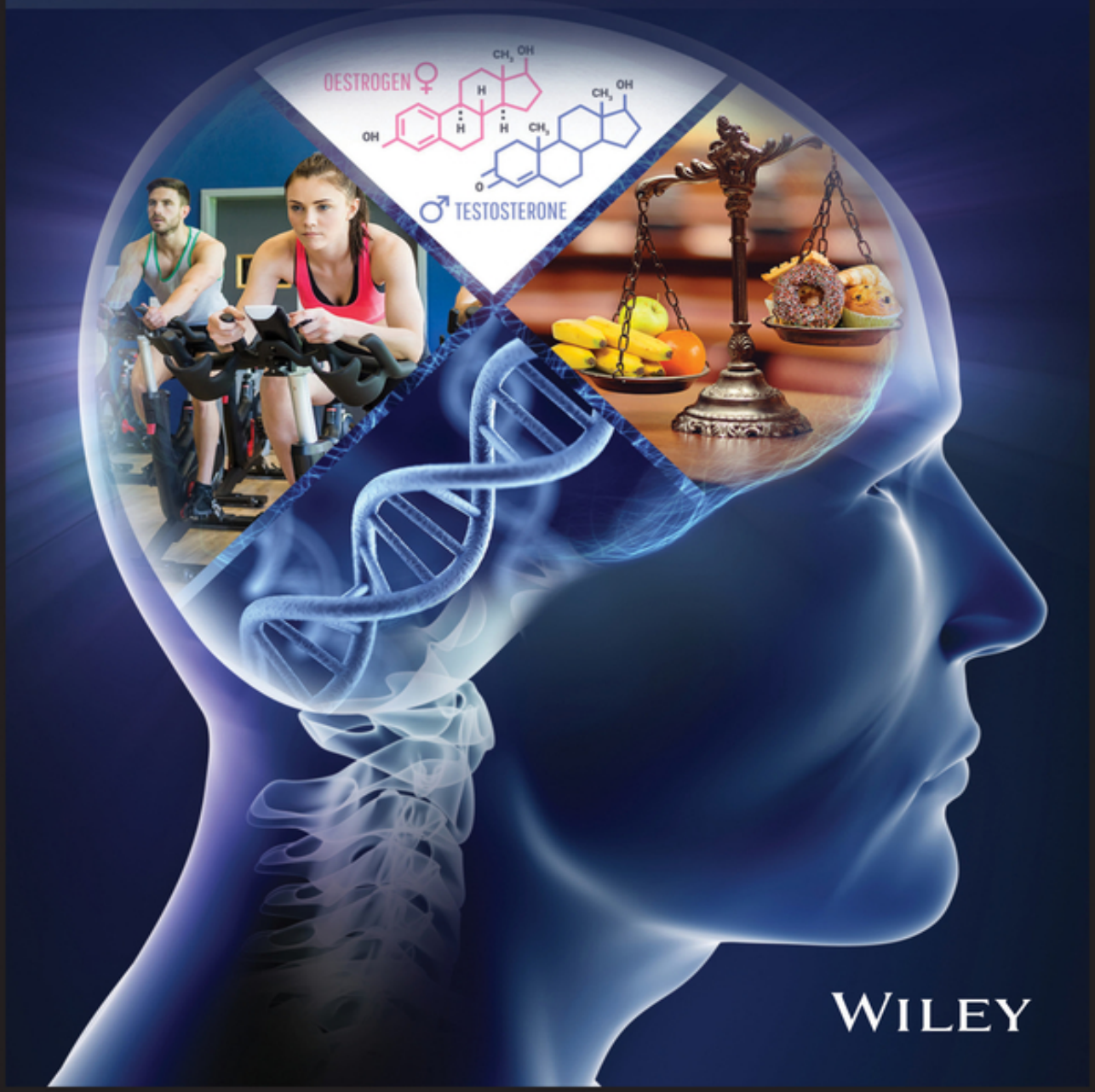
Editors: Ralph N. Martins, Charles S. Brennan
Associate Editors: W.M.A.D. Binosha Fernando,
Margaret A. Brennan, Stephanie J. Fuller

