

Harvard Nutrition Obesity Research Center

Start Date: 1994

Status: Ongoing

Funding Agency: NIDDK

Website: <http://www.hms.harvard.edu/nutrition>

Organization and Goals

The Harvard Nutrition Obesity Research Center (NORC-H) goals are to:

- Promote research in basic areas relevant to clinical nutritional science
- Promote the study of clinical nutrition within the Harvard Medical School (HMS), Harvard School of Public Health (HSPH), and Harvard teaching hospitals
- Promote interactions among scientists exploring diverse fields that share relevance to clinical nutrition
- Develop “state of the art” approaches to nutrition research
- Attract basic investigators to the study of nutrition
- Promote an environment and mechanism to develop new investigators focused on clinical nutrition research

Core Laboratories

Administrative Core: W. Allan Walker, M.D., Director

Biostatistics: David Schoenfeld, M.D., Director

Genomics and Proteomics: Frederick Ausubel, Ph.D., Director

Cell Biology: Haining Shi, D.V.M., Ph.D., Director

Mass Spectrometry: Tom Jaksic, M.D., Ph.D., Director

External Advisory Group Members

- **Dennis Bier, M.D.**, Professor of Pediatrics, Director of the USDA Children’s Nutrition Research Center, Baylor School of Medicine, Houston, TX (Chairman)
- **Curberto Garza, M.D., Ph.D.**, Provost and Dean of Graduate Studies, Boston College, Boston, MA
- **Robert Russell, M.D.**, Professor of Nutrition, Director of USDA Human Nutrition Research Center on Aging (Director Emeritus), Tufts Medical Center, Boston, MA
- **Virginia Stallings, M.D.**, Professor of Pediatrics, University of Pennsylvania; Chief, Nutrition Section, Division GI and Nutrition, Children’s Hospital of Philadelphia, Philadelphia, PA
- **Steven Zeisel, M.D., Ph.D.**, Kenan Distinguished University Professor, Chairman (Emeritus), Department of Nutrition, University of North Carolina (UNC) School of Medicine and Public Health; Director, NORC at UNC-Chapel Hill, Chapel Hill, NC
- **Nevin Scrimshaw, M.D., Ph.D.**, M.I.T. Professor (Emeritus); President, International Nutrition Foundation

Pilot Feasibility Studies (2009–2010)

Katherine E. Gregory, Ph.D., RN, Assistant Professor, Boston College; Nurse Scientist, Brigham and Women’s Hospital (BWH)—“*Metabolic aspects of necrotizing enterocolitis in premature infants*”

Necrotizing enterocolitis (NEC), an inflammatory gastrointestinal disease, is among the most frequent and significant complications of prematurity. It is both life threatening and associated with significant long-term morbidity including short-gut syndrome, complications related to parenteral nutrition, and aberrant growth and development. One of the greatest challenges in caring for premature infants at risk for NEC is its sudden and often unpredictable onset. Initial clinical signs of NEC are often vague, nonspecific, and, therefore, easily misinterpreted by the neonatal intensive care team. Furthermore, once clinical signs of NEC are present, the progression of the disease is rapid. Research on NEC has explored the inflammatory cascade and factors related to enteral feeding with breast milk. Breast milk is one of the few known protective mechanisms against NEC; however the mechanism of action is not fully understood. We suspect that the breast milk fed to infants who develop NEC may differ in composition from the breast milk fed to infants who do not develop NEC. In this study, we aim to initiate sample collection of breast milk in an effort to build a long-range specimen repository for later analysis. In sum, research pertaining to NEC is needed to answer questions in three areas: (1) What is the protective mechanism of breast milk against NEC and how does early nutrition play a role in the development of this disease? (2) What is the mechanism under which NEC evolves and what are useful predictors of the disease? (3) What measures can be successfully implemented to prevent and treat NEC in premature infants? All three areas of research would benefit from an early disease prediction capability and more effective strategies to diagnose and treat the disease. In this study, we will build on the National Institutes of Health (NIH) established bioinformatics and analytical platform in the laboratory of Dr. Kristal, an investigator in the NORC-H, to achieve the following research aim: Conduct feasibility of metabolomic analyses using fecal matter obtained from premature infants and study differences in the metabolites expressed in premature infants who develop NEC and those who do not develop NEC. The central hypothesis is that the fecal elimination of specific metabolites will differentiate a population of premature infants who develop NEC from those who do not develop this devastating gastrointestinal disease. The use of fecal samples for biochemical prediction techniques including metabolomic analyses has the advantage of a noninvasive approach that would not deplete the premature infant of an already limited blood volume.

Ho-Jin Koh, Ph.D., Instructor in Medicine, HMS; Research Associate, Joslin Diabetes Center—“*The effects of type 2 diabetes on SNARK in Skeletal Muscle*”

For individuals with type 2 diabetes, physical exercise is vital in the maintenance of glucose homeostasis, due to its ability to increase glucose uptake in skeletal muscle. The molecular signaling mechanisms by which exercise regulates glucose metabolism in skeletal muscle are not fully understood. Several years ago, AMP-activated protein kinase (AMPK) was proposed as the key regulator of exercise-stimulated glucose uptake. However, recent studies suggest that additional, AMPK-independent mechanisms are involved in this biological process. We have recently studied the protein sucrose non-fermenting AMPK-related kinase (SNARK), which is

activated by metabolic stress. We found that exercise and muscle contraction increase SNARK activity in mouse skeletal muscle. Overexpression of a dominant-negative SNARK and knockout of SNARK significantly decreased exercise-stimulated glucose uptake but had no effect on insulin-stimulated glucose uptake. Furthermore, SNARK expression was also decreased in the muscle of db/db mice and mice fed on a high fat diet. These groundbreaking results identify SNARK as a novel mediator of glucose uptake in skeletal muscle. There have been no studies of SNARK in humans, although we have recently shown that SNARK is expressed in human muscle. The goal of this project is to determine if exercise increases SNARK activity in human skeletal muscle and if the regulation of SNARK is altered in the skeletal muscle of patients with obesity or type 2 diabetes. Furthermore, we will also investigate if caloric restriction regulates SNARK expression or activity in human skeletal muscle. This study will be done in collaboration with Dr. Jorgen Wojtaszewski of the Copenhagen Muscle Research Center, world leader in the study of diabetes and exercise metabolism in human skeletal muscle, and Dr. Anders Thorell of Huddinge University Hospital and Center of Gastrointestinal Disease, world leader in the study of diabetes and caloric restriction in human subjects. This will be the first study of the role of SNARK in regulating glucose homeostasis in humans and will determine its usefulness as a potential target for the treatment of type 2 diabetes.

