played a key role organizing this highly successful event. She earned her bachelor’s degree from Connecticut College and her M.B.A. from Weatherhead School of Management, Case Western Reserve University. We welcome her enthusiasm, and her skills and expertise as a strategic thinker and organizational manager.

Council Hears Update on Stem Cell Study

Drs. Julie Ann Sosa and Sanziana Roman are members of a four-woman interdisciplinary team conducting a unique Pilot Project Program study funded by our center. Accompanied by Roman, Sosa gave an engaging presentation and update of this investigation involving stem cell development to our Council and guests on April 2nd.

The team, which also includes Drs. Diane Krause, Associate Director of the Yale Stem Cell Center, and Betty Lawton, a stem cell scientist who was recruited to Yale specifically for this project, is developing parathyroid cells from federally-approved human embryonic stem cells to replace damaged or inactive parathyroid cells.

The parathyroid glands (located in the neck near the thyroid gland) regulate calcium levels and are vital to maintaining bone health, heart rate and other important functions. These glands can malfunction or are often removed or injured when surgeons are removing a cancerous thyroid, resulting in hypoparathyroidism. This condition results in calcium imbalance that can radically lower quality of life and necessitate frequent oral calcium replacements that can have significant adverse effects.

This project holds special importance for women, as 75 percent of thyroid and parathyroid disease occurs in women, and thyroid cancer is the number one cancer among women under 30 and the type of cancer with the fastest growing incidence rate among women, according to Sosa.

Press Notes...

Media Due-Diligence Lacking on Nicotine Replacement Report

Millions of smokers have used nicotine replacement therapies to help wean themselves off cigarettes since the FDA approved these treatments in the 1980s and 1990s.

More than 100 clinical trials have endorsed their efficacy when the nicotine replacement therapies were used in combinations, doses and durations that matched individual patient needs, and when coupled with effective behavioral strategies.

So the media hype over a recent Harvard School of Public Health study concluding that nicotine gum, skin patches and the like don’t work was a big disappointment to those who know the caveats involved in ensuring these therapies are effective.


The population-based study in question, published in the journal Tobacco Control, concluded that persons who had quit smoking relapsed at equivalent rates, whether they used nicotine replacement therapies to aid their quitting or quit
without the use of medications. Yet this result is *exactly what scientists who study smoking cessation expect.*

Nicotine replacement therapies are aids in quitting, and they work well – doubling the odds of success – when used according to directions. However, these therapies are not aids in avoiding relapse to smoking.

“Staying quit, once you stop medication is a different issue,” says Sherry McKee, Ph.D., Yale Associate Professor of Psychiatry and Director of the Yale Behavioral Pharmacology Laboratory.

As for the media’s treatment of the study, McKee points out from a scientist’s perspective – and I will chime in as a veteran journalist – it is simply inappropriate to base sweeping conclusions on any single study. A thorough reading of this study reveals serious limitations, according to McKee and other smoking-cessation experts. Once again, my advice is to proceed with caution when headlines seem to shout black and white conclusions about a medical study.

**In the News…**

*Effects of Stress Explored in Scientific American*

Dr. Mazure and two Yale colleagues, Drs. Amy Arnsten and Rajita Sinha, had an enlightening article published in the April issue of *Scientific American* on how stress can overwhelm the brain’s self-control circuitry, leading to mental paralysis. The beautifully-illustrated article, entitled “This is Your Brain in Meltdown,” explains how stress “sets off a series of chemical events that weaken the influence of the prefrontal cortex,” the brain’s executive control center. Investigators, the article says, “are now not just trying to understand what happens in your head when you freeze but also developing behavioral and pharmaceutical interventions to help you keep your composure.”

These areas of inquiry are among those of special importance to women’s health and our research. Stress is a more potent pathway to depression for women than men, as Dr. Mazure discovered in some of her early research. And women experience depression at double the rate for men.

**Investigator Speaks at National Conference**

Dr. Andrea Weinberger, Assistant Professor of Psychiatry, attended the Society for Research on Nicotine and Tobacco’s 18th Annual Meeting in Houston, Texas, in March, and presented the findings of her research on depression and smoking.

In a nationally representative survey of women and men, smokers with current or past depression at the start of the study were more likely to still be smoking three years later, and former smokers with current depression at the start were more likely to relapse, Weinberger said.

Depression exerted the same influence over smoking status for women and men. However, because women experience depression at twice the rate for men, the relationship between depression and smoking influences women more than men. It is crucially important, Weinberger said, to consider both depression and gender when designing smoking cessation programs.

**Upcoming Workshop…**

*Department of Psychiatry, Division of Women’s Behavioral Health – Annual Grand Rounds*

“Hormone Therapy and Cognitive Function: A Scientific Update 10 Years After the WHI”

Visiting Speaker: *Pauline Maki, Ph.D.*
Professor Psychiatry & Psychology
University of Illinois at Chicago

Friday, May 25, 2012
10:15—11:45 am

CT Mental Health Center, 34 Park St, New Haven CT
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