Neurodegeneration and Alzheimer's Disease

The Role of Diabetes, Genetics, Hormones, and Lifestyle



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Edited by

Editors:
Ralph N. Martins
Edith Cowan University
Joondalup
Australia

Macquarie University
Sydney
Australia

Charles S. Brennan
Lincoln University
Christchurch
New Zealand

Associate Editors:
W.M.A.D. Binosha Fernando
Edith Cowan University
Joondalup
Australia

Margaret A. Brennan
Lincoln University
Christchurch
New Zealand

Stephanie J. Fuller
Edith Cowan University
Joondalup
Australia

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This edition first published 2019

Registered Office(s)
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030,USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ,UK

Editorial Office
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ,UK

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Library of Congress Cataloging-in-Publication data has been applied for

ISBN: 9781119356783

Cover Design: Wiley
Cover Images: © Irina Shatilova/Shutterstock, © Henrik5000/iStock.com, © corgarashu/Shutterstock, © Andrey Prokhorov/iStock.com

Set in 10/12pt WarnockPro by SPi Global, Chennai, India

10 9 8 7 6 5 4 3 2 1

Contents

List of Contributors

Anna M. Barron
School of Psychiatry and Clinical Neurosciences
University of Western Australia
Perth, WA, Australia

and

Lee Kong Chian School of Medicine
Nanyang Technological University
Singapore

Prashant Bharadwaj
Centre of Excellence for Alzheimer's Disease Research and Care
School of Medical Sciences
Edith Cowan University
Joondalup, WA, Australia

and

School of Pharmacy and Biomedical Sciences
Curtin Health and Innovation Research Institute (CHIRI)
Faculty of Health Sciences
Curtin University
Perth, WA, Australia

and

Australian Alzheimer's Research Foundation
Ralph and Patricia Sarich Neuroscience Research Institute
Nedlands, WA, Australia

Charles S. Brennan
Department of Wine, Food and Molecular Biosciences
Centre for Food Research and Innovation
Lincoln University
Christchurch, New Zealand

and

School of Food Science
South China University of Technology
Guangzhou, China

and

School of Food Science
Tianjin University of Commerce
Tianjin, China

and

Riddett Institute Palmerston North
New Zealand

Margaret A. Brennan
Department of Wine, Food and Molecular Biosciences
Centre for Food Research and Innovation
Lincoln University
Christchurch, New Zealand

and

College of Food Science
South China University of Technology
Guangzhou, China

and

School of Food Science
Tianjin University of Commerce
Tianjin, China

Belinda Brown
School of Psychology and Exercise Science
Murdoch University
Perth, WA, Australia

and

Australian Alzheimer's Research Foundation
Ralph and Patricia Sarich Neuroscience Research Institute
Nedlands, Australia

Michele L. Callisaya
Menzies Institute for Medical Research, University of Tasmania
Hobart, TAS, Australia

and

Peninsula Clinical School
Central Clinical School Monash University
Melbourne, Vic, Australia

Nicholas Carrigan
Older Adult Mental Health Service
Western Australia Country Health Service (SouthWest)
Bunbury, WA, Australia

and

School of Medical and Health Sciences
Centre of Excellence for Alzheimer's Disease Research and Care
Edith Cowan University
Joondalup, WA, Australia

and

Australian Alzheimer's Research Foundation Ralph and Patricia Sarich Neuroscience Research Institute
Nedlands, WA, Australia

Rhona Creegan
Omega Nutrition Health
Perth, WA, Australia

W.M.A.D. Binosha Fernando
Centre of Excellence for Alzheimer's Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Australian Alzheimer's Research Foundation
Ralph and Patricia Sarich Neuroscience Research Institute
Nedlands, WA, Australia

Paul E. Fraser
Tanz Centre for Research in Neurodegenerative Diseases
University of Toronto
Canada

Stephanie J. Fuller
School of Medical and Health Sciences
Centre of Excellence for Alzheimer's Disease Research and Care
Edith Cowan University
Joondalup, WA, Australia

