Nutrition and Health
Series Editor: Adrianne Bendich

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Ronald Ross Watson
Victor R. Preedy *Editors*

Nutrition and Diet in Menopause

Humana Press

Nutrition and Health Series

Adrianne Bendich, PhD, FACN, FASN, Series Editor

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Preface

Marked decreases in estrogen production and other endocrine changes are hallmarks of the menopause and affect physiological and psychological function in women. Indeed, it has been reported that the menopause affects most, if not every, organ system in one way or another. The degree of these changes is determined by a number of modulators such as lifestyle, genetics, and dietary factors. However, some of the adverse changes in menopause are considerable, and impose disadvantaged measures of mortality and morbidity. The family unit and communities are also affected. Thus, there is a considerable cost burden to health care providers and services. As a consequence there is a drive to understand, from a scientific point of view, what menopause entails from the cellular level to lifestyle factors. The ultimate objective of such investigations is the formulation of coherent strategies to prevent or cure the adverse effects of menopause. Thus, to achieve an understanding of menopause a holistic approach is needed. However, obtaining this information in a single comprehensive source is currently problematical. This volume, *Nutrition and Diet in Menopause,* aims to achieve this. It is conveniently divided into five parts as follows:

1. *Overviews and general aspects*
2. *Bone and muscle*
3. *Cardiovascular system, metabolism, and cancer*
4. *Psychological aspects and cognitive function*
5. *Preclinical studies: Implications for human health*

There is wide coverage in *Nutrition and Diet in Menopause* including, for example, overviews, body composition, physiological changes, polyphenols, calcium absorption, fortified soy milk, homocysteine, vitamin B12, folate levels, antioxidant vitamins and carotenoids, isoflavones, soy daidzein, tofu, osteoporosis, curcumin, sarcopenia, flaxseed, cardiovascular risk, magnesium, folic acid supplementation, myoinositol, leptin and obesity, fat distribution, cancers including gynecological and breast cancers, vitamin D and cancer, psychology, cognitive decline, black cohosh, and dietary supplements and cognition. Studies on animal models cover α-zearalanol, flaxseed, herba epimedii, and maslinic acid. Finally there is a chapter on supplemental reading and resources.

The contributors are authors of international and national standing, leaders in the field, and trendsetters. Emerging fields of science and important discoveries relating to the menopause are also incorporated in *Nutrition and Diet in Menopause.* The book will be essential reading for nutritionists, dieticians, endocrinologists, cardiologists, health care professionals, research scientists, molecular or cellular biochemists, general practitioners, as well as those interested in women's health in general.

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Series Editor Page

The great success of the Nutrition and Health Series is the result of the consistent overriding mission of providing health professionals with texts that are essential because each includes (1) a synthesis of the state of the science and relevant clinical applications; (2) timely, in-depth reviews by the leading researchers in their respective fields; (3) extensive, up-to-date fully annotated reference lists; (4) a detailed index; (5) relevant tables and figures; (6) identification of paradigm shifts and the consequences; (7) virtually no overt overlap of information between chapters, but targeted, inter-chapter referrals; (8) suggestions of areas for future research; and (9) balanced, data-driven answers to patient as well as health professional questions which are based upon the totality of evidence rather than the findings of any single study.

The Series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The editor(s), whose training(s) is (are) both research and practice oriented, has the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authorities to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

Handbook of Nutrition and Diet in Menopause, edited by Professor Caroline J. Hollins Martin, Ph.D., M.Phil., B.Sc., A.D.M., P.G.C.E., R.M.T., R.M., R.G.N., M.B.Ps.S.; Professor Ronald Ross Watson, Ph.D.; and Professor Victor R. Preedy, Ph.D., D.Sc., F.B.S., F.R.S.P.H., F.R.C.Path., F.R.S.C., clearly exemplifies the goals of the Nutrition and Health Series. The major objective of this comprehensive text is to review the growing evidence that the nutrition provided during adulthood directly affects the changes seen during the menopausal transition. This volume includes 34 up-to-date informative reviews of the current major dietary and health-related issues associated with menopause. Practicing health professionals, researchers, and academicians can rely on the chapters in this volume for objective data-driven sources about essential vitamins and minerals, proteins, fats, and carbohydrates; gynecological cancers; obesity; metabolic syndrome; and osteoporosis. This new comprehensive review of the science behind the nutritional strategies to assure the health of the menopausal woman is of great importance to the nutrition community as well as for health professionals who have to answer patient, client, or graduate student questions about the newest clinical research on nutrition and women's midlife health.