Elizabeth A. Lawson, M.D., Instructor in Medicine, HMS; Assistant in Medicine, Massachusetts General Hospital—*“The genetics of appetite-regulation and stress hormones in anorexia nervosa”*

Anorexia nervosa (AN) is an increasingly common disorder of young women that leads to severe nutritional deprivation and a physiologic state of prolonged starvation. This study involves a multidisciplinary approach to understanding the contribution of appetite-regulating and stress hormones to the development of AN. This study proposes a strategy that examines the confluence of the physiology of these appetite and stress hormones and a preliminary investigation of polymorphisms in key genes involved in these pathways.

AN is a disease characterized by self-induced starvation and complex genetic and environmental etiologic factors. Family studies document a 10-fold risk of AN among first-degree relatives, and a Swedish twin study reported a heritability of 56%. A complex disorder, AN likely reflects the influence of multiple genes of modest effect interacting with environmental influences. Hormonal abnormalities identified involving appetite regulation and response to stress may increase susceptibility to AN. Although some alterations in these hormones are expected adaptations to starvation, others are paradoxical, and persistence despite recovery suggests a potential etiologic role. Altered hunger and satiety perception have emerged as candidate physiologic characteristics in AN and appear to have significance in maintaining low weight. Gastrointestinal symptoms are prevalent. Disturbed satiety may trigger and sustain dietary behaviors.

This study explores the genetic of appetite-regulating and stress hormones in AN. The assessment of AN-related physiology will also allow the researchers to define biological phenotypes that will enhance the power of the genetic analyses. To the researchers' knowledge, no published genetic studies have examined the association between specific genes and physiologic features of AN, making this a novel, albeit exploratory, set of analyses.

Di Meng, M.D., Ph.D., Instructor in Pediatrics, HMS; Research Associate, Massachusetts General Hospital—“Mechanism of UEA1 oral therapy from recovery from intestinal inflammation”

Inflammatory bowel disease (IBD) is caused by excessive tissue inflammation by microbiota after injury. However, the mechanisms and etiology of IBD are unknown. The role of normal microbiota and fucosylated intestinal mucosa during the recovery from mucosal injury is not understood. Therefore, this study has begun to investigate the recovery rate from Dextran Sodium Sulfate (DSS)-induced acute intestinal injury in bacteria-depleted and conventionally raised mice. Unlike conventionally raised mice, bacteria-depleted mice fail to recover from intestinal injury. Intestinal toll-like receptor-4 (TLR4) is key in the protection mediated by the gut microbiota and we have shown that, in the bacteria-depleted mice, TLR4 is highly fucosylated. Also, oral supplementation with Ulex europaeus agglutinin-1 (UEA-1), a specific ligand for α 1,2-fucosylated glycans such as intestinal TLR4 in BD mice, rescues bacteria-depleted mice after DSS-induced injury. Similarly to gut microbiota, oral UEA-1 therapy was able to recruit neutrophil via fucosylated TLR4-dependent monocyte inhibitory peptide 2 (MIP2) induction in the BD mice, but this was not observed in TLR4 and MyD88 knockout mice. However, the cellular and molecular mechanism by which oral UEA-1 therapy activates TLR4-dependent signaling is undefined. TLR4-mediated crosstalk also protects the host from DSS-induced colitis: TLR4^{-/-} mutants were unable to generate fucosylated gut and failed to recover from DSS-induced colitis. Therefore, the researchers hypothesize that TLR4-mediated communication between microbiota and colonic epithelium leads to a highly fucosylated mucosa that is essential for recovery from enteric insult and mucosal restitution. Oral UEA-1 therapy activates fucosylated TLR4-dependent mechanisms to recruit neutrophils and hence promote recovery from colitis. Therefore, the specific aims are to (1) determine the cellular mechanism by which dietary supplementation with UEA-1 rescues BD mice from injury; and (2) define which fucosylated TLR4-induced chemoattractants are necessary for neutrophil recruitment for DSS-induced colitis recovery in BD mice. This study hopes to elucidate the cellular and molecular pathways necessary for recovery from colitis.

Yaakov Nahmias, Ph.D., Instructor in Surgery and Bioengineering, HMS; Department of Surgery, Massachusetts General Hospital—“Study of the Hepatitis C virus (HCV) antiviral properties of polymethoxyflavones”

The hepatitis C virus (HCV) affects over 3% of the world population and is the leading cause of chronic liver disease worldwide. HCV infection develops into a chronic condition in over 70% of patients, ultimately leading to cirrhosis and hepatocellular carcinoma. Current standards of care consist of interferon and ribavirin, a treatment previously shown to be effective in only 50% of the cases. In addition, interferon treatment is poorly tolerated and is associated with significant side effects. Therefore, there is a pressing need for the development of alternative treatment strategies to combat HCV infection. Recently, this study's group demonstrated that HCV is actively secreted by hepatocytes while bound to very low density lipoprotein (VLDL). Therefore, dietary supplements previously shown to block VLDL secretion would exert a similar effect on HCV. One such supplement is the citrus flavanone naringenin, an aglycon of the grapefruit flavonoid glycoside naringin, which is responsible for the bitter taste of grapefruit juice. Naringenin has been previously shown to inhibit VLDL secretion in hepatocytes. In support of this hypothesis, the researchers have recently demonstrated that naringenin blocks HCV

secretion/infectivity of the virus in the JFH1/Huh7.5.1 full lifecycle model of HCV infection. The hypothesis is that HCV is actively secreted by the liver of infected patients while bound to VLDL, and that the grapefruit flavonoid naringenin could be used to block HCV secretion and, therefore, lower the circulating viral titers. The novel aspect of this proposal is the ability to modulate HCV infection/secretion by influencing cellular cholesterol and fatty acid metabolism using dietary supplements. This pilot feasibility project will study the pharmacokinetics of a single-dose naringenin treatment and its effect on circulating VLDL and HCV titer in infected patients. In addition, this work will provide important information on the role of cholesterol and fatty acid metabolism on the development of HCV infectivity *in vivo*.

