16

CYTOKINES, "DEPRESSION DUE TO A GENERAL MEDICAL CONDITION," AND ANTIDEPRESSANT DRUGS

Raz Yirmiya,[1] Joseph Weidenfeld,[2] Yehuda Pollak,[1] Michal Morag,[1] Avraham Morag,[3] Ronit Avitsur,[1] Ohr Barak,[1] Avraham Reichenberg,[1] Edna Cohen,[1] Yehuda Shavit,[1] and Haim Ovadia[2]

[1] Department of Psychology, Mount Scopus
The Hebrew University of Jerusalem
[2] Departments of Neurology
[3] Department of Clinical Virology
Hadassah-Hebrew University Hospital, Ein Karem, Jerusalem, Israel

1. INTRODUCTION

Activation of the immune system during various medical conditions produces neural, neuroendocrine, and behavioral effects. The psychological and physiological effects of immune activation resemble many characteristics of depression. The essential features of depression are depressed mood and loss of interest or pleasure in all, or almost all activities (anhedonia). Several associated symptoms are also present, including, appetite disturbance, change in body weight, sleep disturbance, psychomotor disturbance, fatigue, loss of energy, and difficulty in thinking or concentrating (DSM-IV, 1994). Depression is also characterized by specific alterations in the functioning of neurochemical and neuroendocrine systems, including monoaminergic systems and the hypothalamic-pituitary-adrenal (HPA) axis (Brown, Steinberg, & van Praag, 1994; Holsboer, 1995). Most of these psychological and neuroendocrine symptoms appear both in humans and animals during diseases that involve immune activation. Based on these findings, and on several additional lines of evidence that will be presented below, we have recently argued that immune activation is involved in the etiology and symptomatology of depression associated with various medical conditions (Yirmiya, 1997).

The physiological and psychological effects of immune activation (collectively termed "sickness behavior") are mediated by cytokines (Connor & Leonard, 1998; Dantzer, Bluthe, Aubert, Goodall, Bret-Dibat, Kent, Goujon, Laye, Parnet, &

Cytokines, Stress, and Depression, edited by Dantzer *et al.*
Kluwer Academic / Plenum Publishers, New York, 1999.

The original version of this chapter was revised.
A correction to this chapter can be found at
DOI 10.1007/978-0-585-37970-8_18.

Kelley, 1996; Hart, 1988; Kent, Bluthe, Kelley, & Dantzer, 1992a; Maier & Watkins, 1998 Yirmiya, 1997). Most immune challenges produce their initial effects in the periphery, but information regarding their presence is almost immediately transmitted to the brain, in a sensory-like process. Communication between the immune system and the brain is at least partly mediated by proinflammatory cytokines, particularly IL-1β, TNFα, IL-6, and interferons. Two major communication pathways, a humoral and a neural one, have been described (Dantzer et al., 1996; Maier & Watkins, 1998; Watkins, Maier, & Goehler, 1995a). Blood-borne cytokines do not cross the blood brain barrier (BBB), but can still penetrate the brain via the circumventricular organs (which lack BBB), or be transported into the brain by carrier molecules, or bind to endothelial cells of the cerebral vasculature and induce the release of secondary mediators within the brain parenchyma (Watkins et al., 1995a). In addition to the humoral mechanisms, a neural pathway has been recently discovered: Locally-released cytokines activate receptors on peripheral nerves (primarily the vagus), which, in turn, transmit messages to the brain (Dantzer et al., 1996; Maier & Watkins, 1998; Watkins et al., 1995a). Within the brain, this immune-related information activates several areas, including the solitary nucleus, the paraventricular nucleus of the hypothalamus, and the central nucleus of the amygdala (Day & Akil, 1996). The neural activity within these areas is at least partly mediated by cytokines (e.g., IL-1β and TNFα), which are released locally by glia cells and neurons, and serve as neurotransmitters and neuroregulators (Dantzer et al., 1996; Wong, Bongiorno, Rettori, McCann, & Licinio, 1997).

