Personalized Nutrition
Translating Nutrigenetic/Nutrigenomic Research into Dietary Guidelines
Personalized Nutrition

Translating Nutrigenetic/Nutrigenomic Research into Dietary Guidelines

Volume Editors

Artemis P. Simopoulos
The Center for Genetics, Nutrition and Health, Washington, D.C., USA

John A. Milner
National Institutes of Health, Health and Human Services, Rockville, MD

19 figures and 15 tables, 2010
Contents

VII  List of Contributors

XI  Preface
   Simopoulos, A.P. (Washington, D.C.); Milner, J.A. (Bethesda, Md.)

1  Opportunities and Challenges in Nutrigenetics/Nutrigenomics and Health
   De Caterina, R. (Pisa)

8  Genome-Wide Association Studies and Diet
   Ferguson, L.R. (Auckland)

15  Copy Number Variation, Eicosapentaenoic Acid and Neurological Disorders.
    With Particular Reference to Huntington’s Disease and Associated CAG Repeats,
    and to Myalgic Encephalomyelitis and Viral Infection
   Puri, B.K. (London); Manku, M.S. (Oxford)

21  Nutrigenetics: A Tool to Provide Personalized Nutritional Therapy to the Obese
   Marti, A.; Goyenechea, E.; Martinez, J.A. (Pamplona)

34  Xenobiotic Metabolizing Genes, Meat-Related Exposures, and Risk of Advanced
    Colorectal Adenoma
   Ferrucci, L.M. (Bethesda, Md./New Haven, Conn.); Cross, A.J. (Bethesda, Md.); Gunter, M.J.;
   Ahn, J. (New York, N.Y.); Mayne, S.T.; Ma, X. (New Haven, Conn.); Chanock, S.J.; Yeager, M.;
   Graubard, B.I.; Berndt, S.J.; Huang, W.-Y. (Bethesda, Md.); Hayes, R.B. (New York, N.Y.);
   Sinha, R. (Bethesda, Md.)

46  Strategies to Improve Detection of Hypertension Genes
   Hunt, S.C. (Salt Lake City, Utah)

56  Diet, Nutrition and Modulation of Genomic Expression in Fetal Origins of
    Adult Disease
   Jackson, A.A.; Burdge, G.C.; Lillycrop, K.A. (Southampton)

73  Choline: Clinical Nutrigenetic/Nutrigenomic Approaches for Identification of
    Functions and Dietary Requirements
   Zeisel, S.H. (Chapel Hill, N.C.)

84  Dietary Polyphenols, Deacetylases and Chromatin Remodeling in
    Inflammation
   Rahman, I.; Chung, S. (Rochester, N.Y.)

95  Dietary Manipulation of Histone Structure and Function
   Ho, E.; Dashwood, R.H. (Corvallis, Oreg.)
103 Changes in Human Adipose Tissue Gene Expression during Diet-Induced Weight Loss

115 Toxicogenomics and Studies of Genomic Effects of Dietary Components
Thompson, K. (Silver Spring, Md.)

123 Dietary Methyl Deficiency, microRNA Expression and Susceptibility to Liver Carcinogenesis

131 Redox Dysregulation and Oxidative Stress in Schizophrenia: Nutrigenetics as a Challenge in Psychiatric Disease Prevention
Do, K.Q.; Conus, P; Cuenod, M. (Lausanne)

154 Nutrigenomics and Agriculture: A Perspective
Spence, J.T. (Beltsville, Md.)

160 Opportunities and Challenges in Nutrigenetics/Nutrigenomics: Building Industry-Academia Partnerships
Gillies, P.J. (Wilmington, De.); Kris-Etherton, P.M. (University Park, Pa.)

169 Tailoring Foods to Match People’s Genes in New Zealand: Opportunities for Collaboration
Ferguson, L.R.; Hu, R.; Lam, W.J.; Munday, K.; Triggs, C.M. (Auckland)

176 Author Index
177 Subject Index
List of Contributors

Jiyoung Ahn  
Division of Epidemiology  
Department of Environmental Medicine  
New York University School of Medicine  
New York, NY 10016 (USA)

Frederick A. Beland  
Division of Biochemical Toxicology  
National Center for Toxicological Research  
3900 NCTR Rd.  
Jefferson, AR 72079 (USA)

Sonja I. Berndt  
Division of Cancer Epidemiology and Genetics  
National Cancer Institute  
National Institutes of Health  
Department of Health and Human Services  
Bethesda, MD 20892 (USA)

Graham C. Burdge  
Institute of Human Nutrition  
University of Southampton School of Medicine  
IDS Building, MP88  
Southampton General Hospital  
Tremona Road  
Southampton SO16 6YD (UK)