Funding Derived From Previous Pilot and Feasibility Studies

R01 HD12437 (PI: W. Allan Walker, M.D.)

02/01/09–01/31/14

NIH

The effect of colostrum on gut maturation and host defense

This grant was recently re-funded. It will use the Genomics Core of the NORC-H to examine fetal human intestine, using isolated fetal enterocytes, for the effects of breast milk factors (TGF- β , oligosaccharide and omega-3-fatty acids) on anti-inflammatory genes.

R56 AI089700 (PI: Bobby Cherayil, M.D.)

07/01/10–06/30/11

NIH

Cross talk between iron metabolism and intestinal inflammation

Dr. Cherayil was funded as a type 2 Pilot and Feasibility (P/F) awardee to study iron metabolism in bacteria (*Salmonella*) gastroenteritis. He has carefully determined the cellular role of iron in the pathogenesis of *Salmonella* infection. The observations made in this P/F have been helped by the Cell Biology Core and have led to an R01 grant.

1K23HD060066–01 (PI: Amy DiVasta, M.D.)

01/05/09–12/31/13

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), NIH

Biomechanical stimulation and skeletal health in adolescents with anorexia nervosa

Dr. DiVasta was a recent P/F awardee who, through this support, was able to obtain a K–23 award on the same subject. She used the Statistics Program in her studies.

R21–AT005119 (PI: Michael Donnino, M.D.)

12/01/09–11/30/12

NIH

Thiamine as a metabolic resuscitator in septic shock

Dr. Donnino, an Emergency Room doctor with an interest in clinical research, was recently awarded a P/F from the NORC-H. As a result of the data obtained from this study he has applied for an R21. He is determining the clinical role of thiamine in the treatment of septic shock in human patients.

R01 HD060827–01 (PI: Madhu Misra, M.D.)

07/01/09–06/30/14

NIH/NICHD

Fat mediated modulation of reproductive and endocrine function in young athletes

Dr. Misra's research to date has focused on clarifying neuroendocrine causes of anorexia nervosa, body composition, and bone alterations in conditions spanning the nutrition spectrum in teenage athletes in order to understand the impact of subtle energy deficit states on the hypothalamus-pituitary-gonada (H-P-G) axis and bone accrual.

R01 HD05926 (PI: Nanda Nanthakumar, Ph.D.) 02/12/09–01/31/14

NIH

Maturation of intestinal innate immunity and NEC

Dr. Nanthakumar received a P/F three years ago to define the protective mechanisms of secreted products from clinically protective probiotics in NEC. Using the Genomics and Cell Biology Cores, he has been able to show that these probiotics reduce the excessive IL-8 inflammatory response to stimuli by activating the maturation of the innate immune response genes in human fetal intestine.

R01 CA050385 (PI: Walter Willett, M.D.) 08/01/09–05/31/14

NIH/NCI

Risk factors for breast cancer in young nurses

Dr. Willett, using the database from the Nurses Health Study at Harvard, will study the epidemiologic factors in diet that affect the risk of breast cancer.

R01 AG031881 (PI: Simin Meydani, M.D.) 07/01/10–06/30/15

NIH (pending)

Zinc intervention in elderly for prevention of pneumonia

Dr. Meydani has begun an intervention study in an elderly population to determine the protective effect of zinc supplement with regard to infections.

R01 DK082427 (PI: Haining Shi, DVM, Ph.D.) 04/01/10–03/31/15

NIH

Immunomodulatory effects of Helminths on mucosal immunity

Dr. Shi, the new Director of the Cell Biology Core, has obtained R01 funding to study the protective role of Helminths, an intestinal parasite, in food allergy.

R01 AI081845 (PI: Wayne Shreffler, M.D.) 12/01/09–11/30/14

NIH/ National Institute of Allergy and Infectious Diseases

Relationship between mouse antigen exposure and immune response

Dr. Shreffler has obtained new R01 funding to study food antigens in a mouse model for allergy.

CA 128963 (PI: Joann Manson, M.D.) 09/01/09–08/31/14

NIH

The vitamin D and omega-3 trial

Dr. Manson, the Director of Women's Health at Harvard, has begun a clinical/epidemiologic trial to determine if vitamin D and omega-3 fatty acids decrease the incidence of cancer in women.

R01 HD043869 (PI: Catherine Gordon, M.D.) 09/01/10–08/31/11

NIH

Hormonal replacement in women with anorexia nervosa

Dr. Gordon, an expert in bone metabolism in adolescent patients, was recently funded to study the role of hormone replacement in the osteoporosis of women with anorexia nervosa.

R01 HD034586 (PI: Matthew Gillman, M.D.; Co-PI Elsie Taveras, M.D.) 06/10/10–05/31/15
NIH

Pre- and peri-natal predictors of childhood obesity

Dr. Elsie Taveras has become an investigator in the NORC-H by obtaining a R01 to determine the pre- and postnatal predictors of childhood obesity.

Scientific Advances/Accomplishments

The NORC-H's productivity is underscored by specific advances in nutrition-relevant studies made by NORC-H investigators and P/F recipients, supported by resources from the Harvard Clinical and Translational Science Center (CATALYST). These advances have been accomplished by collaboration among NORC-H investigators with support of the NORC-H Core laboratories. Several of the areas of advancement are summarized in this section.

Associations of gestational weight gain with short- and longer term maternal and child health outcomes. *Am J Epidemiol.* 2009;170(2):173–80. **PMCID: PMC2727269.** As part of a multicenter perspective clinical epidemiologic study, Dr. Gillman and his research team have begun to determine the role of intrauterine and perinatal nutrition on neurodevelopment in a large number of infants followed from conception. The researchers are particularly interested in omega-3 fatty acid supplementation during pregnancy.