The aim of the present chapter is to review the current knowledge on cytokine-mediated depressive-like symptoms that accompany various medical conditions in humans, and experimental models of these conditions in animals. In addition, our recent efforts to evaluate the relationship between depressive behavior and sickness symptoms, by investigating the effects of antidepressants on sickness behavior in rats, will be presented and discussed.

2. PSYCHOLOGICAL EFFECTS OF IMMUNE ACTIVATION IN HUMANS

Depression is a common, disturbing concomitant of medical conditions. The reported prevalence of major depression episodes in physically-ill varies from 5% to more than 40% (Chochinov, Wilson, Enns, & Lander, 1994). Because depression is often unrecognized and undertreated in sick patients, the prevalence reported in most studies is probably underestimated (Katon & Sullivan, 1990; Laghrissi-Thode, Pollock, Szanto, & Reynolds, 1996). Depression associated with medical conditions has serious implications. For example, the majority (74%) of men committing suicide during an episode of major depression were receiving treatment for a medical condition at the time of death (Isometsa, Aro, Henriksson, Heikkinen, & Lonnqvist, 1994).

Several particular medical conditions have been described in humans, which are associated with both immune activation and high prevalence of behavioral symptoms characteristic of both sickness behavior and depression. In most of these conditions the behavioral symptoms are not explained by direct effects of pathogens on neural tissues. Thus, the effects of pathogens on brain and behavior are usually mediated by indirect mechanisms, such as immune factors.

2.1. Psychological Effects of Acute and Chronic Infectious Diseases

Acute infectious illness, such as influenza, upper respiratory tract infections, gastroenteritis, Epstein-Barr virus, and cytomegalovirus, are associated with a range of depressive symptoms, including fatigue, psychomotor retardation, anorexia, somnolence, lethargy, muscle aches, cognitive disturbances, and depressed mood (Hickie & Lloyd, 1995). The evidence for these alterations is mainly anecdotal and only few studies examined these symptoms systematically. Experimentally-induced viral infections (e.g., common cold, influenza) are associated with decreased psychomotor performance of simple reaction-time tasks and memory impairments (Smith, Thomas, Brockman, Kent, & Nicholson 1993; Smith, Tyrrell, Al-Nakib, Coyle, Donovan, Higgins, & Willman, 1987; Smith, Tyrrell, Al-Nakib, Coyle, Donovan, Higgins, & Willman, 1988). In addition, they are often associated with long term psychiatric effects, particularly depression. Experimentally-induced influenza (but not infections with coronavirus or other minor cold viruses; see Smith, Tyrrell, & Barrow, 1992), as well as natural occurrence of upper respiratory tract illness (Hall & Smith, 1996a), produce a general negative mood state. Moreover, following infection with influenza, subjects showed depressive symptoms, including depressed mood, reduced appetite, sleep disturbances, sense of guilt, marked difficulty in decision making and memory impairments; these symptoms could be detected even months after the onset of the infection (Meijer, Zakay-Rones, & Morag, 1988). Similar disturbances have also been reported following herpesvirus infections (Greenwood, 1987), mononucleosis (Hall & Smith, 1996b; Hendler, 1987), and infections with Borna Disease virus (Bode, Zimmerman, Ferszt, Steinbach, & Ludwig, 1995) and HIV (Maj, 1996). For example, the results of a WHO Neuropsychiatric AIDS study, conducted in 5 geographical locations with a total of 955 subjects, strongly suggest that HIV infection is associated with an increased prevalence of depressive symptoms, and in some locations also with higher incidence of major depression (Maj, 1996). There is also a preliminary evidence for a direct relationship between brain TNFα production and cognitive deterioration in AIDS patients (Seilhean, Kobayashi, He, Uchihara, Rosenblum, Katlama, Bricaire, Duyckaerts, & Hauw, 1997).

