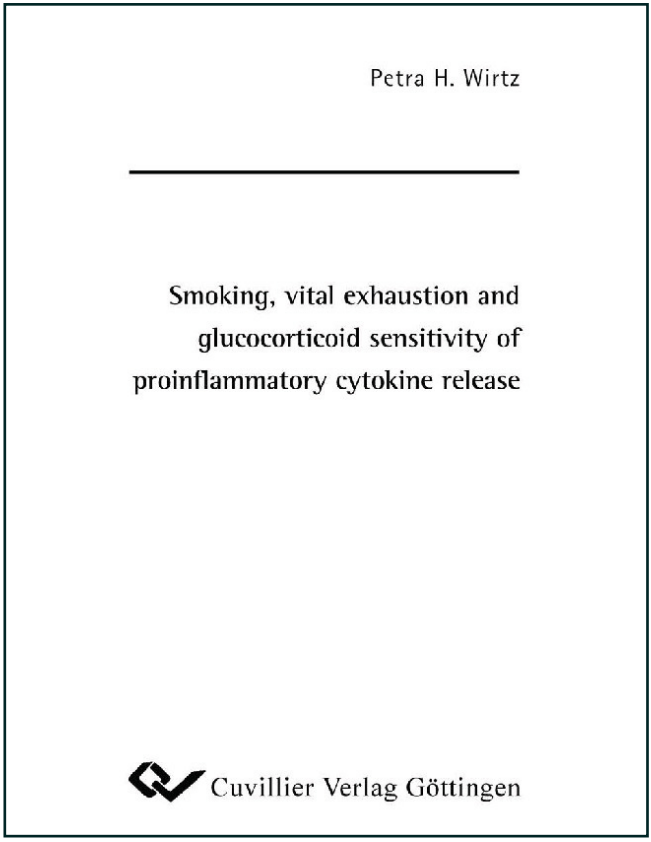

# 1 INTRODUCTION

Despite changes in lifestyle and the use of new pharmacological approaches to lower plasma cholesterol concentrations, cardiovascular disease continues to be the principle cause of death in the United States, Europe, and much of Asia (Ross, 1999). The process of atherosclerosis is central the pathogenesis of cardiovascular diseases, in particular coronary artery disease. It has long been viewed as the consequence of mechanic and chemical strain on the blood vessel (Wagner, 1992). Hence, pharmacological interventions emphasized the control of blood pressure and the lowering of elevated plasma levels of circulating lipids, in particular low density lipoproteins (Wagner, 1992). More recently, it has been understood that the process underlying atherosclerosis is inflammatory, and that early stages of this process can be observed even in newborns (Ross, 1999). A particular class of circulating white blood cells, the monocytes, play a key role in the atherosclerotic process and in disease progression. Blood derived monocytes are the first inflammatory cells that adhere to sites of pre-lesions at the blood vessel wall by entering the pre-lesion they mature to macrophages, thereby triggering and participating in an inflammatory response (Plutzky, 2001; Ross, 1999). Their ability to secrete soluble molecules by which immune cells communicate (cytokines) is strongly involved in this process. The regulation of this process may be viewed as a main determinant of disease progression. A focus on the inflammatory nature of atherosclerosis has opened up the possibility to investigate new biological pathways to understand the pathogenic relationship between mental states (for example vital exhaustion) and atherogenesis (Appels, 1999; Appels et al., 2000). Central to this research direction is to elucidate the effect of mental states and/or behavior on the

regulation of the activity of monocytes, in particular up- and down-regulation of the inflammatory response. *In vitro* assays have recently been established that allow investigating monocytes properties. One of these bioassays known as glucocorticoid sensitivity assay , allows for the assessment of glucocorticoid sensitivity of circulating monocytes (DeRijk et al., 1997; DeRijk et al., 1996). Hitherto, most data on glucocorticoid sensitivity of immune responses have been derived from small populations under experimental conditions. In this thesis project we performed a cross-sectional study on glucocorticoid sensitivity in middle-aged employees of the manufacturing industry. We were particularly interested to elucidate possible relationships between mental states, health related behavior and glucocorticoid sensitivity . We hypothesized that conditions known to act as independent risk factors for cardiovascular disease (smoking and the mental state vital exhaustion) would be associated with altered *in vitro* up- and down-regulation of monocyte inflammatory activity. In the present thesis we focus on the effect of a specific risk behavior (habitual smoking), and of a specific chronic mental state (vital exhaustion) on glucocorticoid sensitivity in healthy males.

The presentation is organized as follows: The introduction briefly reviews the pathogenesis of atherosclerosis with a specific emphasis on the role of monocytes, pro-inflammatory cytokines and on a particular cytokine-induced acute-phase protein. This section is followed by a more detailed exploration of the known effects of smoking in the pathogenesis of atherosclerosis and by a section reviewing the observed association between vital exhaustion and cardiovascular disease. The third part of the introduction briefly introduces glucocorticoids and illustrates their role in immunity, inflammation and susceptibility to inflammatory diseases,

with particular emphasis on what is known about glucocorticoid secretions in smokers and subjects with vital exhaustion. The final part of the introduction provides a detailed account of the methodological assessment of glucocorticoid sensitivity as well as an overview of results from other research groups investigating this topic. This part ends with the presentation of molecular determinants of glucocorticoid sensitivity . Following the introduction, the data from two sub-projects are presented in separate chapters, two detailed analyses of the relationship between smoking and glucocorticoid sensitivity on the one hand and vital exhaustion and glucocorticoid sensitivity on the other hand. The thesis is concluded by a general discussion of the obtained results and their implications for future research.