Lena MS Carlsson  
Sahlgrenska Center for Cardiovascular and Metabolic Research  
Department of Molecular and Clinical Medicine  
The Sahlgrenska Academy at University of Gothenburg  
SOS-sekr, Vita Stråket 15  
SE-413 45 Gothenburg (Sweden)

Stephen J. Chanock  
Division of Cancer Epidemiology and Genetics  
National Cancer Institute  
National Institutes of Health  
Department of Health and Human Services  
Bethesda, MD 20892 (USA)

Sangwoon Chung  
Department of Environmental Medicine  
Lung Biology and Disease Program  
University of Rochester Medical Center  
MRBX 3.11106, Box 850  
601 Elmwood Ave.  
Rochester, NY 14642 (USA)

Philippe Conus  
Department of Psychiatry  
Lausanne University Hospital  
Site de Cery  
CH-1008 Prilly-Lausanne (Switzerland)

Amanda J. Cross  
Division of Cancer Epidemiology and Genetics  
National Cancer Institute  
National Institutes of Health  
Department of Health and Human Services  
Bethesda, MD 20892 (USA)

Michel Cuenod  
Center for Psychiatric Neuroscience  
Department of Psychiatry  
Lausanne University Hospital  
Site de Cery  
CH-1008 Prilly-Lausanne (Switzerland)
Roderick H. Dashwood
Linus Pauling Institute
Oregon State University
571 Weniger Hall
Corvallis, OR 97331 (USA)

Raffaele De Caterina
Chair and Postgraduate School of Cardiology
“G. d’Annunzio” University – Chieti
C/o Ospedale SS. Annunziata
Via dei Vestini
I-66013 Chieti (Italy)

Kim Q. Do
Center for Psychiatric Neuroscience
Department of Psychiatry
Lausanne University Hospital
Site de Cery
CH-1008 Prilly-Lausanne (Switzerland)

Leah M. Ferrucci
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Department of Health and Human Services,
Bethesda, MD 20892 (USA)

Lynnette R. Ferguson
Discipline of Nutrition
Faculty of Medical and Health Sciences
The University of Auckland
Private Bag 92019
1142 Auckland (New Zealand)

Estibaliz Goyenechea
Institute of Nutrition and Food Sciences
University of Navarra
E-31080 Pamplona (Spain)

Marc J. Gunter
Department of Epidemiology and Population Health
Albert Einstein College of Medicine
Bronx
New York, NY 10461 (USA)

Barry I. Graubard
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Department of Health and Human Services
Bethesda, MD 20892 (USA)

Anders Gummesson
Sahlgrenska Center for Cardiovascular and Metabolic Research
Department of Molecular and Clinical Medicine
The Sahlgrenska Academy at University of Gothenburg
SOS-sekr, Vita Stråket 15
SE-413 45 Gothenburg (Sweden)

Peter J. Gillies
DuPont Applied BioSciences
DuPont Experimental Station, E328/267
Wilmington, DE 19880-0328 (USA)

Richard B. Hayes
Division of Epidemiology
Department of Environmental Medicine
New York University School of Medicine
New York, NY 10016 (USA)

Emily Ho
Department of Nutrition & Exercise Sciences
Oregon State University
117 Milam Hall
Corvallis, OR 97331 (USA)

Rong Hu
Discipline of Nutrition,
Faculty of Medical and Health Sciences,
The University of Auckland
NZ-1142 Auckland (New Zealand)

Wen-Yi Huang
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Department of Health and Human Services
Bethesda, MD 20892 (USA)

Steven C. Hunt
Cardiovascular Genetics Division
Department of Internal Medicine
University of Utah
420 Chipeta Way, Room 1160
Salt Lake City, Utah 84108 (USA)

Alan A. Jackson
Institute of Human Nutrition,
Southampton General Hospital (MP 113)
Tremona Road
Southampton SO16 6YD (UK)
Penny M. Kris-Etherton  
The Pennsylvania State University  
University Park, PA 16802-1294 (USA)

Oksana Kosyk  
Department of Environmental Sciences and Engineering  
University of North Carolina  
135 Dauer Dr.  
Chapel Hill, NC 27599 (USA)

Wen Jiu Lam  
Discipline of Nutrition,  
Faculty of Medical and Health Sciences  
The University of Auckland  
NZ-1142 Auckland (New Zealand)

Karen A. Lillycrop  
Developmental and Cell Biology  
University of Southampton  
Southampton SO16 7PX (UK)

John A. Milner  
Nutritional Science Research Group  
Division of Cancer Prevention  
National Cancer Institute  
National Institutes of Health  
Health and Human Services  
6130 Executive Boulevard  
Executive Plaza North Suite 3164  
Rockville, MD 20892 (USA)

Karen Munday  
Institute of Food, Nutrition and Health  
Massey University,  
NZ-4474 Palmerston North (New Zealand)

Xiaomei Ma  
Yale School of Public Health  
New Haven, CT 06520-8034 (USA)

