Hormones, gender and the aging brain

The significance of hormone action in psychiatry has long been studied, but only very recently has this study included the psychiatric effects of hormones on the aging process. This is the first clinical reference to address the hormonal basis of mental disorders in older people. Hormones influence a wide range of states and conditions, from pain tolerance and anorexia to attention, mood, immunity, cardiovascular and cognitive function, schizophrenia and Alzheimer's disease.

Written by an eminent team of psychiatrists, psychologists, geriatricians and neuropharmacologists, this book brings together established information and recent findings in four sections:

- an overview of the basic science of neurosteroids
- sex difference and the roles that cortisol, thyroid hormone, and the sex steroids estrogen, progesterone, dehydroepiandrosterone and testosterone play in common mental disorders and pain sensitivity
- psychoneuroimmunology in relation to age
- sex differences and hormones in psychotropic drug metabolism in the elderly.

Clinicians and researchers alike will value this comprehensive review of a complex and sometimes controversial area of psychiatry.

Mary F. Morrison is Assistant Professor of Psychiatry and Internal Medicine at the University of Pennsylvania School of Medicine and is the recipient of a career development award to study the role of estradiol in mild to moderate depressive disorders in aging women.

Hormones, gender and the aging brain

The endocrine basis of geriatric psychiatry

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To my husband, Mickey, and my son, Nathaniel

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Preface

Two of the great mysteries of life for those beyond the age of 30 are: Why do we age? What can we do about it? The idea of 'successful aging' has captured the interest of researchers in the biological and social sciences as well as the interest of the public. While our hopes for our retirement years focus on unencumbered time pursuing interests and adventures with leisure, we fear that changes in our physical and emotional/cognitive integrity, brought on by the aging process, may get in the way of realizing those hopes. The process of aging holds many risks, including medical illness, pain, and living with disability. Our fears may focus on the loss of self and others to new onset psychiatric conditions such as depression, anxiety, psychosis, and cognitive disorders. The high prevalence of medical comorbidity in the aged and the biology of aging create especially challenging issues in geriatric mental health.

This book begins to clarify the growing body of knowledge on the hormonal causes and treatment of mental disorders among the elderly. The interplay between endocrinology and psychiatry has a long and fascinating history, but only recently has research into this area included the elderly.

Here, perspectives on the role of hormones in mental function in aging are presented in four sections: basic science overview; endocrine aspects of mental disorders in aging; psychoneuroimmunology; and pharmacology. A first chapter by John Morley comprehensively integrates the endocrine changes in aging with the behavioral effects of hormones that have received less attention. An overview of the anorexia of aging and the involvement of hormones and nitric oxide is presented.

The book's first part also reviews the basic biosynthesis and pharmacological interactions of neurosteroids. Loretta Flanagan-Cato reviews the basic mechanisms of hormone effects in the brain, with an emphasis on the biosynthesis, the site of action, and the diverse cellular mechanisms employed by hormones that affect neuronal function.

Part II, Chapters 3 through 12, integrates basic sciences research with clinical data in reviewing the common mental disorders in aging populations and their relationship to hormonal changes. Mood disorders, changes in cognitive function including Alzheimer's disease, anxiety disorders, schizophrenia, and chronic pain, are influenced by hormonal changes.

In Chapter 3, John Kasckow provides a synopsis of recent research into the role of the hypothalamic–pituitary–adrenal (HPA) axis in geriatric populations, reviewing both basic and clinical research. The chapter discusses alterations in the HPA axis that occur with normal aging and relates these to alterations in cognition and mood in the elderly. Chapter 4, by Gabriel Tsuboyama, summarizes the characteristics of the aging thyroid axis and the role of the thyroid axis in geriatric major depression.

Chapters 5 and 6 are devoted to the role of estrogen in depression in aging women and the role of testosterone in depression in aging men. A growing body of evidence implicates the reduction in circulating estrogen in the pathophysiology of mood disorders, Alzheimer's disease, osteoporosis, and heart disease in aging women, and estrogen replacement has led to therapeutics research with important public health implications. But the effects of declining testosterone levels in aging men are less understood. Stuart Seidman provides an overview of research into the link between testosterone levels and depression in men, as well as an overview of research into the neurovegetative, cognitive, affective, and sexual effects of exogenous testosterone administration.

In Chapter 7, Owen Wolkowitz examines current data regarding the effects of dehydroepiandrosterone on mood and cognition in the elderly, particularly its possible efficacy in treating neuropsychiatric illness in the middle-aged and elderly.