Kathryn G. Goozee
Department of Biomedical Sciences
Macquarie University
Sydney, NSW, Australia

and

School of Psychiatry and Clinical Neurosciences
University of Western Australia
Perth, WA, Australia

and

Cooperative Research Centre for Mental Health
Carlton, Vic, Australia

and

Kara Institute of Neurological Diseases
Sydney, NSW, Australia

and

Anglicare
Sydney, NSW, Australia

Aleksandra K. Gozt
Collaborative Genomic Group
Centre of Excellence for Alzheimer's Disease Research and Care
School of Medical Sciences
Edith Cowan University
Joondalup, WA, Australia

Veer B. Gupta
School of Medicine
Deakin University
Geelong, Vic, Australia

Eugene Hone
Centre of Excellence for Alzheimer's Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Cooperative Research Centre for Mental Health
Carlton, Vic, Australia

Vijay Jayasena
School of Science and Health
Western Sydney University
Sydney, NSW, Australia

Shanmugam Kirubakaran
Department of Pharmacology and Molecular Medicine Research Group
School of Medicine
Western Sydney University
Sydney, NSW, Australia

Simon M. Laws
Collaborative Genomic Group
Centre of Excellence for Alzheimer's Disease Research and Care
School of Medical Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Cooperative Research Centre for Mental Health
Carlton, Vic, Australia

and

School of Pharmacy and Biomedical Sciences
Faculty of Health Sciences
Curtin Health Innovation Research Institute
Curtin University
Bentley, WA, Australia

Florence Lim
Centre of Excellence for Alzheimer's Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Cooperative Research Centre for Mental Health
Carlton, Vic, Australia

Ian J. Martins
Centre of Excellence for Alzheimer's Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Cooperative Research Centre for Mental Health
Carlton, Vic, Australia

Ralph N. Martins
School of Medical and Health Sciences
Centre of Excellence for Alzheimer's Disease Research and Care
Edith Cowan University
Joondalup, WA, Australia

and

Department of Biomedical Sciences
Macquarie University
Sydney, NSW, Australia

and

School of Psychiatry and Clinical Neurosciences
University of Western Australia
Perth, WA, Australia

and

KaRa Institute of Neurological Diseases
Sydney, NSW, Australia

and

Australian Alzheimer's Research Foundation
Ralph and Patricia Sarich Neuroscience Research Institute
Nedlands, WA, Australia

Francis L. Mastaglia
Institute for Immunology and Infectious Diseases
Murdoch University
Murdoch, WA, Australia

Mike Morici
Centre of Excellence for Alzheimer's Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

Gerald Münch
Department of Pharmacology and Molecular Medicine Research Group
School of Medicine
Western Sydney University
Sydney, NSW, Australia

Steve Pedrini
Centre of Excellence for Alzheimer's Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Australian Alzheimer's Research Foundation
Ralph and Patricia Sarich Neuroscience Research Institute
Nedlands, WA, Australia

Tenielle Porter
Collaborative Genomic Group
Centre of Excellence for Alzheimer's Disease Research and Care
School of Medical Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Cooperative Research Centre for Mental Health
Carlton, Vic, Australia

Stephanie R. Rainey-Smith
Centre of Excellence for Alzheimer's Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Australia Alzheimer's Research Foundation
Ralph and Patricia Sarich Neuroscience Research Institute
Nedlands, WA, Australia

Anoop Sankaranarayanan
Department of Psychiatry
School of Medicine
Western Sydney University
Sydney, NSW, Australia

Tejal M. Shah
Department of Biomedical Sciences
Macquarie University
Sydney, NSW, Australia

and

Centre of Excellence for Alzheimer's Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

Matthew J. Sharman
School of Health Sciences
University of Tasmania
Launceston, TAS, Australia

Hamid R. Sohrabi
School of Medical and Health Sciences
Centre of Excellence for Alzheimer's Disease Research and Care
Edith Cowan University
Joondalup, WA, Australia

and

Department of Biomedical Sciences
Macquarie University
Sydney, NSW, Australia

and

School of Psychiatry and Clinical Neurosciences
University of Western Australia
Perth, WA, Australia

and

Cooperative Research Centre for Mental Health
Carlton, Vic, Australia

and

KaRa Institute of Neurological Diseases
Sydney, NSW, Australia

and

Australian Alzheimer's Research Foundation
Ralph and Patricia Sarich Neuroscience Research Institute
Nedlands, WA, Australia

