The Importance of Immunonutrition
Nestlé Nutrition Institute Workshop Series

Vol. 77
The Importance of Immunonutrition

Editors

Maria Makrides  North Adelaide, Australia
Juan B. Ochoa   Florham Park, NJ, USA
Hania Szajewska  Warsaw, Poland
Contents

VII Preface
IX Foreword
XIII Contributors

Modulation of Immune Responses and Nutrition

1 Arginine and Asthma
Morris, C.R. (USA)

17 Changes in Arginine Metabolism during Sepsis and Critical Illness in Children
de Betue, C.T.I. (The Netherlands); Deutz, N.E.P. (USA)

29 Arginine Deficiency Caused by Myeloid Cells: Importance, Identification and Treatment
Ochoa, J.B. (USA)

47 Glutamine Supplementation in Neonates: Is There a Future?
Neu, J. (USA)

57 Insulin in Human Milk and the Use of Hormones in Infant Formulas
Shamir, R.; Shehadeh, N. (Israel)

Microbiota and Pro-/Prebiotics

65 Diet, Gut Enterotypes and Health: Is There a Link?
Bushman, F.D.; Lewis, J.D.; Wu, G.D. (USA)

75 Understanding Immunomodulatory Effects of Probiotics
Pot, B.; Foligné, B.; Daniel, C.; Grangette, C. (France)

91 Transforming Growth Factor and Intestinal Inflammation: The Role of Nutrition
Ruemmele, F.M.; Garnier-Lengliné, H. (France)

99 Microbiota Modulation: Can Probiotics Prevent/Treat Disease in Pediatrics?
Szajewska, H. (Poland)
Contents

Lipids

111 Membrane Composition and Cellular Responses to Fatty Acid Intakes and Factors Explaining the Variation in Response
    Agostoni, C.; Risé, P.; Marangoni, F. (Italy)

121 Docosahexaenoic Acid and Its Derivative Neuroprotectin D1 Display Neuroprotective Properties in the Retina, Brain and Central Nervous System
    Bazan, N.G.; Calandria, J.M.; Gordon, W.C. (USA)

133 Branched-Chain Fatty Acids in the Neonatal Gut and Estimated Dietary Intake in Infancy and Adulthood
    Ran-Ressler, R.R.; Glahn, R.P.; Bae, S.; Brenna, J.T. (USA)

145 Clinical Overview of Effects of Dietary Long-Chain Polyunsaturated Fatty Acids during the Perinatal Period
    Scholtz, S.A.; Colombo, J.; Carlson, S.E. (USA)

155 Dietary n-3 LC-PUFA during the Perinatal Period as a Strategy to Minimize Childhood Allergic Disease
    Makrides, M.; Gunaratne, A.W.; Collins, C.T. (Australia)

163 Concluding Remarks

171 Subject Index

For more information on related publications, please consult the NNI website: www.nestlenutrition-institute.org
Preface

A healthy immune system is essential for normal existence and recovery from illness. Innate immunity, activated during illness, prepares us for successfully combating infection and healing wounds. Adaptive immune responses allow for long-term monitoring protecting us from neoplasia, fungi and mycobacterial infections among others. Successful immune responses require a careful orchestration of complex checks and balances avoiding excessive inflammation while preventing anergy. Uncontrolled inflammation can lead to self-injury as is observed in autoimmune diseases such as rheumatoid arthritis. On the other hand, dysfunctional T lymphocyte responses lead to uncontrolled opportunistic infections and tumor growth.

Nutrients in our diet form the necessary building blocks and substrate for all cellular function. We are indeed ‘what we eat’, literally. In just one generation, humanity has gone from struggling at finding ways to feed all to an epidemic of obesity that grips the entire world. Modern dietary habits are a causative factor for abnormal immune responses and illness. Type 2 diabetes, hypertension, atherosclerosis, and a growing list of cancers are linked to inflammation caused by the same dietary habits that cause obesity. The types of lipids and carbohydrates (and the amount) that we eat make us sick. Obesity is associated with uncontrolled inflammation and with an increased incidence of certain tumors.