We have recently used a double-blind prospective design to investigate the immediate and prolonged psychological and physiological effects of a specific viral infection in humans (Morag, Yirmiya, Lerer, & Morag, in press). Subjects were teenager girls who were vaccinated with live attenuated rubella virus. Based on analysis of levels of antibodies to rubella, subjects were divided into two groups: An experimental group (n = 60), comprised of subjects who were initially seronegative and were infected following vaccination, and a control group (n = 180), comprised of subjects who were already immune to rubella before vaccination. Compared to control subjects, and to their own baseline, subjects from low socioeconomic status (SES) within the experimental group exhibited more severe depressed mood, as measured by the Children Depression Inventory (CDI) (Fig. 1). In addition, the same subjects exhibited more social and attention problems and delinquent behavior, as measured by the Achenbach Child Behavior Checklist. Subjects from high and middle SES did not show these disturbances (Morag et al., in press). The particular vulnerability of low SES subjects to immunization-induced depression is consistent with previous epidemiological studies, demonstrating that people of low SES have higher rates of major, as well as chronic and recurrent depression (Anderson & Armstead, 1995; Bruce, Takeuchi, & Leaf, 1991; Murphy, Olivier,

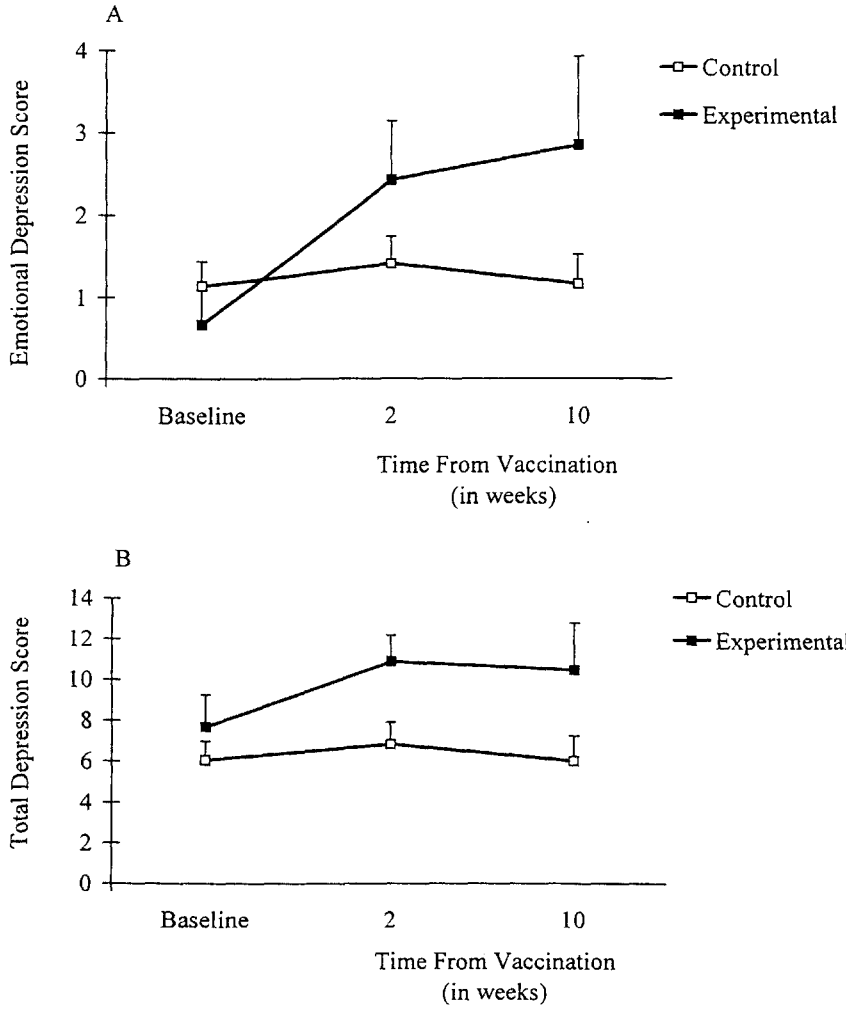

Figure 1. Effect of vaccination with live-attenuated rubella virus on depression scores, measured by the Children Depression Inventory in 12-years old girls with low socioeconomic status.

