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Personalized Nutrition

Translating Nutrigenetic/Nutrigenomic Research into Dietary Guidelines

Volume Editors

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Preface

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,