Reducing endoplasmic reticulum stress through a macrophage lipid chaperone alleviates atherosclerosis. *Nat Med.* 2009;12:1383–91. **PMCID: PMC2790330.** Dr. Gokhan Hotamisligil, a NORC-H investigator, and his research team have identified a new lipid hormone produced in adipose tissue that contributes to the metabolic syndrome occurring in obesity.

Modulation of PGC-1 co-activator pathways in brown fat differentiation through LRP130. *J Biol Chem* 2010 (in press). Dr. Bruce Spiegelman, a NORC-H investigator, and a talented group of postdoctoral fellows continue to identify cellular and metabolic pathways in brown fat that distinguishes its function from other forms of adipose tissue.

Plasma sex hormones and the risk of developing type 2 diabetes in women. *Diabetologia.* 2008;50:2076–2084. Dr. Manson, head of the Women's Health Center at the Brigham and Women's Hospital and the Harvard School of Public Health, has conducted a large clinical epidemiologic trial to determine the role of sex hormone levels in obese women and the development of type 2 diabetes.

A 22-year prospective study of fish, N-3 fatty acid, intake in colorectal cancer risk in men. *Cancer Epidemiol Biomarkers.* *Prev* 2009;19:1142–1150. Using a large patient cohort, (the Physician's Health Study), Dr. Willett and his nutritional epidemiologists have identified an association between colorectal cancer risk in men and the long-term intake of N-3 fatty acid from fish consumption. This observation helps in the recommendation for taking dietary supplements.

Age-associated changes in immune and inflammatory response: role of nutritional intervention. *J Leuk Biol.* 2009;86:900–914. Dr. Meydani, a nutritional immunologist and Director of the U. S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University School of Medicine, has begun to determine those nutrients in the elderly population that maximally affects immunologic function and protects against infections and cancerous disease.

Adrenal glucocorticoid and androgen precursor dissociation in anorexia nervosa. *J Clin Endocrinol Metab.* 2009;94:1367–71. PMID: PMC2682472. Dr. Lawson, a recent P/F awardee, has begun to determine the hormonal effects of anorexia nervosa.

Specific Accomplishments

Division of Nutrition

In 1996, the Faculty Council at HMS established a Division of Nutrition (DON). The DON is charged with organizing the nutritional community at HMS and in its major teaching hospitals (MGH, Brigham & Women's, Beth Israel Deaconess, and Children's Hospital) to provide teaching of nutrition at the undergraduate medical school level and at the postgraduate level. In addition, the DON has the responsibility for promoting nutrition basic and clinical research and postgraduate education. Dr. Walker is the Director of the DON and George Blackburn, M.D., Ph.D., is its Associate Director. Dr. Walker has concentrated over the last few years on generating foundation and industry support to help fund additional P/F and educational programs for undergraduate medical students and postgraduate practicing doctors. This effort has resulted in an educational grant from the Nestle Foundation to fund E-education (electronic education using the Internet) for the HMS students as a prototype for other medical school curricula and to begin a Continuing Medical Education E-learning program in pediatric nutrition for worldwide postgraduate medical education. The DON works closely with the NORC-H and the Department of Nutrition at HSPH. This association has helped broaden the research base of NORC-H and has generated many novel P/F applications. The DON has recently completed a Bristol Myers Unrestricted Research Grant to expand the P/F Program and provide additional funds for postgraduate education.

Division of Complementary and Alternative Medicine at HMS

Dr. David Eisenberg, at BIDMC, is the new director of this division. He works closely with the NORC-H and the DON in undergraduate teaching and clinical research projects. As a result of the investigators and core facilities in the NORC-H, Dr. Eisenberg will apply for a Complementary and Alternative Medicine Center grant from the NIH next year. Dr. Walker is on the new division's executive committee. Members of both divisions are eligible to apply for pilot feasibility funding. A joint project on alternative medicine/nutrition treatment of aged patients will be funded by a private foundation. A joint project between this Division at the Brigham and Women's Hospital and the DON to establish a "Kitchen-Clinic" has been used to instruct patients in appropriate diets for a variety of chronic illnesses and to instruct practicing primary care physicians in the importance of a healthy diet to maintain good health. The DON and the Division of Complementary and Alternative Medicine also jointly sponsor summer fellowships for HMS students to follow chronically ill patients regarding healthy diet.

Women's Health Initiative at Harvard

The Division of Preventive Medicine at Brigham and Women's Hospital is headed by Dr. Joann Manson. In 2002, Dr. Manson became the Co-Director of the Connors Center for Women's Health and Gender Biology at the Brigham and Women's Hospital. In 2003, she was the first recipient of the newly established Elizabeth F. Brigham Endowed Professorship in Women's Health at HMS. After participating in the NORC-H annual symposium several years ago on "Nutrition and Women's Health," Dr. Manson joined the NORC-H as an investigator. As a result of this move, NORC-H has attracted additional investigators (**Gillman, Christen, and Buring**) and Associate Investigators (**Tavares and Oken**) into the Center. **Dr. Christen** received a pilot feasibility award from the Center last year. These additions to the Center have allowed us to establish a new program of investigators in our biomedical base. Dr. Oken, a P/F recipient, has recently obtained R01 funding from the NIDDK.

In 1995, Stanley Lewis, M.D., Chief of Clinical Cardiology at HMS, and Isil Yasar, Ph.D., Manager of Cardiology at HMS, asked Francine Welty, M.D. and Ph.D., who was then at Western Reserve University in Cleveland, to be the Director of the Women's Cardiovascular Health Program at Deaconess Hospital and to utilize her expertise in preventive cardiology in women including the use of hormone replacement therapy and lipid-lowering drugs. She has published on gender differences in coronary angioplasty using the very large Deaconess Hospital database. In addition, she has published invited reviews on gender differences in coronary heart disease and use of nutrition to treat hyperlipidemia. When Dr. Welty, working with Dr. Walker, successfully applied for a Nutrition Academic Award from NIDDK (**K07 DK029474**) as part of the DON, she was introduced to the NORC-H. As a result of joining the Center as an associate investigator, she successfully competed for a P/F grant which has led to RO1 funding and investigator status in the NORC-H renewal. When the Deaconess-Beth Israel merger occurred, Dr. Welty became the Director of Cardiovascular Care for Women at the West Campus. She also consults on patients in the Cardiovascular Health and Lipid Center at the Beth Israel-Deaconess Medical Center (BIDMC) and focuses on nutrition management of hyperlipidemia. *This important new addition on the management of hyperlipidemia to the NORC-H priority programs adds to our strong theme in lipid metabolism and prevention of cardiac disease in the Biomedical Research Base. Dr. Welty also teaches electives for fourth year HMS students to determine the role of diet in cardiac health.*

Obesity Programs

HMS and the Harvard School of Public Health have multiple programs that deal with obesity prevention, weight reduction, and the prevention and care of metabolic syndrome including type 2 diabetes. Programs at the three teaching hospitals—BIDMC, Massachusetts General Hospital (MGH), Children's Hospital (CH)—are summarized below.