Mehar S. Manku  
Amarin Neuroscience  
Oxford OX4 4GA (UK)

Amelia Marti  
Institute of Nutrition and Food Sciences  
University of Navarra  
E-31080 Pamplona (Spain)

J. Alfredo Martinez  
Institute of Nutrition and Food Sciences  
University of Navarra  
E-31080 Pamplona (Spain)

Susan T. Mayne  
Yale School of Public Health,  
New Haven, CT 06520-8034 (USA)

Igor P. Pogribny  
Division of Biochemical Toxicology,  
National Center for Toxicological Research  
3900 NCTR Rd.  
Jefferson, AR 72079 (USA)

Irfan Rahman  
Department of Environmental Medicine  
Lung Biology and Disease Program  
University of Rochester Medical Center  
MRBX 3.11106, Box 850  
601 Elmwood Ave.  
Rochester, NY 14642 (USA)

Basant K. Puri  
MRI Unit  
Imaging Sciences Department  
MRC Clinical Sciences Centre  
Imperial College London  
Hammersmith Hospital  
London W12 0HS (UK)

Sharon R. Ross  
Nutritional Science Research Group  
Division of Cancer Prevention  
National Cancer Institute  
National Institutes of Health  
Department of Health and Human Services  
6130 Executive Blvd.  
Bethesda, MD  20892-7328 (USA)

Ivan Rusyn  
Department of Environmental Sciences and Engineering  
University of North Carolina  
135 Dauer Dr.  
Chapel Hill, NC 27599 (USA)

Artemis P. Simopoulos  
The Center for Genetics, Nutrition and Health  
2001 S Street, N.W.  
Suite 530  
Washington, DC 20009 (USA)
Rashmi Sinha  
Division of Cancer Epidemiology and Genetics  
National Cancer Institute  
National Institutes of Health  
Department of Health and Human Services  
Bethesda, MD 20892 (USA)

Kajsa Sjöholm  
Sahlgrenska Center for Cardiovascular and Metabolic Research  
Department of Molecular and Clinical Medicine  
The Sahlgrenska Academy at University of Gothenburg  
SOS-sekr, Vita Stråket 15  
SE-413 45 Gothenburg (Sweden)

Joseph T. Spence, Ph.D.  
Beltsville Agricultural Research Center  
Building 003, Room 238  
10300 Baltimore Avenue  
Beltsville, MD 20705 (USA)

Athena Starlard-Davenport  
Division of Biochemical Toxicology, National Center for Toxicological Research  
3900 NCTR Rd.  
Jefferson, AR 72079 (USA)

Per-Arne Svensson  
Sahlgrenska Center for Cardiovascular and Metabolic Research  
Department of Molecular and Clinical Medicine  
The Sahlgrenska Academy at University of Gothenburg  
SOS-sekr, Vita Stråket 15  
SE-413 45 Gothenburg (Sweden)

Karol Thompson  
US Food and Drug Administration  
Life Science Building 64, Rm 2036  
10903 New Hampshire Ave  
Silver Spring, MD 20993-0002 (USA)

Christopher M. Triggs  
Department of Biostatistics, Nutrigenomics  
The University of Auckland  
NZ-1142 Auckland (New Zealand)

Volodymyr Tryndyak  
Division of Biochemical Toxicology, National Center for Toxicological Research  
3900 NCTR Rd.  
Jefferson, AR 72079 (USA)

Meredith Yeager  
Division of Cancer Epidemiology and Genetics  
National Cancer Institute  
National Institutes of Health  
Department of Health and Human Services  
Bethesda, MD 20892 (USA)

Steven Zeisel  
Gillings School of Global Public Health and School of Medicine  
University of North Carolina at Chapel Hill  
Nutrition Research Institute at Kannapolis  
500 Laureate Way  
Kannapolis, NC 28081-4332 (USA)
Volume 101 in the series *World Reviews of Nutrition and Dietetics* consists of selected papers presented at the Third Congress of the International Society of Nutrigenetics/Nutrigenomics (ISNN). The congress was held at the National Institutes of Health (NIH) campus in Bethesda (Md., USA) on October 21–23, 2009. The congress was truly international, with speakers and participants from 14 countries of North and South America, Europe, Asia and Africa. The congress was co-chaired by Dr. John Milner of the National Cancer Institute, NIH, and Dr. Artemis P. Simopoulos, President of the ISNN. The congress's focus was that 'research and its translation into medical practice and dietary recommendations must be based on a solid foundation of knowledge derived from studies on nutrigenetics and nutrigenomics'. The congress consisted of 7 sessions. In keeping with the theme of the congress, sessions I and II addressed 'Frontiers in Nutrigenetics', session III focused on 'Frontiers in Epigenetics', session IV addressed the 'Impact of Transcriptomics on Nutrigenomics', session V centered on 'Non-coding RNAs and Post-translational Gene Regulation', session VI was called 'Moving Beyond Genomics', and session VII was titled on 'Frontiers in Nutrigenetics/Nutrigenomics. Building Partnerships: the Challenges and Opportunities Facing Governments, International Organizations, Academia and Industry'.