Just as certain nutrients make us sick, others could potentially be beneficial in the prevention or management of illness. These nutrients appear to work by modifying immune responses (hence the name immunonutrition) when given during illness. Progressively, and sometimes painstakingly, we have accrued knowledge as to their mechanisms of action. This book summarizes the work performed by scientists at the forefront of studying immunonutrients in health and disease and provides the compilation of the data presented at 77th Nestlé Nutrition Institute Workshop on Immunonutrition. This book will discuss several different topics on immunonutrition: (1) arginine and glutamine; (2) lipids, including fish oil and branched-chain fatty acids, and (3) probiotics.
tion, this book will also discuss the presence of insulin, TGF-β and other bioactive peptides in milk.

Arginine and glutamine are two closely related amino acids described as being ‘conditionally’ essential, meaning that deficiencies in these amino acids develop during illnesses and may require dietary replacement to maintain or restore normal biological functions. Deficiencies in arginine are now being recognized in a number of illnesses and conditions such as asthma and sickle cell disease and after trauma. Arginine deficiency may also be important in the pathophysiology of sepsis. Glutamine may be highly important for maintaining mucosal trophism.

Milk contains more than just a combination of macro- and micronutrients with bioactive peptides such as insulin, TGF-β and others. The roles of peptides are progressively being understood. Insulin for example may play important roles in mucosal trophism for the GI tract, while it has been suggested that TGF-β may help regulate inflammation in inflammatory bowel disease.

Lipids may modify immune responses through several mechanisms. The type of lipid in the diet may determine the type of prostaglandin generated by cyclooxygenases. Eicosapentaenoic acid may play biological roles in T cells as agonists for peroxisome proliferator-activated receptors. Docosahexaenoic acid (DHA) is an essential fatty acid in the growth of the brain. Neuroprotectin 1 produced from DHA may regulate inflammation in the brain.

Humans have ten times more microbial cells than human cells, with the highest concentration of microorganisms located within the digestive tract. Around 1,000 different species have been identified with current microbiological techniques. Microbiota mediates many key functions, including metabolic, trophic, and protective (barrier) functions. Many of the microbes maintain health, while others are potential pathogens and can cause illness. Though the concept is not new, surprisingly little is known about the exact role and mechanisms by which these microorganisms contribute to human health or disease. Significant progress at identifying the gut microbiome has led to a better understanding of the interactions between them and our organs and tissues. Probiotics, while not considered a nutrient, are certainly part of our diet. The roles that resident or ingested organisms may play in disease are now potential targets of treatment.

It is our hope that you find this book useful in your practices, be it in the research lab or at the bedside.

Maria Makrides
Juan B. Ochoa
Hania Szajewska
Foreword

Nutrients have a tremendous potential to modulate the actions of the immune system, a fact which has a significant impact on public health and clinical practice.

The concept of pharmaconutrition – a central element of intensive care management – implies a bridge between drugs and nutrition. During the last decade, the role of nutrition, beyond providing the calories and the macro- and micronutrients for survival, has been well established and clinically proven. At the 77th Nestlé Nutrition Institute Workshop held from October 28th to November 1st 2012, world experts gathered in Panama City to present their latest findings on how nutrient status can modulate immunity and improve health conditions in pediatric patients. The 3 sessions of this workshop covered major aspects of the interplay between nutrients and the regulation of immunity and inflammatory processes.

The first session explored the pharmaceutical value of specific amino acids (arginine and glutamine) and hormones for addressing immune disorders and infant development. It is now understood that some amino acids have the ability to speed up the recovery of children admitted to intensive care. We took a closer look at the relationship between arginine metabolism and asthma, the role of this amino acid in T-lymphocyte function, and investigated the rationale for glutamine supplementation to improve outcomes in premature infants.

Many immune disorders and diseases are associated with dysregulation of the gut microbial homeostasis. The second session revolved around gut function and immunity, and the right balance of probiotics. The right microbiome can modulate the immune system and help protect from infectious disease, obesity and allergy. Getting the right mix of probiotics is key to unlocking their full benefits. The overview of the MetaHIT project presented during this session showed that individuals can be clustered based on their microbial metagenome profile, thus laying the framework for profiling health and disease.
The third session explored the role of lipid mediators and how their types and proportions can tip the balance in favor of health or disease. Given in the right time and conditions, lipids can prevent allergy, modulate the inflammatory process in the gut and play a protective role when cell homeostasis is threatened by neurodegeneration. It was discussed that early LC-PUFA supplementation not only supports cognitive function but also may program brain development in later life stages.

