STRESS, DEPRESSION, AND THE ROLE OF CYTOKINES

B. E. Leonard¹ and Cai Song²

¹ Department of Pharmacology, National University of Ireland
Galway, Ireland
² Life Sciences Research Institute, Carlton University
Ottawa, Ontario, Canada

INTRODUCTION

The concept of an inter-relationship between the psychological state of a depressed patient and the immune status can be traced back to Galen who, in 200 AD, suggested that melancholic women are more susceptible to breast cancer than sanguine women (Leonard, 1987). Over the past 15 years it has become apparent that the central nervous system (CNS) and the immune system are intimately connected and that a functional bidirectional communication exists between these systems (Ballieux, 1992). Indeed, it may be possible to conceive of the nervous, endocrine, and immune systems as being part of a single integrated network rather than three separate systems. The study of the interactions between these systems has given rise to the new discipline of psychoimmunology, a term first coined by Ader, Felten, and Cohen in 1987.

It is widely accepted that stress and psychiatric illness can compromise immune function (Leonard, 1990; 1995). Furthermore, soluble mediators released by immune cells can influence brain function and cause changes in behaviour in both man and lower animals. In addition to the behavioural changes that occur in depressed patients, there are also profound alterations in the endocrine and immune systems (Connor and Leonard, 1998). Most of the initial studies of the immune changes in depression indicated that a suppression of immune function occurs as indicated by an impaired zymosan induced neutrophil phagocytosis (O’Neill and Leonard, 1990), mitogen-stimulated lymphocyte proliferation (Kronfol and House, 1989) and natural killer cell (NKC) activity (Irwin, Lacher, and Caldwell, 1992).

In addition to the immune changes that occur in depressed patients, a number of studies have concentrated on indices of immune function in those who have been exposed to stressful life events such as bereavement, divorce, and academic examinations. Exposure to such stressful events has also been reported to cause impairment in

Cytokines, Stress, and Depression, edited by Dantzer et al.
various aspects of cellular immune function that qualitatively resemble those changes reported to occur in depression (Irwin, 1995).

Despite these changes demonstrating that immunosuppression occurs in those exposed to psychological stress or to depression, there is also evidence that activation of some aspects of the immune system can also arise (Maes, Smith, and Scharpe, 1995). This serves to emphasize the complex interrelationship that exists between external or internal stressors, activation of the pituitary adrenal axis and the subsequent changes in immune function.

The purpose of this review is to present the evidence that implicates the proinflammatory cytokines as the causal factors in depression and in the impact of stress that may trigger the onset of depression.

1. STRESS, ITS DEFINITION AND CLASSIFICATION

Stress may be defined as the physical or psychological stimulus which, when impinging upon an individual, produces strain or disequilibrium. A more complex definition proposed by Sklar and Anisman (1981), defines stress as the reactions of the body to forces of a deleterious nature, infections, and various abnormal states that tend to disturb its normal physiological equilibrium or homeostasis. The stimulus that causes such a disruption is referred to as the stressor.

From such definitions, it is clear that stress is a very broad concept that must be clarified in terms of the severity of the stressor, its duration and the age, gender and genetic composition of the subject upon whom the stress impinges. Thus in regard to the classification of stress, it is essential to determine whether the stress is acute or chronic, whether it is unavoidable or avoidable, physical or psychological. Furthermore, many types of physical stress will have direct metabolic consequences (for example, cold or heat exposure) which will have an impact on the general metabolism in addition to causing psychophysiological changes.

Knowledge of the effects of stress on the immune, neurotransmitter, and endocrine systems has been derived from animal experiments. The pioneering studies of Rasmussen (1969) and Solomon (1969) produced evidence to indicate that certain forms of stress could cause decreased immunocompetence. Such research led other investigators to study the relationship between stress induced immunity and cancer in animals (Gottesfeld and Liehr, 1987; Tejwani, Gudehithlu, Gienapp, Malarkey, and Hanissian, 1991) and man (Shekelle, Raynor, and Ostfeld, 1981). The connection between predisposition to certain types of cancer, stress, and depression was based upon studies indicating that those individuals with a certain personality were more prone to cancer, an event which appeared to be linked to a suppression of some aspects of cellular immunity (Cooper, 1984; Cox and MacKay, 1982). Many studies have subsequently shown that the predisposition to cancer, and more recently the development of AIDS following a prolonged HIV infection, is related to the severity and duration of the stress to which the individual is subjected (Levy, Herberman, Lippman, and d’Angelo, 1987).

Given the complexity of the stressors that have been used to investigate the changes in the immune system, and the differences in the responses of the individual to these stressors depending on the age, sex, genetic composition, etc., it is perhaps not surprising to find a wide variation in their results that are expressed in the literature regarding the causal relationship between stress and the immune system.