Dr. Simopoulos and Dr. Milner opened the congress and welcomed everyone. The keynote address was given by Dr. Raffaele De Caterina, Vice-President of the ISNN who spoke on ‘Opportunities and Challenges in Nutrigenetics/Nutrigenomics and Health.’ Dr. De Caterina emphasized that, like drugs, nutrients have the ability to interact and modulate molecular mechanisms underlying an organism's physiological functions. Awareness of the different effects of nutrients according to our genetic constitution (nutrigenetics) and how nutrients may affect gene expression (nutrigenomics) is prompting a revolution in the field of nutrition. Nutritional sciences have always studied the effects of nutrients in terms of ‘average’ responses, without bothering much about inter-individual variability and the underlying causes. The creation of nutrigenetics and nutrigenomics, with distinct approaches to elucidate the interaction between diet and genes, but with the common ultimate goal of optimizing health through personalized diet, provides powerful approaches to unravel the complex relationships among nutritional molecules, genetic variants and the biological
system. Translated as the simple concept of ‘personalized nutrition’ the promise of nutrigenetics/nutrigenomics is a major step forward in the understanding of individual responses to a component nutrient or to our changing environment. Referring to the future, Dr. De Caterina stated two major challenges. One is the reluctance to embrace this concept, primarily due to the fear of being unable to manage the overwhelming quantity and complexity of biological data that will require interpretation and – to a large extent – simplification to be translated into practical messages. The danger of the consequent simplification would be to take the results of a single study on a very specific outcome, very often on intermediate (surrogate) endpoints, and to infer that such results are applicable to the complexity of a living organism, where no single organ or tissue is independent of the others. The second challenge is the need to be aware that the area of ‘personalized nutrition’ is seen by disguised amateurs as a golden opportunity for marketing enterprises before solid knowledge in any specific area is acquired. Although the first challenge is manageable by the ever-increasing availability of biomedical and statistical tools and the wisdom necessary in health inference – a general problem in medical science – the second challenge requires great attention and wisdom and poses important ethical and scientific issues. A scientific society, such as the ISNN, devoted to the study of nutrigenetics/nutrigenomics can indeed serve the commendable roles of (1) promoting science and favoring scientific communication and (2) permanently working as a ‘clearing house’ to prevent disqualifying logical jumps, correct or stop unwarranted claims, and prevent the creation of unwarranted expectations in patients and in the general public.

In the next paper Dr. Lynnette Ferguson focuses on ‘Genome-Wide Association Studies and Diet’. Dr. Ferguson points out that genome-wide association studies (GWAS) are not only validating genes and single-nucleotide polymorphisms (SNPs) that have been anticipated by knowledge of biochemical pathways, but are also revealing new gene-disease associations not anticipated from prior knowledge (e.g. Crohn’s disease). Dr. Ferguson emphasizes that current GWAS methods need to be complemented with innovative methodologies in order to characterize the impact of food and to take the field to another level of value for human diet, development and optimized health through personalized nutrition.

Genetic variants are caused by SNPs through substitutions, additions or deletions. Copy number variants are the most recent discovery that accounts for genetic variation in humans and may be responsible for much more individuality than previously considered. In their paper, ‘Copy Number Variation, Eicosapentaenoic Acid and Neurological Disorders’ Dr. Basant Puri and Dr. Mehar Manku discuss the way in which the clinical response of neurological disorders to treatment with the semi-synthetic omega-3 long-chain polyunsaturated fatty acid derivative ethyl-eicosapentaenoic acid (ethyl-EPA) varies according to copy number variation. Two examples of neurological disorders are given, namely Huntington’s disease, which is caused by increased CAG repeats at 4p16.3, and myalgic encephalomyelitis, which has recently been associated with evidence of retroviral infection with XMRV. These
findings are likely to apply to other neurological disorders and indeed also to the differential response to ethyl-EPA of psychiatric disorders, such as depression and schizophrenia.

Obesity is a multigenetic and multifactorial condition in which SNPs involved in the regulation of food intake (e.g. MC4R, LEP, LEPLR, POMC, FTO) fat metabolism and thermogenesis (e.g. PPARG, ADBRs, UCPs) inflammation, and signaling (e.g. IL-6, ADIPOQ, CD36) induce different responses to energy-restricted diets, or macronutrient content (fat or fiber) during weight loss, along with beneficial effects on elements such as insulin sensitivity, lipid biomarkers and satiety. Dr. Amelia Marti and colleagues in their paper ‘Nutrigenetics: A Tool to Provide Personalized Nutritional Therapy for the Obese’ present an extensive review of the field. Their review includes observational studies that showcase gene-nutrient interactions on weight gain and international studies on genetic modification effects following weight loss and maintenance.