We wish to thank the three chairpersons – Prof. M. Makrides, Prof. J. Ochoa and Prof. H. Szajewska for establishing an excellent scientific workshop program. We are also indebted to the renowned speakers who have further debated and increased our understanding of this important topic through their presentations and participation. We thank the many experts who came from across the globe to review and discuss the importance of immunonutrition.

Finally, we wish to thank and congratulate Luis Carlos Delgado and his team from Nestlé Nutrition LATAM for their excellent logistical support and hospitality that allowed us to not only enjoy the scientific program but also experience the historical spirit of Panama City.

Ferdinand Haschke, MD, PhD  
Chairman  
Nestlé Nutrition Institute  
Vevey, Switzerland

Natalia Wagemans, MD, PhD  
Global Medical Advisor  
Nestlé Nutrition Institute  
Vevey, Switzerland
Contributors

Chairpersons & Speakers

Prof. Carlo Agostoni
Department of Maternal and Pediatric Sciences
University of Milan
Fondazione IRCCS Ca’ Granda – Ospedale Maggiore Policlinico
Via della Commenda 9
IT–20122 Milano
Italy
E-Mail agostoc@tin.it

Prof. Nicolas G. Bazan
LSU Health New Orleans
School of Medicine Neuroscience Center of Excellence and
Department of Ophthalmology
2020 Gravier Street, Suite D
New Orleans, LA 70112
USA
E-Mail Nbazan@lsuhsc.edu

Prof. James Thomas Brenna
Cornell University
Division of Nutritional Sciences
Savage Hall
244 Garden Ave
Ithaca, NY 14853
USA
E-Mail jtb4@cornell.edu

Prof. Susan E. Carlson
University of Kansas Medical Center
Department of Dietetics and Nutrition
MS 4013, 3901 Rainbow Boulevard
Kansas City, KS 66160
USA
E-Mail scarlson@kumc.edu

Dr. Carlijn T.I. de Betue
Erasmus MC – Sophia Children’s Hospital
Department of Pediatric Surgery
Dr. Molewaterplein 60
NL–3015 GJ Rotterdam
The Netherlands
E-Mail carlijndebetue@gmail.com

Prof. Maria Makrides
Women’s & Children’s Health Research Institute
University of Adelaide
72 King William Road
North Adelaide SA 5006
Australia
E-Mail maria.makrides@health.sa.gov.au

Dr. Claudia R. Morris
Emory University School of Medicine
Department of Pediatrics
1645 Tullie Circle
Atlanta, CA 30322
USA
E-Mail Claudiamorris@comcast.net
Prof. Josef Neu
University of Florida
1600 SW Archer Road
Gainesville, FL 32610-0296
USA
E-Mail neuj@peds.ufl.edu

Dr. Juan B. Ochoa
Nestlé Nutrition
12 Vreeland Road, 2nd floor
Florham Park, NJ 07932
USA
E-Mail Juan.ochoa@us.nestle.com

Prof. Bruno Pot
Institut Pasteur de Lille
1, Rue du Prof Calmette
FR–59000 Lille Cedex
France
E-Mail bruno.pot@pandora.be

Prof. Frank M. Ruemmele
Hospital Necker-Enfants Malades
149 Rue de Sèvres
FR–75015 Paris
France
E-Mail frank.ruemmele@nck.aphp.fr

Prof. Raanan Shamir
Institute of Gastroenterology, Nutrition and Liver Diseases
Schneider Children’s Medical Center of Israel
14 Kaplan Street, Petach-Tikva
IL–49202 Israel
E-Mail shamirraanan@gmail.com

Prof. Hania Szajewska
The Medical University of Warsaw
Department of Pediatrics
Dzialdowska 1
PL–01-184 Warsaw
Poland
E-Mail hania@ipgate.pl

Prof. Gary D. Wu
University of Pennsylvania
Perelman School of Medicine
Suite 600 CRB
415 Curie Blvd
Philadelphia, PA 19104
USA
E-Mail gdwu@mail.med.upenn.edu

