

# HOSPITAL PHYSICIAN®

## CARDIOLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Cardiology Board Review Manual* is a peer-reviewed study guide for fellows and practicing physicians preparing for board examinations in cardiology. Each bi-monthly manual reviews a topic essential to the current practice of cardiology.

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## Stress Response and the Metabolic Syndrome

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# Stress Response and the Metabolic Syndrome

Viola Vaccarino, MD, PhD, and J. Douglas Bremner, MD

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## INTRODUCTION

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The metabolic syndrome, characterized by abdominal obesity, elevated serum triglycerides, high blood pressure, and increased fasting glucose levels and low concentrations of high-density lipoprotein (HDL) cholesterol, has an estimated prevalence of almost 25% in the US population.<sup>1</sup> The underlying abnormality causing these conditions to cluster together is thought to be insulin resistance. Recently, the metabolic syndrome has been recognized as an important risk factor for cardiovascular disease and all-cause mortality,<sup>2–5</sup> and it was listed as a secondary target of therapy in the National Cholesterol Education Program's Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).<sup>6</sup>

Although genetic and biological factors play a major role in the development of obesity, hypertension, insulin resistance, and diabetes, these common disorders that are part of the metabolic syndrome are probably influenced by other factors. Evidence suggests that these disorders are mediated by a complex interplay between genetics, biology, and the environment (**Figure 1**). Stress, whether related to depression,<sup>7</sup> environmental stressors,<sup>8</sup> or perceived stress,<sup>9</sup> is associated with increased release of corticosteroids and other neurohormonal factors that may predispose to abdominal obesity, insulin resistance, and the other features of the metabolic syndrome.<sup>9–20</sup> This manual is the second in a series on the metabolic syndrome. Its goal is to review the literature linking stress and the neurohormonal stress response to the metabolic syndrome and to discuss the pathophysiological mechanisms that are involved in these relationships.

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## CURRENT CONCEPTS ON STRESS

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The stress system coordinates adaptive responses of the organism to stressors.<sup>21</sup> Two main components mediate the neurohormonal response to stress: the

hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). This stress-responsive system is regulated by centers in the hypothalamus and the brainstem. These regulatory centers include neurons in the paraventricular nucleus (PVN) of the hypothalamus, which secrete corticotropin-releasing hormone (CRH) and arginine-vasopressin, and the noradrenergic neurons of the locus ceruleus of the brain stem, which secrete norepinephrine centrally in the brain.<sup>21</sup> The different components of the stress system innervate and stimulate each other and have unique basal and stress-related patterns of activity. In individual subjects, the secretion of the end-product of the HPA axis, cortisol, is maintained within a quite stable and narrow range by a tightly regulated feedback system that prevents excessive and prolonged cortisol secretion that would be detrimental to the organism.<sup>22</sup>

In addition to affecting the HPA axis and the autonomic nervous system, activation of the stress system produces a variety of other effects, including influences on brain functions involved in emotion, cognitive function, and behavior as well as the reproductive system, the endocrine system, and immune function. In general, these behavioral and biological changes are meant to improve the ability of the organism to effectively counteract the stressor. Repeated or chronic activation of the stress system or a malfunctioning stress system characterized by sustained hyperactivity or hypoactivity may contribute to various pathophysiological abnormalities across a wide range of organ systems, potentially resulting in endocrine, inflammatory, and psychiatric disorders.<sup>21</sup>

Selye<sup>23</sup> provided one of the first comprehensive descriptions of the stress response, including how the organism responds to stressors and the role of stress in physical disease. Chrousos<sup>21</sup> introduced the concept of stress-related disorders, highlighting the role of stress in leading to maladaptive physiological responses that could predispose to physical conditions. Following a similar paradigm, Sterling and Eyer<sup>24</sup> coined the term *allostasis*, defined as the ability of the body to increase or decrease vital functions in response to changing