Center for the Study of Nutrition and Medicine at BIDMC

Now in its eighth year of operation, the Center for the Study of Nutrition and Medicine (CSNM) has continued to advance the interdisciplinary field of nutritional medicine. The Center has supported the Nutrition Screening Initiative, which focuses on nutritional screening in the elderly, as well as the Massachusetts Medical Society's Nutrition Committee and the U.S. Department of Health and Human Services' effort to establish healthy weights for adult

Americans. In keeping with the priority of technology transfer, the Center's efforts are communicated both in professional journals and lay publications, including the *New England Journal of Medicine Health News*. As a result of the NORC-H enrichment programs, **Dr. Blackburn and Lee Kaplan, M.D. and Ph.D., at MGH** have combined forces to begin a large clinical trial on the role of calcium addition and reduction in sucrose in orange juice in the treatment of overweight patients. In addition, **Jin Rong Zhou, Ph.D.**, a junior faculty member in the Center for the Study of Nutrition and Medicine, obtained a P/F award and has subsequently received R01 funding on the same topic. The long-term focus in the Nutrition Metabolism Laboratory of Dr. Blackburn's research is to study the role that diet and nutrition may play in the prevention and treatment of certain types of cancer, such as breast, prostate, pancreatic, and bladder cancers, and to investigate and elucidate the mechanisms of action of active dietary and nutritional components. Several research projects are aimed at investigating the potential effects of certain dietary bioactive components on prevention and treatment of breast cancer, prostate cancer, and bladder cancer. This important research strategy is to integrate several research components that are essential for effective identification, efficacy evaluation, and mechanism elucidation of nutritional and natural active compounds in a synergistic manner. The integrated system described above includes application of clinically relevant tumor animal models to evaluate the efficacies of dietary/nutritional regimens and to elucidate the underlying cellular, molecular, and epigenetic mechanisms of active components actions, the use of bioactivity-guided fractionation and purification approaches to further identify anti-cancer active natural components, and to search for potentially novel risk factors of cancer development and progression, aiming at designing novel nutritional regimens for effective cancer prevention. **Dr. Blackburn and Bruce Bistrain, M.D., Ph.D.**, from the Nutrition Programs at BIDMC provide an added commitment to the NORC-H application to further broaden the nutrition enrichment base. These established clinical nutrition investigators will add to our Biomedical Research Base and utilize the **GCRC at BIDMC and the Mass Spectrometry Core at the NORC-H**.

Obesity Center at MGH

Dr. Kaplan is the director of the newly formed Massachusetts General Hospital Weight Center. The goal of this combined research and clinical Center is to identify means of stratifying obesity into distinct clinical syndromes. Clinical programs of the Center include comprehensive evaluation and multidisciplinary care for adults and children with obesity. Most patients seen in the Center participate in one or more components of the Center's clinical research activities. The main focus of clinical research during the initial establishment of the Center is the design and development of an Obesity Registry Database and a Tissue, DNA, Cell, and Serum Repository. Now that the database and repository are established, these clinical resources are used to support epidemiological, genetic, and clinical studies of obesity and its treatment. **Alison Hoppin, M.D.**, a pediatric nutritionist, has worked with Dr. Kaplan to determine nutritional factors *in utero* that predict childhood obesity. She has had a K08 award (**K08 DK02754**) and Center P/F funding to study this problem in animal models and plans to apply for an R-21 award to complete the observations. Dr. Kaplan has also been added to the Executive Committee to represent obesity programs within the Harvard medical community. His current study is the biologic set point of bypass surgery for obesity.

Optimal Weight for Life (OWL) Program at CH

The OWL Program at CH in Boston is a multi-disciplinary care clinic dedicated to the evaluation and treatment of children who are overweight. **David Ludwig, M.D., Ph.D.**, leads the team composed of physicians, nurse practitioners, dietitians, and a psychologist, specializing in endocrinology, gastroenterology, and behavioral medicine. Their goal is to provide state-of-the-art care for overweight children, to develop innovative treatments for pediatric obesity through clinical research, and to promote public awareness and prevention effects. Since its inception in June 1997, the OWL Program has treated over 700 children from infancy through adolescence and have sponsored several major clinical research protocols. These protocols on the GCRC at CH will also utilize the **Mass Spectrometry Core**. **Cara Ebbeling, Ph.D.**, an Assistant Professor of Pediatrics at HMS, is a P/F awardee and associate investigator in the NORC-H. She works closely with **Dr. Ludwig**.

AIDS

Significant progress has been made over the prior year among investigators in the Program in Nutritional Metabolism, led by Steven Grinspoon, M.D. Investigation of the cardiovascular consequences of acquired visceral adiposity and subcutaneous fat loss in HIV- infected patients with the lipodystrophy syndrome continued to be a major research focus. In this regard, use of physiological growth hormone (GH) among relatively GH-deficient patients was shown to reduce visceral fat almost 10% over 18 months, without any effects on subcutaneous fat. This selective effect of low-dose GH on visceral fat suggests a new treatment strategy for visceral obesity. Program researchers extended their investigations to patients with generalized obesity and determined that such patients have a marked reduction in GH in proportion to excess visceral adiposity, and that relative GH deficiency might contribute to increased CVD risk independent of total fat mass per se. Investigation of Growth Hormone Releasing Hormone to increase endogenous pulsatile GH is also now underway both in HIV-infected patients with excess visceral adiposity and non-HIV infected patients with generalized obesity.