Handbook of Nutrition and Diet in Menopause contains in-depth chapters that review the potential long-term consequences of menopause on the overall health of women, not only at the physical level, including hot flushes (flashes), alterations to the genitourinary system, skin changes, decreased cardiovascular functions, hypertension, headache, back pain, and constipation, as examples. Also examined in relevant chapters are effects on the psychological responses including increased mental tension, irritability, anxiety, sadness, and concentration and memory problems; lack of self-confidence; sleep

changes; and libido changes. It is to the credit of Profs. Martin, Watson, and Preedy that they have organized this volume so that it provides an in-depth overview of the critical issues involved in the determination of the best nutrition for middle-aged women, including those with medical conditions that require specific dietary interventions.

The volume contains five related parts. The first part includes chapters containing excellent tables and figures that provide an overview of the physiological changes seen during the menopausal transition. The four chapters include reviews of the endocrine changes and their resulting effects on areas including, but not limited to, loss of fertility, vasomotor symptoms, psychological alterations, body composition, lipid metabolism, increased blood pressure, and the critical role of diet and exercise on maintaining mental as well as physical health during the transition. Perimenopausal changes and postmenopausal health risks are reviewed in detail. Specific physiological areas discussed include the decline of estrogen, thyroid hormone, and growth hormone levels and decreases in the estrogen/androgen ratio. The consequences of these hormonal changes are discussed with regard to body composition changes and weight gain. It is well documented that menopause results in weight gain and fat accumulation, especially visceral fat accumulation, which accelerates as estrogen levels decline. Recent studies are reviewed and point to the potential beneficial effects of moderate exercise and maintenance of body weight as two tactics for reducing certain of the adverse health effects seen in menopausal women. The last chapter in this part reviews the data on the associations between diets rich in polyphenols, especially flavonoids in soy and tea, and reductions in some of the physiological consequences and symptoms of menopause.

The second part on bone and muscle contains ten chapters. Calcium intake is critical to bone health as this essential nutrient is not well absorbed and usual diets do not contain sufficient bioavailable calcium sources. The major food group that contains bioavailable calcium is the dairy group. Several chapters review the effects of reduced estrogen on calcium absorption and transport to bone. This complex biochemical process involves numerous hormones, vitamin D, calcium transport and binding proteins, cell membrane pumps, and other cellular components. Additionally, the type of calcium and the matrix, either from animals or plants, or from supplements, can affect absorption.

Several epidemiological studies have shown that Japanese women have fewer menopausal symptoms based on their soy intake. Soy milk can be used as a calcium source and the bioavailability of the calcium which is fortified in soy milk is dependent upon the type of calcium salt added as well as the acidity of the milk. Soybeans and soy-derived foods, such as tofu, also contain phytoestrogens which are plant derived, phenolic compounds (genistein and daidzein) that are similar in structure to estrogen, although these are not as biologically active. However, a review of randomized control trials that studied the effect of soy isoflavones on bone density reported no significant benefit at major fracture sites in 11 out of 14 trials involving 2,971 postmenopausal women. In contrast, a major study in Japanese women who consumed high levels of soy protein found a decrease in bone fractures. Currently there is an S-equol soy supplement clinical trial under way that may provide a new approach for treatment of menopausal symptoms and osteoporosis.

Oxidative stress adversely affects osteocyte functions. Naturally occurring antioxidants, such as vitamin C and vitamin E are found in diets containing high intakes of nuts, fruits, and vegetables that also contain carotenoids including β-cryptoxanthin and β-carotene. Japanese women, whose diets have included long-term consumption of the β-cryptoxanthin-rich Japanese mandarin orange, have seen benefits to their bone health. The evidence is reviewed in Chap. 8. There is a separate chapter that objectively examines the data linking low intakes of the flavonoid curcumin to osteoporotic risk in menopausal women and concludes that clinical data are needed as animal study findings have been inconsistent.