Monson, Sobol, Federman, & Leighton, 1991). This vulnerability may be associated with several characteristics of low SES, including higher `incidence of stressful life events, and fewer sources of social support (Adler, Boyce, Chesney, Cohen, Folkman, Khan, & Syme, 1994; Anderson & Armstead, 1995; Dohrenwend, 1973; Ranchor, Bouma, & Sanderman, 1996). As demonstrated (Cohen, 1995; Kiecolt-Glaser & Glaser, 1991), these factors modulate the responsiveness to immune challenges. Thus, even a mild viral infection can produce prolonged increase in depressive symptomatology in vulnerable individuals.

Mean (±S.E.M.) emotional depression score (A) and total depression score (B) were assessed before, and 2 and 10 weeks after vaccination. Subjects who were initially seronegative and were infected following vaccination (experimental group) had higher depression scores than subjects who were already immune to rubella before vaccination (control group), at both 2 and 10 weeks post-vaccination.

2.2. Psychological Effects of Non-Infectious Conditions Associated with Immune Activation

Chronic activation of the immune system and enhanced secretion of cytokines may be associated with several types of non-infectious conditions (Dinarello & Wolff, 1993). High incidence of depression is observed in such cases too.

Autoimmune diseases: Cytokines play an important role in the etiology and pathology of many autoimmune diseases (Cavallo, Pozzilli, & Thorpe, 1993; Dinarello & Wolff, 1993), which are also associated with a high prevalence of depression. Particularly high incidence of depression has been demonstrated in patients with multiple sclerosis (Foley, Traugott, LaRocca, Smith, Perlman, Caruso, & Scheinberg, 1992; Minden & Schiffer, 1990; Schiffer & Babigian, 1984; Schubert & Foliart, 1993; Whitlock & Siskind, 1980). According to several estimates, the prevalence of depression in MS patients is in the range of 42–54% (Joffe, Lippert, Gray, Sawa, & Horvath, 1987; Minden, Orav, & Reich, 1987; Sadovnick, Remick, Allen, Swartz, Lee, Eisen, Farquhar, Hashimoto, Hooge, Kastrukoff, Morrison, Nelson, Ogar, & Paty, 1996). Other autoimmune conditions associated with high prevalence of depression, include rheumatoid arthritis (Parker, Smarr, Anderson, Hewett, Walker, Bridges, & Caldwell, 1992; Pincus, Griffith, Pearce, & Isenberg, 1996), systemic lupus erythematosus (Denburg, Carbotte, & Denburg, 1997; Hutchinson, Nehall, & Simeon, 1996; Lim, Ron, Ormerod, David, Miller, Logsdail, Walport, & Harding, 1988; Magner, 1991; Schneebaöm, Singleton, & West, 1991), and allergy (Marshal, 1993). Detailed studies of some of these conditions suggest that, rather than psychological reactions to the medical condition per-se, illness-associated depression is causally related to immune activation (see below).

Stroke and trauma: Stroke and some other types of brain traumas are associated with increased secretion of cytokines. For example, the levels of TNFα and IL-1β are dramatically increased in the brain following stroke or head trauma (Arvin, Neville, Barone, & Feuerstein, 1996). IFNα and its receptors have been identified in cerebral infarct tissues (Yamada & Yamanaka, 1995). Depression is the most common neuropsychiatric consequence of stroke, affecting up to 40% of the patients (Robinson, 1997; Schwartz, Speed, Brunberg, Brewe, Brown, & Greden, 1993). A relationship between the appearance and severity of depression to the location of the injury within the brain has been demonstrated in several cases (Robinson, 1997). However, most depressive symptoms are not explained by a direct localized neural impairment, suggesting an involvement of a more general mechanism, such as immune activation.