Obesity Prevention Program

Dr. Gillman, a medicine-pediatric nutritional epidemiologist, directs the Obesity Prevention Program at the Department of Ambulatory Care and Prevention, HMS/Harvard Pilgrim Health Care. The foci of the Program are using epidemiologic methods to discovering the origins of obesity at the earliest stages of human development, to mount state-of-the art prevention interventions in early life, and to evaluate related questions in health services and health policy. Dr. Gillman has won mentoring awards from HMS and Harvard School of Public Health. He, his junior faculty (including Center faculty Drs. Oken and Taveras), and trainees have published widely on how the pre- and perinatal nutritional environments influence chronic nutrition-related diseases over the lifespan, including obesity, diabetes, cardiovascular disease, asthma, and cognition. This team has secured P/F funding and will use the **Mass Spectrometry Core** and Biostatistics Program. Several medical students interested in nutrition have taken summer fellowships sponsored by the DON with Dr. Gillman and his associates. One of them, **Ms. Jenny Stillwagon**, was awarded a predoctoral fellowship and worked productively for most of the year following her summer fellowship year with **Drs. Oken and Gillman**. **Ms. Sonia Miller**, a senior medical student, has worked closely with Dr. Oken on nutrition during pregnancy.

International AIDS Program at HSPH

Wafai Fawzi, M.D., Ph.D., a Professor of Nutrition at HSPH and an investigator in a NIH-supported study of protective nutrient effects in the prevention of AIDS in offsprings of HIV positive mothers in Tanzania, has become a member of NORC-H. Preliminary results of the study have recently been published in the *New England Journal of Medicine*. Dr. Fawzi was attracted to the Center after an interaction with Dr. Walker through a Fogarty International Training Grant application that they shared, which funded medical doctors from Tanzania and China to train at Harvard. One of his junior faculty members, Dr. Dura, has a funded P/F. He works closely with **Christopher Duggan, M.D., M.P.H.**, at CH on this project. They participated in a symposium on nutrition and global health this year.

Inflammatory Bowel Disease

Two major studies related to IBD have been funded by NORC-H in the last two years. These include a P/F study by **Dr. Cherayil** on the role of iron in pathogen-induced intestinal inflammation. This project has resulted in a Senior Fellowship Award to Dr. Cherayil from the Cronh's and Colitis Foundation of America and an R21 award from the NIDDK. This project also was the basis for a DSc thesis in nutritional biochemistry at the HSPH by a medical doctor from China who will study nutrition in IBD when he returns home. A second pending P/F to **Dr. Di Meng**, involves the role of fucose lectins in the protecting mice from DSS colitis. It is anticipated that this observation will lead to a R01 application next fall. Most recently, in a collaborative venture, the NORC-H is setting up a Microbiota Core in association with the Genomics Core of the Center to provide analysis of stools and a variety of diseases for multiple Centers in Boston and for the CATALYST Program at Harvard. In addition, the NORC-H has collaborated for the last four years with the Center for the Study of Inflammatory Bowel Disease (CSIBD), funded as a gastrointestinal center by NIDDK, to provide an introductory lecture and laboratory course in molecular biology to fellows and junior faculty in the NORC-H and the CSIBD.

The Harvard Clinical and Translational Science Center (CATALYST)

In May 2008, a Harvard-wide university enterprise dedicated to improving human health was funded by a \$117,500,000 grant from the NIH. This grant consolidated individual CTSUs at MGH, BWH, CH, BIDMC, and MIT and provided resources to fund in-patient and out-patient clinical studies at the HMS teaching hospitals along with clinical care laboratory support, P/F grants between basic and clinical researchers at various institutions, and various KL2 MeRIT training awards for aspiring junior faculty. To date, 10 investigators and associate investigators from the NORC-H have received either pilot grants or advanced training grants to fund nutrition related projects. To illustrate this asset, **Dr. David Nathan, Director of the MGH CTSU**, is an investigator and has been a member of the Executive Committee of the NORC-H. As part of the *renewal* application, a special emphasis will be made to link PFP applications and associate investigators into possible protocols for the CTSU at MGH, CH, BWH, and BIDMC. Conversely, the directors of these CTSUs will encourage protocols through approvals to consider PFP applications when appropriate. Dr. Nathan has had extensive experience in clinical investigation in the field of carbohydrate metabolism. He has trained a number of Investigators including, **Karen Miller, M.D.**, a staff physician in the Endocrine Unit at MGH, and **Dr. Grinspoon**, currently the Associate Director of the NORC-H. He and **Anne Klibanski, M.D.**,

overall director of in-patient and out-patient facilities for the CTSUs at Harvard, will be available to advise young investigators on appropriateness of clinical protocols that could compete for P/F funds. At MGH they work closely with **David Schoenfeld, Ph.D.**, and **William Crowley, M.D.**, to provide an effective enrichment program in clinical nutrition investigation. This resource has been expanded to provide courses in study design, statistics, and so forth for formal training of clinical investigators in nutrition through the CTSU and the Clinical Research Program.

Educational Activities

HMS Nutrition Curriculum Committee

The DON and NORC-H have established a subcommittee of the HMS Curriculum Committee. This committee—composed of student representatives from all four years of HMS, as well as educators and nutritionists—has critiqued the 4-year curriculum and has begun to add nutrition lectures, cases, and electives to help educate medical students. In the last 2 years, the HMS has revised its curriculum to better prepare its students for interaction with patients. The curriculum for the first 2 years has been condensed into an 18-month curriculum, and, as a result, the very popular **Nutrition and Disease Prevention Course** has been discontinued. Members of the HMS Nutrition Curriculum Committee have worked closely with the Dean of Education to include all topics previously covered in the course and other introductions to medical courses. As part of the revision, this year the subcommittee has reassessed the entire 4-year medical school curriculum to include practical nutrition in courses during all 4 years. Two pilot programs on clinical rotations have included nutrition in the history and physical exams and have been very popular with students. The DON has also funded a summer research program for first-year students to have summer experiences in various aspects of nutrition. We have also expanded our website for students to be able to include our annual nutrition symposium and selected Longwood Nutrition Conferences as webcasts on the website. Most recently in cooperation with the CME postgraduate program, we have begun an E-learning program to supplement major courses with nutrition information.