Chapters 8 and 9 focus on the role of sex steroids in cognition in aging populations. In Chapter 8, Kristine Yaffe reviews the differences in cognitive functioning between aging men and women and the role of estrogen and testosterone. Estrogen replacement has been linked to a decreased risk of Alzheimer's disease. Robert Gibbs summarizes the recent animal research pertaining to potential mechanisms by which estrogen may help to reduce the risk and severity of Alzheimer's related dementia in women. In particular, estrogen has beneficial effects on the cholinergic neurons which project to the hippocampus and cortex and are involved in memory.

Gender differences exist in the clinical course of schizophrenia and anxiety. Even in the elderly, these gender differences are thought to be at least partly mediated by gonadal hormones. In Chapter 10, Laurie Lindamer analyzes ongoing research into the role of gender on specific aspects of schizophrenia, including the interaction of dopamine and estrogen. Difference in time of onset of illness and clinical course in schizophrenia may be related to the presence of estrogen in women. In Chapter 11, Teresa Pigott reviews anxiety disorders in aging population and data suggesting that sex steroids may play a role in the increased prevalence of anxiety disorders in women throughout the lifespan.

Chronic pain is a significant problem in aging populations and in many people pain both causes and is exacerbated by depression. Less commonly appreciated is

the fact that men and women experience pain differently. In Chapter 12, Wendy Sternberg examines the role of hormonal mechanisms in acute and chronic pain in the elderly, including how sex steroids may explain some of the sex differences in endogenous pain inhibition. The clinical implications of a novel pain mechanism in female rodents is discussed.

Part III provides an understanding of the field of psychoneuroimmunology in relation to aging. In Chapter 13, Mary Burleson summarizes estrogen's immunomodulatory effects and estrogen-related differences in cardiovascular and neuroendocrine reactivity to brief stressors in women. She includes research on estrogen's effects on immune reactivity to stress, and speculates on the possibility that estrogen may moderate hormonal and immunological responses to stress through alterations in sympathetic nervous system reactivity and through regulation of corticotropin-releasing hormone. In Chapter 14, Eva Redei investigates sex differences in regulation of immune function at the cellular level. She explores the hypothesis that common genes are involved in certain autoimmune diseases and mood disorders. Aging and hormone replacement therapy may affect the expression of these genes since many of them are known to be regulated by estrogen.

In Part IV, Chapters 15 and 16 review the influences of gender, hormones, and aging on the metabolism of drugs. Older women are the greatest consumers of all classes of psychotropics, with evidence indicating that the elderly in general, and women in particular, experience a higher frequency of adverse drug reactions. Information on gender differences in pharmocokinetics is minimal, however, and rarely being used in clinical practice, according to Bruce Pollack. In Chapter 15, he reviews the research on the effects of endogenous and exogenous estrogens on the metabolism of psychotropics and gender and on gender-related differences in the half-lives of psychotropics. Finally, in Chapter 16, Patricia Kroboth reviews data that demonstrate that aging and ovarian hormones, specifically progesterone metabolites, affect benzodiazepines levels either by altering drug metabolism or by changing the effect-concentration relationship.

'You are old, Father William,' the young man said,
'And your hair has become very white;
And yet you incessantly stand on your head –
Do you think, at your age, it is right?"

'In my youth,' Father William replied to his son,
'I feared it might injure the brain;
But now that I'm perfectly sure I have none,
Why I do it again and again.'

excerpted from 'Father William' by Lewis Carroll

Father William demonstrates that spirited independence and sense of humor we all hope to express in our old age. Central to that goal, however, is the preservation of cognition, good mood, personality, and health. This book enhances our understanding of the role hormones play in the geriatric mental disorders that can threaten our relationships and self. The endocrine basis of geriatric psychiatry is a new area of investigation, and our field does not yet have the data to comprehensively review all hormones involved in mental disorders and the aging. As research progresses, our understanding of the pathogenesis of these disorders will increase and lead us to more effective hormonal interventions and, possibly, the ability to prevent some of these debilitating disorders.

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My family has been crucial in this project. My parents, Helen and Herbert Morrison, and my sister, Margaret Gimmy, have my warmest acknowledgments. My son, Nathaniel Selzer, and my stepchildren, Molly and C. J. Selzer, are a continual source of delight, ideas, and inspiration. And, finally, I am always grateful to my husband, Michael Selzer, for his loving support and the warm, glittering mysteries that we share together.

Mary F. Morrison, editor