Velandai Srikanth
Department of Medicine, Peninsula Health
Melbourne, Vic, Australia

and

Peninsula Clinical School, Central Clinical School
Monash University
Melbourne, Vic, Australia

Giuseppe Verdile
School of Pharmacy and Biomedical Sciences
Faculty of Health Sciences
Curtin Health Innovation Research Institute
Curtin University of Technology
Bentley, WA, Australia

and

Centre of Excellence for Alzheimer's Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Australian Alzheimer's Research Foundation
Ralph and Patricia Sarich Neuroscience Research Institute
Nedlands, WA, Australia

Michael Weinborn
School of Psychology
University of Western Australia
Crawley, WA, Australia

and

Centre of Excellence for Alzheimer's Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Australian Alzheimer's Research Foundation
Ralph and Patricia Sarich Neuroscience Research Institute
Nedlands, WA, Australia

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Current Understanding of Alzheimer's Disease and Other Neurodegenerative Diseases, and the Potential Role of Diet and Lifestyle in Reducing the Risks of Alzheimer's Disease and Cognitive Decline

Charles S. Brennan[1,2,3,4], *Margaret A. Brennan*[1,2,4], *W.M.A.D. Binosha Fernando*[5,9] *and Ralph N. Martins*[5,6,7,8,9]

[1] *Department of Wine, Food and Molecular Biosciences, Centre for Food Research and Innovation, Lincoln University, PO Box 85084, Lincoln, Christchurch, New Zealand*
[2] *School of Food Science, South China University of Technology, Guangzhou, China*
[3] *Riddet Institute, Palmerston North, New Zealand*
[4] *School of Food Science, Tianjin University of Commerce, Tianjin, China*
[5] *School of Medical and Health Sciences, Centre of Excellence for Alzheimer's Disease Research and Care, Edith Cowan University, Joondalup, WA, Australia*
[6] *Department of Biomedical Sciences, Macquarie University, Sydney, NSW, Australia*
[7] *School of Psychiatry and Clinical Neurosciences, University of Western Australia, Perth, WA, Australia*
[8] *KaRa Institute of Neurological Diseases, Sydney, NSW, Australia*
[9] *Australian Alzheimer's Research Foundation, Ralph and Patricia Sarich Neuroscience Research Institute, Nedlands, WA, Australia*

This book is intended to give an up-to-date overview of what is currently known about neurodegenerative diseases, focusing particularly on Alzheimer's disease (AD). Current and developing diagnostic tests are described, and the pathological relationships between AD and other conditions now believed to be risk factors for AD are also described. In particular, we discuss cardiovascular disease, obesity, insulin resistance and type 2 diabetes, focusing on abnormal lipid and sugar metabolism linked to these conditions, and how this is related to AD risk. We provide evidence that improved diet and exercise may reduce AD risk, not just the risk of the other conditions mentioned above. Hopefully this book will provide some food for thought concerning easily adoptable non-pharmacological methods to reduce AD risk, which would need to be adopted at early pre-clinical stages of the disease.

Diet and health are intrinsically linked, and the effect of dietary intakes on our health has been researched and documented for millennia. The consumption of protein, fat, carbohydrates, vitamins and minerals is required for our physiological function. Certain food-based chemicals – bioactive compounds – yield health benefits beyond their mere chemical constituents, and can modify the biological functionality and health of our cells. These bioactive compounds may help enhance repair of our bodies from injuries, mediate the risk of certain diseases (cancer, coronary heart disease) through altering the physiological functions of our cells and organs. There is strong public awareness in terms of the old adage 'you are what you eat', however the information available to the public ranges from scientifically based research, to traditional dietary remedies, to dangerous fad diets. There is also a plethora of food products that have been designed by the food

Neurodegeneration and Alzheimer's Disease: The Role of Diabetes, Genetics, Hormones, and Lifestyle, First Edition. Edited by Ralph N. Martins, Charles S. Brennan, W.M.A.D. Binosha Fernando, Margaret A. Brennan and Stephanie J. Fuller.

industry to provide consumers with foods or supplements designed to combat all sorts of illnesses and disorders.