Scott Butsch, M.D., of MGH has recently won a fellowship from the HMS Education Academy to develop an E-learning Nutrition Education Program for HMS students. He has begun to supplement courses during each of the 4 years of medical school. He and his Nutrition Curriculum Subcommittee provide additional didactics in nutrition that underscore its importance in basic and clinical medicine. The subcommittee has also established selectives and electives for senior medical students wishing a more in-depth clinical experience in nutrition as a preventive measure for chronic disease.

Cardiovascular Health

Recognizing the importance of nutrition in preventive medicine, the HMS Department of Preventive Medicine, since its establishment in 1991, has emphasized nutrition in its educational mission. Nutrition programs are presented primarily to medical students through an elective course offering, to the public through an evening nutrition course, and to scientists through a postdoctoral fellowship program in preventive medicine.

Course in Nutrition and Health for the Public

A class in healthy nutrition is given 4 times per year in the evenings for the public. Individuals and their spouses are encouraged to enroll, and emphasis is on diets that reduce blood lipids and cholesterol and foster nutritionally prudent dietary habits. The course is taught by dietitians with participation of cardiologists (**Drs. Welty and Lo**) and internists (**Drs. Grinspoon and Misra**) and includes a didactic session, answering questions of the attendees, and a cooking demonstration with a meal served and recipes provided. This 2-hour class is held weekly for 6 weeks and has been growing in popularity. Two programs working closely with the NORC-H for this purpose are the NEMC Food Study Program and the Harvard Business School Food Policy Committee.

Lipid Clinic

Professionals at a weekly Lipid Clinic at the MGH and CH sees patients with various serum lipid disorders or coronary heart disease and uses dietary modification of fat intake as the mainstay of its cholesterol and triglyceride reduction program as well as for weight control. Dr. Hoppin of MGH and Sara DiFerranti, M.D., of CH participate in this program.

Preventive Medicine Newsletter

Because of the interest of the Cardiovascular Health Center staff in the potential of omega-3 fatty acids of marine origin to prevent atherosclerosis, the staff publishes a quarterly 6-to-8-page newsletter *Omega 3 News* for public circulation to inform interested individuals about the current status of research on omega-3 fatty acids in nutrition. This responsibility has now been assumed by the *Newsletter from the International Society for the Study of Fatty Acids and Lipids*. The food and fishing industries support and subscribe to this newsletter, as do many investigators in academic and industrial settings. Subscriptions in the fourth year of this quarterly publication number some 2500. The newsletter has a distinguished editorial board with members from the United States, Canada, and Europe representing both academia and fishing interests.

Pediatric Nutrition Lay Education

The Combined Program in Pediatric Gastroenterology and Nutrition at Harvard has a quarterly newsletter that covers topics in nutrition for pediatric patients (food-borne illness, vitamins, obesity) and that it distributes to 70,000 plus readers. In addition, Harvard Publications and McGraw Hill Publishers asked Dr. Walker and the DON to provide two books for parents regarding nutrition. *Eat, Drink and Be Healthy for Kids* and *Nutrition and Pregnancy: Impact on Newborn and Childhood Health*, written with help from a medical writer, provide patients with insight into these nutritional issues.

E-journal in Nutrition

A new E-journal with greater than 5,000 subscribers titled *Functional Food Reviews* has been launched by Drs. Walker and Philip Sherman, Editors-in-Chief. The associate editors and editorial board are authorities in the field, and contributors to four issues yearly are well known in the field of their review.

Lay Public Newsletter

The *Harvard Health Letter* is distributed to more than 20,000 lay readers. Under the direction of Dr. Bruce Bistrian, an investigator in our program, it provides timely articles on healthy diets and on inappropriate dietary habits.

DON Website

In 2002, the NORC-H revised its website (<http://www.hms.harvard.edu/nutrition>). Part of this site provides information on healthy diet for the public to access. This site also allows access to other sites specifically geared for public information, including an obesity information site and cancer and nutrition information websites at the NIH. NORC-H also coordinate efforts with the DON at HMS and the Department of Nutrition at HSPH to provide additional information for cancer patients, patients with post-myocardial infarction, and patients in the weight reduction programs at MGH and CH. This information includes referral information for nutrition preventive programs in the Boston area. These efforts have resulted in an additional link to a newly established website in the Department of Nutrition at the HSPH developed by Lillian Cheng, Ph.D., to update the public on the latest information about dietary supplements and functional foods. In addition, staff has linked our education information on the NORC-H website and the Harvard DON website to an education website for HMS students as an additional resource for their nutrition education. In the last 4 years, the DON has webcast the annual nutrition symposium for student access. Staff has also webcast selected Longwood Nutrition Conferences (e.g. electives in nutrition) to allow students to access postgraduate education during their free time when they can absorb the information.

Annual Nutrition Symposium at HMS

Each year beginning in 1996, the NORC-H in conjunction with the DON at HMS and the Department of Nutrition at HSPH jointly sponsor a nutrition symposium. The funding for this program comes from industry (Dannon, Mead Johnson, Abbott Nutritionals), the American Digestive Health Foundation, and conference grants from the NIH. Speakers from throughout the United States, as experts on the topic, are asked to review their work. Academic nutritionists and scientists from industry attend and participate in extensive discussion. These symposia have catalyzed industry-sponsored research programs and collaborations among investigators. This year's symposium was entitled "Nutritional and Global Health," and the symposium in 2009 was titled "Protective Nutrients: Are They Here to Stay?" (2009). Others included the following: "The Genetics of Obesity" (2008); "Obesity in Inflammation" (2007); "Metabolic Syndrome and Prevention of Cancer" (2006); "Pediatric Obesity: Prevention and Identification" (2005); "How Do We Deal With the Obesity Epidemic? Perspective from Industry, Government, and Academia" (2004). All are available via webcast on the NORC-H website

Longwood Medical Area Nutrition Conference

This group comprises the four Nutrition Support Services (NSS) in the Longwood Medical area. It includes CH, BWH, the New England Deaconess Hospital and the Beth Israel Hospital (now the BIDMC). Conferences are held bi-monthly. In 1997, the NSS at MGH was included. The format is case presentations (three sessions) and didactic sessions on current clinical nutrition problems. This forum provides an opportunity to exchange both clinical and research expertise as well as to teach fellows, students, and inexperienced clinicians the practical aspects of nutrition support.

