Molecular Basis of Health and Disease
Molecular Basis of Health and Disease
To
My Wife Lakshmi
and
Daughter Arundhati, Son Aditya
and Son-in-Law Dr. Kalasagar Madugula
Several studies have suggested that low-grade systemic inflammation plays a significant role in the pathogenesis of obesity, insulin resistance, essential hypertension, type 2 diabetes, atherosclerosis, coronary heart disease, metabolic syndrome, dyslipidemia, lupus, rheumatoid arthritis and other autoimmune diseases, schizophrenia, depression, Alzheimer’s disease and cancer. This is supported by the observation that plasma C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), markers of inflammation, levels are elevated in these subjects.

With ageing, plasma levels of CRP, IL-6 and TNF-α tend to increase and produce insulin resistance and secondary hyperinsulinemia. Alzheimer’s disease, schizophrenia, and depression are also associated with an increase in plasma and cerebrospinal fluid CRP, IL-6, TNF-α, and lipids peroxides. In all these conditions, similar, if not identical, changes in the plasma, RBC, and tissue concentrations of polyunsaturated fatty acids and anti-oxidants have been described. Similarity in the molecular events at the cellular level suggest that methods designed to suppress inappropriate inflammation and augment resolution of inflammation and tissue repair could be of therapeutic benefit in these conditions.

In this context, it is of particular significance that alterations in the metabolism of essential fatty acids and the formation of their anti-inflammatory metabolites such as lipoxins, resolvins, protectins, maresins and nitrolipids seem to be responsible for the onset of low-grade systemic inflammation in these diseases. In view of this understanding the factors and co-factors, both endogenous and exogenous, that have the ability to modulate the metabolism of essential fatty acids and the formation of their anti-inflammatory products is important. Since these anti-inflammatory lipid compounds suppress the production of pro-inflammatory eicosanoids, it appears that a disturbed balance between these pro- and anti-inflammatory products of polyunsaturated fatty acids play a significant role in the pathobiology of several adult diseases.

This is particularly relevant to the pathobiology of the metabolic syndrome that has been attributed to lack of exercise, increase in the consumption of energy-dense food and environmental changes. It is likely that insulin resistance, low-grade systemic inflammation, low-birth weight (especially in the Indian sub-continent), maternal malnutrition (both over and under-nutrition), perinatal and early childhood high
carbohydrate and saturated fat diet and low polyunsaturated fatty acid intake could be responsible for this disease.

There is reasonable evidence to suggest that obesity, insulin resistance, type 2 diabetes mellitus, hypertension which are all the components of the metabolic syndrome, may occur as a result of dysfunction of specific hypothalamic nuclei and their peptide and monoaminergic neurotransmitters, an issue that needs due attention.

Human brain is rich in polyunsaturated fatty acids (PUFAs) and so they are likely to play a significant role in the pathogenesis of the metabolic syndrome, neurological conditions such as Alzheimer’s disease, schizophrenia and depression.

PUFAs play a significant role in brain growth and development, modulate the actions of various neurotransmitters that have an important role in the pathobiology of the metabolic syndrome and Alzheimer’s disease, schizophrenia and depression suggesting that perinatal supplementation of PUFAs could be of significant help in the prevention of these diseases since brain development occurs predominantly during the second and third trimester of pregnancy and first 5 years of life. Thus, metabolic syndrome could be a disorder of the brain. This explains why breast fed subjects have low incidence of these diseases since human breast milk is rich in PUFAs.

Vagus nerve has a regulatory role in insulin secretion, modulates inflammation, influences the levels of (BDNF) brain-derived neurotrophic factor and its stimulation increases the secretion of incretins from the gut, suggesting that vagus nerve stimulation could exploited in the treatment of insulin resistance, type 2 diabetes mellitus and metabolic syndrome and Alzheimer’s disease, schizophrenia and depression; in addition to its already established role in the treatment of resistant epilepsy.

Cancer is also a low-grade systemic inflammatory condition. Some PUFAs selectively kill tumor cells without harming normal cells. Hence, it is possible to use monoclonal antibodies against growth factors that are complexed with PUFAs in the treatment of cancer. Thus, a combination of PUFAs, BDNF, vagus nerve stimulation, and other strategies could be adopted to prevent and manage several adult diseases.

I trust that several of new concepts proposed in this book would interest many scientists and encourage them to test them out.

Shaker Heights, OH

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About the Author

Undurti N. Das is an M.D. in Internal Medicine from Osmania Medical College, India; a Fellow of the National Academy of Medical Sciences, India, and Shanti Swaroop Bhatnagar prize awardee. His current interests include the epidemiological aspects of diabetes mellitus, hypertension, CVD and metabolic syndrome. Dr. Das was formerly a scientist at Efamol Research Institute, Kentville, Canada; Professor of Medicine at Nizam’s Institute of Medical Sciences, India and Research Professor of Surgery and Nutrition at SUNY (State University of New York) Upstate Medical University, Syracuse, USA. At present, he is the Chairman and Research Director of UND Life Sciences, USA. Dr. Das is also the Editor-in-Chief of: Lipids in Health and Disease. Dr. Das has more than 400 international publications and has been awarded 4 USA patents. Dr. Das is in receipt of Ramalingaswami Fellowship of the Department of Biotechnology of India during the tenure of writing this book. Previous books by Dr. U N Das include: A Perinatal Strategy for Preventing Adult Disease: The Role of Long-Chain Polyunsaturated Fatty Acids, Kluwer Academic Press, 2002; and Metabolic Syndrome Pathophysiology: The Role of Essential Fatty Acids, Wiley-Blackwell, 2010. Address: UND Life Sciences, 13800 Fairhill Road, #321, Shaker Heights, OH 44120, USA, Tel.: +1-216-231-5548, Fax: +1-928-833-0316, e-mail: Undurti@hotmail.com; School of Biotechnology, Jawaharlal Nehru Technological University, Kakinada 533003, India
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