We have long known that there is a connection between the over-consumption of calories and weight gain, particularly fats and carbohydrates. For example, an excess of refined carbohydrates has been associated with overweight, obesity, type 2 diabetes and a number of metabolic disorders and now also, as described in this book, neurodegenerative diseases such as AD and cerebrovascular disease. However, despite this knowledge, and despite the introduction of numerous public health intervention programmes by governments and medical bodies, the percentage of the population which can be classified as overweight or obese continues to rise. Though there is research evidence that some genetic traits predispose certain people to easier weight gain, leading to obesity, this rise in obesity is believed by most to be mainly a result of increased calorie intake and reduced calorie expenditure.

Recently there has been an increased interest in the role the food industry has played in the production of modern food materials. Researchers and popular writers alike are keen to blame the food industry for today's nutritional problems by suggesting that modern food processing techniques produce what some people call high-calorie, energy-dense, nutrient-poor foods, and it would be foolish to ignore the fact that the food industry has played a part in the situation we find ourselves in. If we are consuming more calories as a population than we were 20 or 50 or 70 years ago, and if many of the foods consumed are highly processed, then this has a double impact on our nutritional status. Combine this with the fact that most of us are becoming more sedentary in our work and social lives, then the balance would be that we will be prone to storing excess calories. As described in this book, overweight and obesity as well as high consumption of refined carbohydrates lead to insulin resistance, type 2 diabetes and cardiovascular disease, which are in epidemic proportions in western countries. There is a train of thought that suggests that this overconsumption of calories is a 'western' problem; however, the situation is manifesting itself to be a global problem, with dramatic increases in Asian countries in recent years (for instance, rapid rises in obesity and diabetes levels in China, Malaysia, Singapore and Taiwan, to name a few).

Fat and lipid metabolism has been studied at length in relation to cardiovascular health, and more recently this topic has become important in AD studies. A few decades ago, all fats were regarded as unhealthy, and a high fat intake, particularly cholesterol, was considered to be the main dietary problem when taking into account the increasing rate of obesity, hypertension and cardiovascular disease in western countries. This led to the food industry generating products that were low in fat. However, to compensate on flavour, these foods often contained higher sugar and salt levels than previously. More recent research indicates that cholesterol is not the main problem, that long-chain saturated fat is a greater problem than cholesterol, and that high sugar intake from carbonated drinks, confectionery and processed foods has only exacerbated the increasing obesity level. Furthermore, lifestyle changes [1] have created a demand for more convenience foods, and foods with a long shelf life. These foods are generally more highly processed than those which were available 30–70 years ago. There is also scientific research which indicates that food processing affects the structure of the protein, fat and carbohydrate components (including sugar in the carbohydrate fraction) in foods. These changes may have led to longer shelf-life, or made the foods more desirable, however many have a high salt or high sugar content,

and may contain undesirable fats such as trans-fatty acids. In addition, our intake of essential fatty acids has changed with the advent of processed foods and other western dietary changes. The intake of essential polyunsaturated fatty acids, in particular the omega-3 and omega-6 fatty acids, has considerable influence on our brain health, levels of inflammation and brain function, yet our intake, and the ratio of omega-6 : omega-3 fatty acids has changed over the millennia. There is evidence that we evolved on a diet with a ratio of omega-6 : omega-3 fats of approximately 1 : 1, yet a western diet has a ratio of approximately 15 : 1, and omega-6 fatty acids are linked to increased brain inflammation, as discussed in this book.

Several chapters in this book describe how excess refined carbohydrate intake disrupts the metabolic functions of the body. Once these are compromised, the body is subjected to stress. This stress is in the form of chronic inflammation and oxidative stress [2], which then negatively influences cellular functionality, cellular signalling and in the brain – neurological function. These are some of the findings of studies illustrating that obesity and type 2 diabetes are significant risk factors for the development of neurological disorders including AD [3].