There have been many studies on the relationship between diet and various forms of cancer. Among those that have been studied extensively are the carcinogenic actions of compounds during cooking of meat, such as heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs) and N-nitroso compounds (NOCs). In their paper ‘Xenobiotic Metabolizing Genes, Meat-Related Exposures, and Risk of Advanced Colorectal Adenoma,’ Dr. Leah Ferrucci and colleagues evaluate SNPs in xenobiotic metabolizing enzyme genes and possible alteration in the activation/detoxification of HCAs, PAHs and NOCs. A number of possible interactions are noted between certain SNPs in relation to colorectal adenoma. The authors conclude that common variants in xenobiotic metabolizing enzyme genes may modify the association of HCAs, PAHs and NOCs and advanced colorectal adenoma, but further investigations in other populations are needed.

Animal models with kidney transplants have unequivocally shown that hypertension follows the kidney. There is also evidence for differential, possibly additive, influences of central versus kidney-specific hormonal blood pressure control of salt balance. In any homeostatic system, such as salt balance, multiple factors are involved in counteracting any factor that perturbs the system. These compensating factors, if working efficiently, should return the system back to balance. Should environmental or genetic effects prevent appropriate compensation over the long term, hypertension will likely develop. However, there are also likely to be genetic initiating factors that would lead to hypertension if not adequately compensated and that may be strong enough so that complete compensation is not attained. Dr. Steven Hunt in his paper ‘Strategies to Improve Detection of Hypertension Genes’ points out that when studying the genetics of the initiating factors, associations will be masked by the degree of compensation and perhaps not even found if compensation is nearly complete. Detecting the genetic initiators may require studying associations after acute interventions and prior to long-term compensation. Detection also may depend on the genetic backgrounds of the subjects being studied: subjects with few hypertension genes may
show little association with any particular gene, whereas subjects with many hypertension-susceptibility genes may show strong associations. Although some genes have been consistently related to elevated blood pressure and hypertension, the observed effects of these genes are small and difficult to replicate. These common genes have almost always been related to renal electrolyte handling, similar to mechanisms of the rarer monogenic hypertension disorders. Several large studies now have the power to detect hypertension genes with smaller effect sizes and to assess interactions with diet and other environmental risk factors for hypertension. Intervention studies appear to magnify the baseline effects of genes so that they are more easily detected. In addition to genetic interactions with dietary salt on blood pressure, there appear to be important but less understood genetic interactions with dietary fat and cholesterol on blood pressure pathways. Multiple interventions – including less dietary salt, increased dietary potassium, increased intake of fruits and vegetables, lower fat intake, weight loss and drug treatment – appear to help reduce blood pressure to a greater extent in subjects genetically susceptible to hypertension than those not as susceptible. It appears that those at highest genetic risk of hypertension show a greater improvement in blood pressure for interventions that target the defective genetic pathways than do those at low risk. There remains an urgent need for the addition of dietary and pharmacologic interventions to genetic studies and vice versa, so that biological mechanisms may be uncovered, represented by these statistical interactions, and additional interactions discovered. Knowledge arising from such studies may be used to design specific dietary, exercise, weight loss and drug interventions for the subset of patients that will benefit the most from that intervention.

For the past century, broad social development has been reflected in changes in height. There is convincing evidence from population studies that achieved height marks a significantly increased risk for some cancers. Major cancers are associated with increased adiposity, especially with centrally deposited fat for some. Thus, findings of epidemiological studies of the relationship between prenatal growth and risk for specific cancers, metabolic disease and cardiovascular disease suggest that early life environment is a causal component in the etiology of these conditions. Mechanistic studies provide some evidence that explains how variations of diet within the normal range of consumption in early life can set later susceptibility through processes such as DNA methylation and covalent modifications to histones. Dr. Alan Jackson and colleagues in their paper 'Diet, Nutrition and Modulation of Genomic Expression in Fetal Origins of Adult Disease' state that nutrient interventions in laboratory animals during pregnancy and/or lactation show that there is developmental plasticity to environmental stimuli that induces a phenotype that confers survival advantage in the short term but increases susceptibility to pathology in the longer term. These influences can be modified by the dietary pattern during the weaning period, demonstrating an important interaction between prenatal nutrition and food consumption during later life. This is further implied by the common role for altered epigenetic regulation of specific genes and of altered Dnmt activity. Thus, risk of these
seemingly heterogeneous patterns of ill health may reflect a continuum of developmental changes that operate through the same enzymes and pathways that induce epigenetic regulation of specific genes. Risk of specific diseases may reflect the nature and/or magnitude of the environmental exposure during early life. It is not known how these environmental cues may be targeted in a manner that induces altered epigenetic regulation of specific genes or of individual CpG dinucleotides and so lead to increased risk of different disease processes. However, such specificity is implied by emerging evidence that the magnitude of the maternal nutritional challenge and the relative amount of specific nutrients in the maternal diet induce directionally opposite changes in the physiology and epigenotype of the offspring. Overall, these findings support the concept that a range of prenatal nutritional environments, from constraint to abundance, may induce risk of ultimate different pathological processes. The induced epigenetic changes are likely to be permissive for altered gene expression and hence determine the interaction between an organism and its environment over the life course and, in turn, determine whether increased risk due to the early-life environment becomes disease in later life.