Participants
Carlos Lifschitz/Argentina
Jennifer Campbell/Barbados
Jose Enrique Samos/Belize
Christiane Leite/Brazil
Virginia Weffort/Brazil
Sara Bernal/Colombia
Andrés Chacón Jorge/Colombia
Silvana Dadan/Colombia
Wilson Daza/Colombia
Luis Carlos Delgado/Colombia
Monica Escobar/Colombia
David Espinal/Colombia
Patrick Levieil/Colombia
Enilda Puello Mendoza/Colombia
Norberto Salamanca/Colombia
Arturo Abdelnour/Costa Rica
Javier Alvarez/Costa Rica
Ommar Parra/Costa Rica
Carlos Quiros/Costa Rica
Isaura Cornelio/Dominican Republic
Patricia Fernandez/Dominican Republic
Wendy Hamilton/Dominican Republic
Yun Zyon Kim/Dominican Republic
Sara Tolentino/Dominican Republic
Xavier Abril/Ecuador
Hugo Bardellini/Ecuador
Marina Bran/Ecuador
Indira Castillo/Ecuador
Joffre Egas/Ecuador
Rosario Jijon/Ecuador
Alejandro Xavier Lara Borja/Ecuador
Angel Luna/Ecuador
Jean Mero/Ecuador
Carlos Moncayo/Ecuador
Carlos Mosquera/Ecuador
Roberto Nuñez/Ecuador
Amapola Ortiz/Ecuador
Nidia Ortola/Ecuador
Natasha Robalino/Ecuador
Ivan Serpa/Ecuador
Ivan Williams/Ecuador
Jose Oliva/El Salvador
Juan Carlos Reyes Cisneros/El Salvador
Lorena Zeceña/El Salvador
Jean Pierre Chouraqui/France
Dominique Darmaun/France
Víctor Alfonso/Guatemala
Jorge Palacios/Guatemala
Carlos Manuel Perez Valdez/Guatemala
Flor Ramírez/Guatemala
Norma González/Honduras
Karla Fernández/Honduras
Martha Matamoros/Honduras
Giovanni Corsello/Italy
Garfield Badal/Jamaica
Andrea Garbutt/Jamaica
Tracia James Powell/Jamaica
Lyer Ramos/Jamaica
Osmond Tomlinson/Jamaica
Aristóteles Alvarez Cardona/Mexico
Martín Mauricio Bretón La Loza/Mexico
Ana Paola Campos/Mexico
Arturo Castro Cue/Mexico
Alejandra Consuelo/Mexico
Manuel Díaz Gómez/Mexico
Jesús González Frias/Mexico
Manuel Guajardo/Mexico
José Antonio Hurtado/Mexico
Fernando Infante/Mexico
Víctor Javier Lara Díaz/Mexico
Victoria Lima/Mexico
Jesús Magaña/Mexico
Luis Gustavo Orozco/Mexico
Sergio Romero Tapia/Mexico
Edgar Vázquez/Mexico
Osvaldo Zarco Del Cid/Mexico
Benjamín Barbosa/Nicaragua
Ariadne Espinosa/Nicaragua
César López/Nicaragua
Alberto Bissot/Panama

Maria Iované/Panama
Argelia Loo/Panama
Roberto Murgas Torraza/Panama
Katia Rueda/Panama
Jose Luis Gonzales Benavides/Peru
Casilda Maribel Diaz Toledo/Puerto Rico
Etienne Nel/South Africa
Christina West/Sweden
Ferdinand Haschke/Switzerland
Natalia Wagemans/Switzerland
Brenda Babulal/Trinidad and Tobago
Jatinder Bhatia/USA
Andrea Papamandjaris/USA
Abraham Abraham Greege/Venezuela
Jorge Bonini/Venezuela
Maria Jose Castro/Venezuela
Jose Diaz/Venezuela
Claudio Gutierrez/Venezuela
Marianella Herrera/Venezuela
Keira Leon/Venezuela
Cisneros Liz/Venezuela
Ana Nucette/Venezuela
Maria Eugenia Reymundez/Venezuela
Luciano Saglimbeni/Venezuela
Carmen Salazar/Venezuela
Anadina Salvatierra/Venezuela
Rafael Santiago/Venezuela
Rosa María Soto Rodríguez/Venezuela