Two chapters of the book discuss the various common causes and symptoms of dementia, differential diagnosis, AD diagnostic tests, and current treatments. AD is characterised by gradual cognitive impairment, and the risk of developing this condition increases with age, such that, past the age of 65, the risk doubles every five years. Pathologically, the disease is characterised by the death of neurons in the cerebral cortex, hippocampus and forebrain, which is associated with the formation of extracellular amyloid deposits, intracellular neurofibrillary tangles consisting of hyper-phosphorylated tau protein, as well as inflammation [4]. Although medications are available for the treatment of AD, these medications only serve to reduce the cognitive symptoms of some people with AD and then only for a relatively short period. There are also medications that can reduce other symptoms of Alzheimer's, such as anxiety and sleeplessness, and these are all discussed in this book. However, there are currently no medications that can stop the eventual continuing neurological degeneration and resultant cognitive degeneration of Alzheimer's. As mentioned earlier, one of the main messages of this book is that, if we can manipulate our diet and lifestyle at mid-life, and reduce our risks associated with excess calorie intake, overweight, obesity and type 2 diabetes, we may be able to achieve long-term prevention or delay of the disorder.

We should be concerned about food consumption and obesity. This could be discussed in terms of a change in lifestyle opportunities, or self-esteem or peer perception. The way weight issues contribute to psychological and personal well-being has been studied extensively in the past. More importantly, there is a health cost associated with these issues. Increased weight and obesity have been documented to be associated with a reduction in life expectancy through greater risk factors associated with type 2 diabetes, coronary heart disease, metabolic complications and more recently AD and other neurodegenerative diseases.

Epidemiological studies have investigated the effect of certain diets on longevity and health, particularly the Mediterranean diet and Okinawan diets. Laboratory studies have also investigated the relationship between certain food components and the manipulation of physiological effects either through whole animal studies, or through *in vitro* experiments using cell culture. Many epidemiological and longitudinal studies have illustrated that there is an increased risk for AD and cognitive impairment in

future years, in those individuals exhibiting obesity and diabetes. Several chapters of this book discuss glucose metabolism [5], insulin resistance, carbohydrate metabolism, and how a high intake of refined carbohydrate and sugar can lead to dysregulated brain glucose metabolism, inflammation and oxidative stress, and how all of the above are linked to AD.

Many studies have reported a correlation between diets rich in saturated fatty acids and increased low-density lipoprotein, decreased high-density lipoprotein and what is now regarded as high blood cholesterol levels; this in turn has been associated with the development of neurological impairment through cerebral inflammation, and increased development of Aβ deposition in the brain. Other studies have indicated that as people age, the content of docosahexaenoic acid (DHA) in the brain decreases. Furthermore, animal studies have shown that DHA supplementation improves cognitive functions through the regulation of cell lipids and Aβ production. These are some of the findings that support the change from a diet rich in saturated fats to one rich in polyunsaturated fats, particularly the omega-3 fatty acids. Lipids in the diet and how they relate to the risk of AD are discussed in a chapter of this book.

Mounting scientific data indicates that antioxidants contribute to the neutralisation of oxidative reactions occurring in the body [6], and increased intake of dietary fibre can aid weight control, glucose metabolism and the gut–brain axis. For instance, research has suggested that there is a strong link between the consumption of fruits and vegetables in adults, and the diminishing of the risks associated with the onset of cognitive decline, possibly due to the reduction in incidence or severity of the associated conditions of cardiovascular disease, obesity and type 2 diabetes. However, it is fair to mention that neurodegeneration can arise for a number of reasons which are not solely diet-related (such as genetic predisposition to neurodegenerative diseases, environmental stimuli, hormonal imbalances, stress situations), and interestingly mitochondrial dysfunction, or cell energy impairment, apoptosis, and overproduction of reactive oxygen species is the final common pathogenic mechanism in neurodegenerative diseases [2].

Our own natural antioxidant system, which consists of enzymes as well as biochemical compounds, is crucial in balancing the oxidative stress within our bodies and minimising any damage caused by free radicals [7]. These mechanisms are discussed in this book, as well as changes to this system which have been observed in type 2 diabetes, obesity, ageing and AD.