Dr. Steven H. Ziesel in his manuscript 'Choline: Clinical Nutrigenetic/Nutrigenomic Approaches for Identification of Functions and Dietary Requirements' points out that whereas GWAS examine correlations between variants and diseases in terms of thousands of subjects are a mainstay of nutrigenetics/nutrigenomics, less common are the studies that examine the effects of genetic variants on nutritional phenotypes using clinical studies involving smaller numbers of studies – clinical nutrigenetics/nutrigenomics. Dr. Ziesel noted in his and other studies with choline as an example of clinical nutrigenetics. In animal models, there is a critical period during pregnancy when dietary choline intake modulates fetal brain development with structural and functional consequences that last throughout the entire life of the offspring. Maternal intake of diets low in choline negatively impacts the proliferation and survival of neuronal and glial progenitor cells in the fetal hippocampus, septum and cortex, whereas maternal diets high in choline exert the opposite effects on brain development, increasing progenitor cell proliferation and survival and enhancing memory function. One mechanism mediating these changes involves the epigenetic modification of genes in fetal brain that are important regulators of cell division, apoptosis and neural differentiation.

The following paper, by Dr. Irfan Rahman and Dr. Sangwoon Chung, is entitled 'Dietary Polyphenols, Deacetylases and Chromatin Remodeling in Inflammation'. The therapeutic benefits of fruits and vegetables, tea and wine are mostly attributed to the presence of phenolic compounds. Naturally occurring dietary polyphenols such as curcumin (diferuloylmethane) an active component of the spice turmeric and resveratrol (phytoalexin), a flavanoid found in red wine, can directly scavenge reactive oxygen species and modulate signaling pathways mediated by NF-κB and MAP kinase pathways and up-regulate glutathione/phase II enzyme biosynthesis via activation of Nrf2. They also down-regulate the expression of pro-inflammatory mediators,
matrix metalloproteinases, adhesion molecules, and growth-factor receptor genes by inhibiting histone acetyltransferase activity and activating histone deacetylase (HDAC)/sirtuins (SIRTs). The expression of NF-κB-dependent pro-inflammatory genes in response to oxidative stress is regulated by the acetylation-deacetylation status of histones bound to the DNA. It has been reported in severe asthma and in chronic obstructive pulmonary disease (COPD) patients, that oxidative stress not only activates the NF-κB pathway but also alters the histone acetylation and deacetylation balance via post-translational modification of HDACs. Corticosteroids have been one of the major modes of therapy against respiratory diseases such as asthma and COPD. Failure of corticosteroids to ameliorate such disease conditions has been attributed to their failure to recruit either HDAC2 or SIRT1 or to the presence of an oxidatively/post-translationally modified HDAC2/SIRT1 in asthmatics and COPD patients. Dietary polyphenols such as curcumin, resveratrol and catechins have been reported to modulate epigenetic alterations in various experimental models. The anti-inflammatory properties of curcumin, resveratrol and catechins may be due to their ability to induce HDACs/SIRT1 activity, and thereby restore the efficacy of glucocorticoids or overcome its resistance. Thus, these polyphenolic compounds have value as antioxidant, anti-inflammatory and adjuvant therapies with steroids against chronic inflammatory epigenetically regulated diseases. The current knowledge on the mechanism of action of these polyphenols in the light of deacetylases in regulation of chromatin remodeling in inflammation is extensively presented.

Dr. Emily Ho and Dr. Roderick Dashwood in their manuscript ‘Dietary Manipulation of Histone Structure and Function’ point out that the influence of epigenetic alterations during cancer has gained increasing attention and has resulted in a paradigm shift in our understanding of mechanisms leading to cancer susceptibility. The reversible acetylation of histones is an important mechanism of gene regulation. Targeting the epigenome, including the use of HDAC inhibitors, is a novel strategy for cancer chemoprevention. The authors have found that sulforaphane, a compound found in cruciferous vegetables, inhibits HDAC activity in human colorectal and prostate cancer cells. The ability of sulforaphane to target aberrant acetylation patterns, in addition to effects on phase 2 enzymes, may make it an effective chemoprevention agent. Other dietary agents such as butyrate, allyl sulfides and organoselenium compounds have also shown promise as HDAC inhibitors. These studies are significant because of the potential to qualify or change recommendations for high-risk cancer patients, thereby increasing their survival through simple dietary choices, such as incorporating easily accessible foods into a patient’s diet. The findings provide a scientific foundation for future large-scale human clinical intervention studies with dietary agents that affect the epigenome.