Alzheimer's disease: Immune activation and cytokine secretion is associated with brain lesions of Alzheimer's disease and other neurodegenerative diseases (McGeer & McGeer, 1995; Rothwell, Luheshi, & Toulmond, 1996). Activated microglia cells and astrocytes that are associated with neuritic plaques produce IL-1. Moreover, IL-1 can upregulate the expression of β-amyloid precursor proteins and various other plaque-associated proteins. Moreover, this process is self propagating, because β-amyloid directly activates microglia, thus inducing further IL-1 production (Mrak, Sheng, & Griffin, 1995). Depression is very common in Alzheimer's patients. In fact, mild to severe depression is the most prevalent psychiatric symptom in these patients (Mendez, Martin, Smyth, & Whitehouse, 1990). For example, a recent study on 109 patients identified major depression in 22% and minor depression in another 27% of the patients (Lyketsos, Steele, Baker, Galik, Kopunek, Steinberg, & Warren, 1997).

Menstrual cycle and post-partum period: Women exhibit higher levels of immune activation than men (Grossman, 1985), and a high incidence of depression (DSM-IV, 1994; Parry, 1995). This relation may be attributed to many factors, but it should be noted that plasma and urinary levels of IL-1 are much higher in women than in men (Cannon & Dinarello, 1985). Moreover, *in vitro* production of IL-1 is much greater in unstimulated mononuclear cells derived from women is in cells derived from men (Lynch, Dinarello, & Cannon, 1994). This effect depends on the phase of the menstrual cycle; compared to men's cells, women's cells isolated during the luteal and follicular phases secreted 5–10 fold and 13–28 fold more IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1ra), respectively (Lynch et al., 1994). Although greater absolute amounts of each species of IL-1 were secreted during the follicular phase, the ratio of agonist to antagonist secreted was greater in the luteal phase (Lynch et al., 1994). This finding is in agreement with the *in vivo* data, which reflected greater IL-1 bioactivity in the plasma during the luteal phase (Cannon & Dinarello, 1985). The time course of IL-1 secretion and bioactivity is correlated with the onset of depressive episodes in women, which is highest during the luteal phase, particularly several days before the menstrual flow (Abramowitz, Baker, & Fleischer, 1982; Parry, 1995). Finally, child delivery, which in some women causes post-partum depression (Parry, 1995), also triggers a marked increase in cytokine secretion (Cox, King, Casey, & Macdonald, 1993).

2.3. Psychological Effects of Cytokine Administration

Administration of cytokines in humans produces marked behavioral and neuroendocrine symptoms that are similar to those induced by viral infection. Administration of alpha interferon (IFNα) was found to cause flu-like symptoms as well as depressive symptoms, including depressed mood, dysphoria, anhedonia, helplessness, mild to severe fatigue, anorexia, and weight loss, hypersomnia, psychomotor retardation, decreased concentration, and confusion (Fent & Zbinden, 1987; McDonald, Mann, & Thomas, 1987; Meyers & Valentine, 1995; Niiranen, Laaksonen, Iivanainen, Mattson, Fakkila, & Cantell, 1988; Okanoue, Sakamoto, Itoh, Minami, Yasui, Sakamoto, Nishioji, Katagishi, Nakagawa, Tada, Sawa, Mizuno, Kagawa, & Kashima, 1996; Pavol, Meyers, Rexer, Valentine, Mattis, & Talpaz, 1995; Renault, Hoofnagle, Park, Mullen, Peters, Jones, Rustgi, & Jones, 1989; Valentine, Meyers, Kling, Richelson, & Hauser, 1998). In some studies, severe depressed mood has been reported in the majority of the cytokine-administered patients (McDonald et al., 1987; Niiranen et al., 1988; Valentine et al., 1998). Depressive symptoms increased with the dose and duration of IFNα treatment (Pavol et al., 1995; Renault et al., 1989; Valentine et al., 1998), and disappeared completely within 2–3 weeks after termination of the treatment. Patients receiving IL-2 or TNFα also exhibited flu-like symptoms and some depressive symptoms, including depressed mood, severe fatigue, weakness, lethargy, decreased concentration and confusion (Fent & Zbinden, 1987; Meyers, Valentine, Wong, & Leeds, 1994; Spriggs, Sherman, Michie, Arthur, Imamura, Wilmore, Frei, & Kufe, 1988; Walker, Walker, Heys, Lolley, Wesnes, & Eremin, 1997; Walker, Wesnes, Heys, Walker, Lolley, & Eremin, 1996). It should be noted that the effects of these cytokines on depressive symptomatology may be mediated by a cascade of other cytokines; for example, IFNα induces the expression and secretion of IL-1 and other cytokines in the periphery (Arenzana-Seisdedos & Virelizer, 1983) and within the CNS (Licinio, Kling, & Hauser, 1998).