It is known now that AD develops in the brain for around 20 years before cognitive symptoms emerge. Eventually the cognitive impairment reaches a level where a diagnosis of possible/probable AD is made, using the diagnostic criteria described in detail in a chapter in this book. Again, there is somewhat of a chicken and egg situation regarding dietary imbalances – a bad diet may increase risk of AD and accelerate its development in the brain, then once a person has some level of cognitive impairment, either as self-reported memory loss or as diagnosed, measured mild-cognitive impairment (but not yet clinical AD), there is the risk of withdrawal from normal social life, and the development of depression and anxiety, and these can increase the likelihood of developing dietary problems such as a lower quality of nutrition. In turn this can lead to weight loss, lack of mobility and a further reduction in the quality of life. Intervention studies using rat models as well as clinical studies have indicated that there is a potential to slow the progression of neurological impairment using dietary and lifestyle interventions. This could be in the form of improving the overall diet, promoting

the consumption of bioactive ingredients from certain foods, a reduction in energy consumption, improved mineral uptake and/or maintenance/increased levels of physical activity to improve physiological function and cardiovascular health. The important message here is that if we know a person is in the early preclinical stages of Alzheimer's, there may be sufficient time (at least 10 years) in which preventative treatments or diets can be applied, with the aim of delaying cognitive decline.

Good vitamin and antioxidant [6] intake has been associated with resistance to cognitive decline, and vitamins are discussed in this book, in relation to oxidative stress and AD. For instance folic acid, vitamin B6, and vitamin B12 have been reported to be related to the maintenance of cognitive function [3, 8]. Part of the mechanisms behind this could relate to the fact that these vitamins are physiologically important for the development and repair of neuronal networks, and this may also be associated with the links between vitamins and minerals in cell signalling and development. Individuals who have low levels of vitamin B12 appear to be more prone to the development of neurological impairments. Similarly, it has been suggested that avoiding vitamin C deficiencies can help maintain cognitive function through immunomodulation and protection of neurons [9]. The form in which these vitamins and minerals are ingested is of importance, most likely due to their bioavailability, so that it has been suggested that ingestion of foods rich in antioxidant vitamins (rather than supplements), or combinations of vitamins (such as C and E) may help delay the onset of AD [10], and in fact it has been shown that dietary supplementation using individual vitamins has little effect. Furthermore, studies which investigate the potential use of single refined compounds on neurodegenerative diseases may be hard to translate to normal dietary situations, and it is most likely that a combination of healthy foods is likely to be most effective.

Within this book you will find a variety of tests for determining cognitive impairment, and tests to distinguish between several different types of neurodegenerative conditions, including AD, dementia with Lewy bodies, and fronto-temporal dementia, for example. You will also discover many novel potential methods for the diagnosis of AD. Diagnosis at preclinical stages is the aim now, as the prevention or the slowing of the onset of AD, when the disease is in the very early stages of development, is emerging as the most likely avenue for an effective reduction in AD incidence. Therefore, intervention studies need to be carried out on people with very early stages of AD, preferably well before the onset of symptoms, to determine how dietary change and particular food components may affect the development of AD as well as other neurological disorders. However, a diagnosis of Alzheimer's is clearly not necessary to adopt a healthier diet and lifestyle.

One area of research that has proven of considerable interest in recent years is the antioxidant and medicinal value of plant-based foods, with the aim of providing treatments, including preventative treatments for many conditions. Harnessing these ingredients is not new: traditional European, western or Chinese medicine practices are rich in examples of such uses of common plant species. For instance, Chinese medicinal practices utilise mushroom materials to combat a number of metabolic disorders. This has been a particular research focus of our laboratories. Whilst the consumer in the UK, USA or NZ may be accustomed to 4–5 different types of mushroom species which are commonly available in the supermarkets, there are over 900 different species of mushroom in China. We have shown that mushrooms are a rich source of bioactive compounds such as β-glucans, peptides, chitinous substances, terpenes, sterols and phenolic compounds [11, 12]. In addition, we and

other researchers have illustrated that these bioactive compounds are useful in terms of anti-inflammatory, antioxidant, anti-cancer, anti-virus, anti-microbial, anti-diabetic and immune modulating ingredients, and some have the potential to stimulate axon generation during brain development [11–13]. With respect to AD, the capacity of several medicinal mushroom species to inhibit the enzyme BACE-1 (one of the enzymes required to produce Aβ amyloid peptide of AD from its precursor, amyloid precursor protein [APP]) was investigated *in vitro*, and it was discovered that extracts of *Auricularia polytricha* (wood ear mushroom) can reduce the activity of the enzyme [14]. When scopolamine-stressed mice were fed mushroom extracts rich in phenolic compounds (for instance from *Inonotus obliquus*), their performance in memory tests improved; whereas in cell culture experiments involving 6-hydroxydopamine-induced stress, a mushroom compound dihydroxybenzalacetone led to protection against neurodegeneration [15, 16].