Homocysteine is an endogenous amino acid, and higher than average serum concentrations have been associated with lower than normal intakes of folic acid, vitamin B6, and vitamin B12. With regard to menopausal women, data suggest that loss of estrogen is associated with increased homocysteine levels. Higher than average homocysteine levels have been associated with several

cardiovascular and cerebrovascular risks. Additionally, homocysteine is known to interfere with a key enzyme involved in collagen cross-linking. Cross-link formation is critical for normal collagen structure and bone mechanical properties. Thus, higher homocysteine levels may be associated with damage to the bone's mechanical stability and may increase the risk of fractures.

The final chapter in Part 2 reviews the research on the effects of menopause on skeletal muscle structure, strength, and other functions. There is a linear decline in lean mass (that includes muscle) along with an increase in fat mass in postmenopausal women. Moreover, postmenopausal women have twice the concentration of non-contractile muscle tissue, such as intramuscular fat, compared to younger women. This is primarily due to an imbalance between muscle protein synthesis and muscle protein breakdown, and the increase in oxidative stress and inflammation. Additionally, there are declines in estrogen levels, decreased resting metabolic rate, and a loss of neuromuscular function and apoptosis of muscle cells. Increased physical activity and improvements in diet, including optimal intake of vitamin D, are of some help; however, there is an overall increase in the risk of sarcopenia with menopause and advancing age in women.

The ten chapters in the third part examine the role of nutrition and dietary components on the cardiovascular, metabolic, and cancer risks seen in postmenopausal women. The part includes reviews of the nutritional status of women around the world and contrasts unique dietary habits as well as points out common findings that are associated with the physiological changes seen during estrogen depletion. Increased weight gain and obesity as well as increased metabolic syndrome, cardiovascular, and cancer risks are reviewed in unique chapters. For instance, a detailed chapter describes the adverse health consequences associated with higher than average consumption of red meat in Uruguay. There are also chapters from certain European and Asian communities that confirm that eating fried fish increases, while non-fried fish decreases, cardiovascular risks. The metabolic syndrome is reviewed in several chapters that provide an overview of the endocrine effects of estrogen depletion including significantly increased leptin secretion and insulin resistance, and the potential roles of myoinositol and folic acid, vitamin D, and whole flaxseed. The link between lowered estrogen and reduced serum magnesium levels, altered parathyroid hormone, and vitamin D levels is discussed with regard to consequences to the cardiovascular system as well as bone remodeling. The chapter devoted to gynecological cancers examines the potential for phytoestrogens and other flavonoids from fruits, vegetables, teas, and coffee to affect the risk of endometrial, ovarian, and breast cancers. Several chapters discuss the importance of physical activity and maintenance of ideal body weight with the goal of reducing adverse health effects associated with menopause.

The fourth part contains four informative chapters that examine psychological aspects and cognitive changes that may result from lowered estrogen production during menopause. Acute vasomotor responses to fluctuations in estrogen levels are associated with increased physical as well as emotional stress. However, several epidemiological studies document that physical responses, including hot flushes (flashes) and night sweats, are reported more frequently by women living in North America and Europe, and less so by women from Africa and Latin America. Globally, there are consistent reports of menopause-related psychological symptoms including moodiness, irritability, depression, and impairment of cognitive functions such as memory and concentration. The cultural differences in women's responses to menopausal changes are extensively reviewed. The chapters consistently indicate that further research is needed to determine the role of estrogen in brain functions of menopausal women especially during the expected 20+ years of postmenopausal estrogen depletion. There is an extensive review of the many dietary supplements that are purported to reduce menopausal symptoms, including memory loss and cognitive decline. These include soy, red clover, black cohosh, evening primrose oil, dong quai, ginseng, and ginkgo. The 12 placebo-controlled studies that examined the effects of these supplements on cognitive function are carefully reviewed and current data suggest inconsistent and often nonsignificant effects. The detailed review chapter of the clinical data involving studies with black cohosh also suggests the potential for certain adverse effects.