The adipose tissue plays a key role in energy storage but is also a major endocrine organ, communicating with the brain and peripheral tissues through mediators known as adipokines. Adipose tissue function has been implicated in the development of obesity-related diseases such as diabetes, cardiovascular disease and cancer.
Thus, regulation of genes in adipose tissue may be important in the pathogenesis of obesity and obesity-related diseases. In their paper ‘Changes in Human Adipose Tissue Gene Expression during Diet-Induced Weight Loss,’ Dr. Per-Arne Svensson and colleagues state that changes in energy availability have profound effects on adipose tissue metabolism. Expression profiling of human adipose tissue has been used extensively to gain insights into genes and mechanisms implicated in the development of obesity and related metabolic disease. The study of expression profiles from adipose tissue during caloric restriction is a valuable tool to gain such insights. In their review, the authors summarize the major findings from human adipose tissue expression profiling studies performed on subjects undergoing diet-induced weight loss treatment, and the current knowledge on 3 different genes/groups of genes that are regulated in human adipose tissue by diet-induced weight loss.

Dr. Karol Thompson in her manuscript ‘Toxicogenomics and Studies of Genomic Effects of Dietary Components’ points out that toxicogenomics analyses are recognized to be of value in assessments of the clinical relevance of adverse events that are observed in animal models. Resources have been developed to help interpret gene expression profiles within the context of a study. Reference compound datasets and pathway mapping tools provide a basis for differentiating pharmacologic from toxicologic effects. From large sets of gene expression data from control groups in toxicogenomics studies, the normal range of variability of individual genes and the contribution of study factors to baseline variability can be assessed. Sources of biological and technical noise can be controlled using performance standards and metrics that have been developed for rat and human samples. These resources, in content or design, have crossover applications of interest and utility to nutrigenomics research.

Altered expression of microRNAs is frequently detected during tumor development; however, it has not been established if variations in the expression of specific microRNAs are associated with differences in the susceptibility to tumorigenesis. Dr. Athena Starlard-Davenport and colleagues in their manuscript ‘Dietary Methyl Deficiency, microRNA Expression and Susceptibility to Liver Carcinogenesis’ report that inbred male mice (C57BL/6J and DBA/2J) were fed a lipogenic methyl-deficient diet, which causes liver injury that progresses to liver tumors. Differentially expressed microRNAs were identified by μParaflo microRNA microarray analysis and validated by quantitative reverse transcription PCR. They identified 74 significantly up- or down-regulated microRNAs, including miR-29c, miR-34a, miR-122, miR-155, miR-200b, miR-200c and miR-221, in the livers of mice fed a methyl-deficient diet for 12 weeks as compared to their age-matched control mice. The targets for these microRNAs are known to affect cell proliferation, apoptosis, lipid metabolism, oxidative stress, DNA methylation and inflammation. Interestingly, DBA/2J mice, which develop more extensive hepatic steatosis-specific pathomorphological changes, had a greater extent of miR-29c, miR-34a, miR-155 and miR-200b expression. These results demonstrate that alterations in expression of microRNAs are a prominent event during early stages of liver carcinogenesis induced by methyl deficiency. More importantly,
the data link alterations in microRNA expression to the pathogenesis of liver cancer and strongly suggest that differences in the susceptibility to liver carcinogenesis may be determined by the differences in the microRNA expression response.

A developmental dysregulation of glutathione (GSH) synthesis of genetic origin leading to oxidative stress, when combined with environmental risk factors generating reactive oxygen species, can play a critical role in inducing schizophrenia phenotypes. GSH, a major redox regulator and antioxidant, is essential for protection against cellular oxidative damage. Dr. Kim Do and colleagues in their paper 'Redox Dysregulation and Oxidative Stress in Schizophrenia: Nutrigenetics as a Challenge in Psychiatric Diseases Prevention' review the results obtained through a reverse translational approach showing redox dysregulation of genetic origin in schizophrenia patients. Patients have decreased GSH levels in cerebrospinal fluid and prefrontal cortex and abnormal GSH synthesis: a GAG trinucleotide repeat polymorphism in the rate-limiting GSH synthesizing glutamate-cysteine ligase (GCL) catalytic subunit (GCLC) gene is associated with the disease. The associated genotypes correlate with decreased GCLC mRNA, protein expressions, GCL activity and GSH content. As demonstrated in various models, such redox dysregulation underlies structural and functional connectivity anomalies and behavioral deficits. In a clinical trial, the GSH precursor N-acetyl cysteine improved both negative symptoms and auditory evoked potentials. Thus, a genetic GSH synthesis impairment represents one major risk factor in schizophrenia. Redox dysregulation may constitute a 'hub' where genetic and environmental vulnerability factors converge and their timing during neurodevelopment might influence disease phenotypes.