Chinese tea, green tea, and even black teas have been investigated for the effects of tea phenolic compounds on obesity, oxidative stress, diabetes and neurological functionality [17]. Arguably, tea is the most widely consumed beverage in the world, and tea is a rich source of bioactive ingredients, of which catechins and theanine are the two most studied. These components have been shown to have a neuroprotective effect by inhibiting Aβ formation through inhibiting fibrillar aggregation, and via inhibition of acetylcholinesterase [18, 19]. Catechins can make up between 12% and 24% of the dry weight of tea leaves, and mainly include epigallocatechin (EGC), epicatechin (EC), catechin, epicatechin-3-gallate (ECG) and epigallocatechin-3-gallate (EGCG); whereas theanine commonly makes up 1–2% of tea. The process of making tea naturally extracts these compounds into the liquid which we then consume. Both catechins and theanine have been shown to cross the blood–brain barrier and enter brain tissue [17, 20]. The catechins in both green and black tea have been shown to be potent antioxidant compounds. For instance, the antioxidant activity of tea polyphenols has been shown to inhibit the release free radicals and to limit cellular damage [21]. The polyphenol antioxidants in tea are discussed in greater detail in the chapter on inflammation.

The consumption of caffeine has also been shown to protect against cognitive impairment. Finnish researchers evaluated data over a number of years relating to a cohort of over 1000 people, and illustrated that the consumption of three cups of coffee a day can delay the progression of AD. These effects have been suggested to be due to the caffeine content of coffee. Research has indicated that the consumption of 300 micrograms of caffeine daily may reduce the risk of AD, slow cognitive impairment and reduce Aβ levels in the brain and blood [22]. There is also evidence caffeine may inhibit the rate of Aβ production and hence the formation of toxic Aβ fibrils which have been linked with neurodegeneration. Caffeine can act as an antioxidant, however coffee is rich in many other antioxidants, and the combination of these may be providing the benefits of coffee.

The study of the genetics of AD has also revealed that particular forms of many genes are linked to increased risk of the disease. The main risk factor gene is apolipoprotein E, for which possession of the e4 allele increases several-fold the risk of developing AD. However, particular forms of many other genes and genetic mutations have been shown to influence Alzheimer's risk, and the study of these other genes is revealing considerable information about the metabolic and biochemical pathways involved in disease pathogenesis, as described in detail in the chapter on genetics.

Another chapter of the book describes the importance of fermentation in our digestive process. Fermentation in our gut produces short-chain fatty acids which have been shown to have a myriad of beneficial effects, including reducing the risk of type 2 diabetes and inflammation. The importance of prebiotics and probiotics in our diet has become a popular topic in health food conversations, yet more clinical research is needed to gain a better understanding of the gut–brain axis and how it influences our health. Having said this, animal studies have provided a huge amount of valuable information concerning AD, especially the studies of AD-model transgenic mice. The major animal models which have been studied over the years are reviewed in one of the book's chapters, including their uses and limitations.

Epidemiological experiments, as well as the *in vivo* and *in vitro* trials conducted on numerous food items, have given rise to a prolific nutraceutical industry endeavouring to provide consumers with a range of supplements to enhance lifestyles and reduce the incidence of many conditions. However, these nutraceuticals should only be regarded as a supplementation to an enhanced lifestyle which includes physical fitness, reduction of stress and healthy eating. The whole issue of diet and human nutrition is a complex relationship of factors which interact to exert effects on physiological function and health. A key message of this book concerns the deficiencies of the western diet, and how overall dietary changes to mimic the Mediterranean diet or Okinawan diet (both linked to health and longevity) are advisable. Such changes are recommended due to the health promoting properties of antioxidants and anti-inflammatory compounds as well as essential fats and vitamins to be found in fresh foods, coupled with reductions in the intake of meat, processed foods, and especially refined carbohydrates. We hope that the chapters of this book explain the background knowledge of AD and some other neurological conditions, and help illustrate the potential new ways in which we can utilise new knowledge that is being obtained in scientific research, to benefit our health and well-being.

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