The fifth part contains six chapters that examine preclinical studies of animal models of menopause. Several animal models have been developed specifically for the major chronic diseases seen in postmenopausal women as well as aging men. For example, with regard to Alzheimer's disease, there are transgenic mouse models with selective single or multiple mutations. Models for cardiovascular disease include knockout mouse models, rabbit, and large animal models. The ovarectomized rodent, large animal models, and specific knockout mice are used to study prevention of as well as treatments for osteoporosis. The metabolic syndrome has been studied using pancreatectomy models, transgenic and knockout mouse models, dietary interventions, and spontaneous mutant rodents. All of these models are described and the findings reviewed in the chapters within this part. Certain animal models are relevant as a model of menopausal estrogen changes. The follicle-stimulating hormone receptor knockout mice exhibit changes in the central nervous system and also develop aspects of the metabolic syndrome. These and other relevant animal models are presented in comprehensive tables in Chap. 29. Animal models are important in the development of new drugs and supplements that may be of benefit during menopause and in the postmenopause period. The results of studies with a plant-derived phytoestrogen, α-zearalanol (α-ZAL), a potential replacement for estrogen, are described in the next chapter. The third chapter in this part reviews the numerous animal studies using flaxseed alone and in combination with soy and certain drugs in models of menopausal bone loss and cardiovascular disease. Traditional Chinese medicine (TCM) herbs and plant extracts have been tested for potential anti-osteoporotic effects in ovarectomized mouse models; extracts of the herbs also appear to have some promising activities in these models. Two chapters describe compounds that have TCM substances and specific chemical compounds that have been synthesized from these extracts and tested for efficacy in bone and other models. It may be that the specific compounds will be developed as drugs whereas the extracts will remain classified as dietary components. The final chapter in this part provides valuable information concerning relevant literature and electronic resources available to health professionals interested in nutrition and health for menopausal women.

The logical sequence of the parts as well as the chapters within each part enhance the understanding of the latest information on the current standards of gynecological practice in menopause for clinicians, and related health professionals including the dietician, nurse, pharmacist, physical therapist, behaviorist, psychologist, and others involved in the team effort required for successful treatment of symptoms as well as chronic diseases associated with estrogen loss. This comprehensive volume also has great value for academicians involved in the education of graduate students and postdoctoral fellows, medical students, and allied health professionals who plan to interact with menopausal patients with disorders that may be beneficially affected by nutritional support including the treatment of obesity and the metabolic syndrome.

Cutting-edge discussions of the roles of signaling molecules, growth factors, hormones, cellular and nuclear receptors, and all of the cells and tissues directly involved or affected by the loss of estrogen are included in well-organized chapters that put the molecular aspects into clinical perspective. Of great importance, the editors have provided chapters that balance the most technical information with discussions of its importance for clients and patients.

The volume contains over 150 detailed tables and figures that assist the reader in comprehending the complexities of changes associated with menopause as well as the nutritional factors that can be of benefit during this transition. The overriding goal of this volume is to provide the health professional with balanced documentation and awareness of the newest research and therapeutic approaches including an appreciation of the complexity of the interactions between women's health, diet, and hormonal changes and its consequences on cells and tissues throughout the body. Hallmarks of the 33 chapters include key words and bulleted key points at the beginning of each chapter, complete definitions of terms with the abbreviations fully defined for the reader, and consistent use of terms between chapters. There are over 1,600 up-to-date references; all chapters include a conclusion to highlight major findings. The volume also contains a highly annotated index.

This unique text provides practical, data-driven resources based upon the totality of the evidence to help the reader understand the basics, treatments, and preventive strategies that are involved in the understanding of the role dietary components may play in the prevention of certain chronic conditions associated with menopause. Of equal importance, critical issues that involve cultural preferences seen in countries around the globe are reviewed in well-referenced, informative chapters. The overarching goal of the editors is to provide fully referenced information to health professionals so that they may have a balanced perspective on the value of various preventive and treatment options that are available today as well as in the foreseeable future.