Combined Nutrition Conference—CH

Seminars are held 2 to 4 times per month and involve the Clinical Nutrition Service staff and others interested in nutrition (Oncology, Intensive Care, Pulmonary, and so forth). Speakers and topics are chosen by a representative of each service and include both research and applied nutrition subjects.

Didactic Nutrition Sessions

The Clinical Nutrition Service at both CH and MGH actively participate in the nutrition training of the medical, nursing, and dietetic staff at their respective institutions. Regularly scheduled training includes in-house staff core lecture series; lectures on the nursing in-service program; the joint program in neonatology nutrition lectures; and grand rounds, morbidity and mortality rounds, and clinical pathology conferences. As well, the CNS takes an active role in the daily bedside teaching of the medical staff around the practical, applied aspects of nutrition as it relates to direct patient care. Comparable didactic sessions are held about the NSS at BIDMC and MGH for adult patients.

Postgraduate Course for Dietitians and Nutritionists: HMS Nutrition Advances

This course, which is administered by Dr. Blackburn, is held annually at the New England Deaconess Hospital under the auspices of the DON at HMS. Various members of CH's Nutrition Support Service have participated in this 3-day course. Involvement generally includes didactic lectures, case presentations, and/or roundtable participation. In this application, Drs. Blackburn, Willett, Duggan, Walker and Lo join the NORC-H as active teachers in this course. This course is webcast on the DON website.

Postgraduate Education at HMS

As the DON and NORC-H have expanded their influence at HMS, more medical doctors are planning formal postgraduate education experiences in nutritional sciences or a postgraduate degree (MS or DSc) in nutrition at the Harvard School of Public Health. Accordingly, we now have two training grants for medical doctors to obtain clinical and basic research experience in nutrition. Dr. Grinspoon has recently successfully competed for a T-32 (T32 HD052961) through the NICHD. As part of the DON, Dr. Willett has had ten years of T-32 (T32 DK07703) support for the Department of Nutrition at HSPH from the NIDDK.

Benefits and Interactions Resulting From the Existence of the NORC

Beyond the scientific achievements embodied by the specific advances noted above and the publications of Center investigators, the Center has facilitated progress in the field more broadly on a national basis through a number of its activities. These include extending the scope of the Molecular Biology Lecture and Laboratory Course to include investigators in other NIH-supported centers (Center for the Study of Inflammatory Bowel Disease; Reproductive Biology Center at MGH), the Boston NORC, and other NORCs throughout the United States. Approximately 100 scientists from outside the NORC-H have taken this course since its expansion in the second year of the Center's existence.

Division of Nutrition at HMS

The NORC-H has been a catalyst for the establishment of a Division of Nutrition at HMS. The Division of Nutrition now works closely with members of the Department of Nutrition at HSPH to provide medical school and graduate school teaching programs in nutrition and a postgraduate yearly national symposium for academics and industrial scientists. This interaction has also resulted in the addition of new programs—e.g., women's health initiatives, obesity, and foodborne infection—to the Center's educational progress.

NIH Supported Centers in Boston

All NIH supported centers in Boston (two NORCs, two Diabetes Centers and two Digestive Disease Centers) have met to identify ways in which core facilities, educational programs, and information services to the public can be shared or jointly expanded. This recent event will be a major benefit to all participating centers in the future. When the Clinical Nutrition Research Centers at four Harvard teaching hospitals and MIT came together to create the CATALYST program, an increasing need for cooperation among NIH-supported Centers was seen. The NORC-H has actively participated in the newly established programs in Harvard CATALYST. The associate investigators using the Core facilities of the NORC-H have successfully competed for two CATALYST startup grants to study the affect of diet on development of premature infants. Researchers have also applied for Roche 454 sequencing system to establish a Microbiota Core Facility for the CATALYST Program and other NIH-supported Centers. This facility will provide a quantitative analysis of colonic microbiota in a number of clinical conditions including IBD, colon cancer, allergy, and NEC. This represents an example of how the NORC-H has cooperated with other NIH Centers and clinical research programs to enhance the role of nutrition at Harvard.

Health Promotion and Disease Prevention

As a result of the P/F funding and Genomic Core support, Dr. Walker's group advanced a basic observation on the mechanism of the severe gastrointestinal inflammatory disease NEC—which occurs in premature infants (10%; \$500 million of hospital cost per year)—towards a translational/clinical solution. This group has reported that the genes in gut epithelium that regulate the innate immune inflammatory response, which is enhanced in premature human intestine, are developmentally regulated. In human immature intestine there is an overexpression of toll receptors TLR2 and 4, their signaling molecules (MyD88, IRAK, etc.) and transcription factor (NFκB1), and an underexpression of genes that negatively regulate the innate inflammatory response (SIGIRR, Tollip, IRAK-M) leading to an excessive IL-8 response.

In an attempt to prevent the severe intestinal inflammation of NEC, oral probiotics have been introduced with the first oral feeding and have lessened the severity and incidence of disease. Two such probiotics, *Lactobacillus acidophilus* and *Bifidobacteria infantis*, have been used in a clinical study in Taiwan and shown to prevent NEC. This study has subsequently grown these bacteria in culture media, taken the medic secretions of these two probiotics exposed them to human fetal small intestinal xenografts and primary enterocytes from NEC patients, and shown that they can reduce the excessive IL-8 response and stimulate a maturation of the innate immune inflammatory response genes. Based on these observations that probiotic secretions and not live bacteria can affect inflammation in the immature human gut (live probiotics can not be

fed to human prematures in the US—an FDA mandate), this study can now do an *in vivo* trial in an animal model for NEC (using private funding) and then, if positive, a clinical trial followed by a multi-center trial in 20 newborn nurseries in South America (foundation funding). If these observations are positive, this study can then recommend that probiotic secreted molecules be given routinely to prematures as part of general care.