The relationship between nutrition and food production is one that must be considered in any discussion of the value of nutrigenomics. The goal of the development of individualized dietary guidance is dependent on the availability and composition of the agricultural commodities that make up the food supply. Dr. Joseph Spence in the chapter 'Nutrigenomics and Agriculture: A Perspective' explores the recent example of genomic prediction in dairy cattle. The lessons learned in application of the genome-based technologies are related to the development of dietary guidance for humans. An examination of the success of genetic prediction suggests that the identification of individuals at risk for nutritionally related diseases is possible and could form the basis for individualized nutritional advice and guidance. Potential problems in the development of such advice and how an individual might use that information to change their diet are of concern. The use of genomic tools to identify individuals at risk of nutritionally related diseases and to develop individualized dietary advice are possible but is not without pitfalls and problems that will need to be addressed.

Dr. Peter Gillies and Dr. Penny M. Kris-Etherton in their paper 'Opportunities and Challenges in Nutrigenetics/Nutrigenomics: Building Industry-Academia Partnerships' state that the intersection of industry and academia creates a Venn space wherein knowledge, experience and nutrigenomic technology can be leveraged to produce healthier foods and dietary supplements. Notably, such products
are expected to have unprecedented nutritional pharmacology based on emerging principles of molecular nutrition. As the health-promoting properties of functional foods and dietary supplements increase, so does the need to resolve the 'nutrient-drug' debate. In this regard, the translational science of nutrigenomics involves everything from DNA to the FDA, and everybody from the private to the public sectors. The complexity and expense of this science, coupled with its potential for commercial application, inevitably draws industry and academia closer together as collaborators and partners. Although such ties are viewed by some as suspicious, fraught with bias and rife with conflict of interest, relationships based on shared ethical values, rigorous science and carefully selected projects, can be transparent and mutually beneficial. The experience of DuPont and the Pennsylvania State University is offered as a heuristic example of a successful industry-academic partnership and is presented herein in the context of omega-3 fatty acid research and molecular nutrition.

Another collaborative approach is presented by Dr. Lynnette Ferguson and colleagues in their manuscript ‘Tailoring Foods to Match People's Genes in New Zealand: Opportunities for Collaboration’. They point out that Nutrigenomics New Zealand is tasked with developing the necessary competence for the development of genespecific personalized foods (i.e. nutrigenetics). Initial work considers the response of 1 gene or gene variant, usually in the form of a SNP, to individual nutrients. The authors use Crohn's disease as proof of principle. Knowledge of key human Crohn's disease SNPs is incorporated into the design of isogenic cell lines, with and without the variant SNP of interest. Food extracts and components are tested for their ability to restore the normal phenotype in cellular models, before more selective testing in relevant animal models. In parallel, New Zealand Crohn's disease and control populations are tested for key genetic variants, and this information is compared with detailed dietary analysis. For example, a range of different foods show different tolerances in individuals carrying variants in an important Crohn's disease gene, NOD2. A substantial component of the program relies on high-quality data management, bioinformatics and biostatistics. International linkages will be essential for enhanced success of this program. In particular, testing hypotheses on gene-diet interactions will require large numbers of individuals in collaborative studies, with coordinated dietary and genotyping methods, to ensure that conclusions are adequately powered.

These proceedings should be of interest not only to scientists carrying out nutrigenetics/nutrigenomics research in academia, government and industry, but also to anyone interested in the future of personalized medicine, personalized nutrition and the future of agriculture. Such people would include physicians, geneticists, nutritionists, dieticians, food scientists, agriculturists in animal husbandry and horticulture, plant pathologists and persons interested in policy development in academia, industry and government.

*Artemis P. Simopoulos*, Washington, D.C.

*John A. Milner*, Bethesda, Md.
Conference Organization

Conference Co-Chairs

Artemis P. Simopoulos, MD (USA)
John A. Milner, MD (USA)

Planning Committee

Cindy D. Davis, NCI, NIH
Joseph Hibbelin, NIAAA, NIH
David Klurfeld, ARS, USDA
John Paul SanGiovanni, NEI, NIH
Pamela Starke-Reed, NIDDK, NIH

Conference Sponsors

National Cancer Institute
National Eye Institute
National Institute on Alcohol Abuse and Alcoholism
Eunice Kennedy Shriver National Institute of Child Health and Human Development
Division of Nutrition Research Coordination
Office of Dietary Supplements
U.S. Department of Agriculture
U.S. Food and Drug Administration
The Center for Genetics Nutrition and Health
Nutrilite Health Institute
National Dairy Council