In conclusion, *Handbook of Nutrition and Diet in Menopause*, edited by Professor Caroline J. Hollins Martin, Ph.D., M.Phil., B.Sc., A.D.M., P.G.C.E., R.M.T., R.M., R.G.N., M.B.Ps.S.; Professor Ronald Ross Watson, Ph.D.; and Professor Victor R. Preedy, Ph.D., D.Sc., F.B.S., F.R.S.P.H., F.R.C.Path., F.R.S.C., provides health professionals in many areas of research and practice with the most up-to-date, well-referenced, and comprehensive volume on the current state of the science and medical practice guidelines with regard to maintaining the optimal nutritional and health status of the menopausal woman. This volume will serve the reader as the most authoritative resource in the field to date and is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, Ph.D., F.A.C.N., F.A.S.N.
Series Editor

About Series Editor

Adrianne Bendich, Ph.D., F.A.C.N., F.A.S.N. Dr. Bendich has successfully served as Series Editor for the Nutrition and Health book series for 15 years and continues to identify key areas of clinical nutrition research that can benefit from the development of targeted, objective volumes edited by the leading researchers in their fields of investigation.

Prior to retiring in September 2010, Dr. Bendich held the position of Director of Medical Affairs at GlaxoSmithKline Consumer Healthcare, where she was responsible for the Medical leadership for the Venture Group, and provided Medical support for well-known brands including TUMS, FiberChoice, Os-Cal, Geritol, and Citrucel. Additionally, she served as a member of GSK's successful Advisory Committee team in support of FDA's Rx to OTC switch of alli®.

Dr. Bendich is internationally recognized as an expert in Women's Health, calcium and vitamin D in bone health, folic acid and pregnancy outcomes, and antioxidants and carotenoid effects on immune functions. She served as the GSK corporate representative to the Women's Health Initiative (WHI) for 9 years as GSK Consumer Healthcare provided all calcium and vitamin D supplements for the WHI study.

She has held memberships and professional positions (ongoing and former): Editorial Board, *Journal of Nutrition in Gerontology and Geriatrics, Antioxidants*, an e-journal, *Journal of Women's Health and Gender-based Medicine*; Associate Editor for *Nutrition*, the International Journal; Chair, Corporate Advisory Committee, Society for Women's Health Research; Member of the Program Advisory Committee for Helen Keller International; Advisor to the Nutrition Department, Montclair State University; Member: Advisory Board, *Current Topics in Nutraceutical Research*; and member ASN's Industry Board and several RIS groups.

Dr. Bendich was a recipient of the Burroughs-Wellcome Fund Professorship and Roche Research Award; she is listed in Who's Who of American Women Scientists and many other Who's Who volumes; she is a recipient of the CRN Apple Award for contributions to the science of vitamin and mineral supplements. In 2012, Dr. Bendich was elected a Fellow of the American Society for Nutrition, the highest honor of the Society.

Dr. Bendich is the author of more than 100 peer-reviewed publications, and Series Editor of "Nutrition and Health" for Springer/Humana Press which includes 48 volumes such as *Preventive Nutrition*, *Handbook of Clinical Nutrition and Aging*, *Diet and Human Immune Functions, Handbook of Drug–Nutrient Interactions*, and other reference volumes for health professionals as outlined at http://www.springer.com/series/7659.

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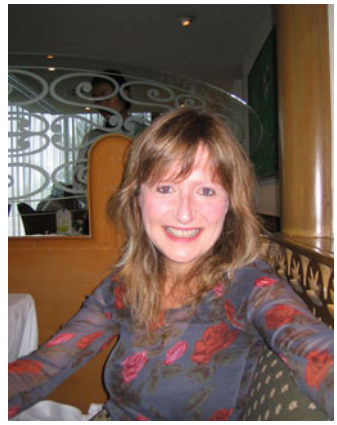

Caroline J. Hollins Martin, Ph.D., M.Phil., B.Sc., A.D.M., P.G.C.E., R.M.T., R.M., R.G.N., M.B.Ps.S., is a Professor in Midwifery in the College of Health and Social Care at the University of Salford. Her background has encompassed a career in women's reproductive health that spans 26 years; the first 11 of these were spent as a clinical midwife in Ayrshire (Scotland) and 15 teaching and researching women's reproductive health within universities. She is an NMC Registered Midwife and Lecturer/Practice Educator. She is also a graduate and postgraduate in psychology and a Member of the British Psychological Society (M.B.Ps.S.). Her research interests lie in social psychology that relates to women's reproductive health, with much of her work relating to obstructing autonomy, evidence-based practice, and providing choice and control to childbearing women. More recently, her focus has shifted to developing useful tools for maternal health practitioners to use in clinical practice, for example, the Birth Participation Scale (BPS) to assess fathers' fears and needs in relation to childbirth and the Birth Satisfaction Scale (BSS) to assess mothers' perceptions of their birth experience. Current research interests lie in shaping perinatal bereavement care, outcomes of maternal activity during labor, and the effects of music upon women's stress levels. To date, she has published 31 peer-reviewed papers, presented 32 conference papers, and written 4 book chapters and is the associate editor for women's reproductive health papers submitted to the *Journal of Nurse Education in Practice*.

Ronald Ross Watson, Ph.D., attended the University of Idaho but graduated from Brigham Young University in Provo, Utah, with a degree in chemistry in 1966. He earned his Ph.D. in biochemistry from Michigan State University in 1971. His postdoctoral schooling in nutrition and microbiology was completed at the Harvard School of Public Health, where he gained 2 years of postdoctoral research experience in immunology and nutrition.

From 1973 to 1974, Dr. Watson was assistant professor of immunology and performed research at the University of Mississippi Medical Center in Jackson. He was assistant professor of microbiology and immunology at the Indiana University Medical School from 1974 to 1978, and associate professor at Purdue University in the Department of Food and Nutrition from 1978 to 1982. In 1982, Dr. Watson joined the faculty at the University of Arizona Health Sciences Center in the Department of Family and Community Medicine of the School of Medicine. He is currently professor of health promotion sciences in the Mel and Enid Zuckerman Arizona College of Public Health.

Dr. Watson is a member of several national and international nutrition, immunology, cancer, and alcoholism research societies. Among his patents he has one on a dietary supplement passion fruit peel extract, with more pending. He had done DHEA research on its effects on mouse AIDS and immune function for 20 years. He edited a previous book on melatonin (Watson RR. *Health Promotion and Aging: The Role of Dehydroepiandrosterone (DHEA)*. Harwood Academic Publishers, 1999, 164 pages). For 30 years he was funded by Wallace Research Foundation to study dietary supplements in health promotion. Dr. Watson has edited more than 100 books on nutrition, dietary supplements and over-the-counter agents, and drugs of abuse, as scientific reference books. He has published more than 500 research and review articles.

Victor R. Preedy, B.Sc., Ph.D., D.Sc., F.S.B., F.R.C.Path., F.R.S.P.H., F.R.S.C., is a senior member of King's College London (Professor of Nutritional Biochemistry) and King's College Hospital (Professor of Clinical Biochemistry). He is attached to both the Diabetes and Nutritional Sciences Division and the Department of Nutrition and Dietetics. He is also Director of the Genomics Centre and a member of the School of Medicine. Professor Preedy graduated in 1974 with an Honors Degree in Biology and Physiology with Pharmacology. He gained his University of London Ph.D. in 1981. In 1992, he received his Membership of the Royal College of Pathologists and in 1993 he gained his second doctoral degree, for his outstanding contribution to protein metabolism in health and disease. Professor Preedy was elected as a Fellow to the Institute of Biology in 1995 and to the Royal College of Pathologists in 2000. Since then he has been elected as a Fellow to the Royal Society for the Promotion of Health (2004) and The Royal Institute of Public Health (2004). In 2009, Professor Preedy became a Fellow of the Royal Society for Public Health and in 2012 a Fellow of the Royal Society of Chemistry. In his career Professor Preedy has carried out research at the National Heart

Hospital (part of Imperial College London) and the MRC Centre at Northwick Park Hospital. He has collaborated with research groups in Finland, Japan, Australia, the USA, and Germany. He is a leading expert on the science of health. He has lectured nationally and internationally. To his credit, Professor Preedy has published over 570 articles, which include 165 peer-reviewed manuscripts based on original research, 100 reviews, and over 50 books and volumes.

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Part I
Overview and General Aspects