The findings on cytokine-induced depression have important theoretical and clinical implications. Clinical research in the "50 demonstrated that the monoamine

depleting drug reserpine, which was then used as an antihypertensive drug, produces severe depression. This observation stimulated the monoamine hypothesis of depression and the development of new and effective antidepressant drugs. In the same way, the finding that exogenous administration of cytokines produces depression can stimulate the cytokinergic hypothesis of depression, and may result in the development of a new generation of effective antidepressant therapeutic procedures.

2.4. The Role of Immune Activation in Depression

2.4.1. Immune Activation and "Depression Due to a General Medical Condition." Studies on depression in randomly selected general medical inpatients indicate that more than one third report some degree of depression (Laghrissi-Thode et al., 1996; Rodin & Voshart, 1986). As discussed earlier, depression rates can be as high as 50% in certain medical conditions that are specifically associated with high levels of immune activation (e.g., autoimmune diseases, allergy, stroke) (Minden & Schiffer, 1990; Parker et al., 1992; Rodin & Voshart, 1986; Schwartz et al., 1993). The high prevalence of depression in various medical conditions is reflected by the special psychiatric diagnostic entity of "depression due to a general medical condition" (DSM IV, 1994). To diagnose this condition "the clinician should establish the presence of a general medical condition, and determine that the depression is etiologically related to the general medical condition through a physiological mechanism" (DSM-IV, 1994, p. 367).

The depressive symptomatology that is associated with physical illness in humans may be produced directly by immune factors or may constitute a psychological reaction to the incapacitation, pain, and losses that accompany the physical disease process. It is difficult to design experiments that will directly differentiate between these two possibilities. However, several lines of evidence support the hypothesis that the direct influence of immune activation on mood and cognition is independent of, and possibly additive to, the maladaptive depressive response to the distress of having a general medical condition:

1) In a study on the neuropsychological effects of experimentally-induced influenza, cognitive disturbances were found to occur not only in sick individuals, but also in subjects with laboratory evidence of viral infection who did not have any clinical symptoms (Smith et al., 1988).

2) In some recurrent infectious conditions, the depressive symptoms precede the clinical manifestations of the disease. For example, in patients with recurrent herpes infections the depressed mood and other psychological alterations are reported by the patients 24–48 hr prior to recurrence of the peripheral skin or genital lesions (Hickie & Lloyd, 1995). This finding had been interpreted as evidence for the effects of depression on the recurrence of the virus, but the temporal relationship between the immunological, psychological, and somatic alterations is more consistent with the hypothesis that viral-induced immune activation is responsible for the psychological changes.

3) The induction of depressed mood and other depressive symptoms in cytokines-treated patients, and the fact that these symptoms appear almost immediately after cytokine administration and usually disappear shortly after termination of the cytokine treatment (Fent & Zbinden, 1987; McDonald et al., 1987; Meyers & Valentine, 1995; Niiranen et al., 1988; Spriggs et al., 1988), strongly suggests a causal role for cytokines in producing the depressive symptoms. Although cytokines are usually administered in the context of a medical condition (e.g., cancer), which by itself could

account for some of the depressive symptoms, at least part of the depressive symptomatology can be directly ascribed to the cytokine treatment. For example, in a controlled study on patients with chronic myelogenous leukemia, 50% of the patients had elevated levels of depression following the onset of IFNα therapy, compared to 25% following the onset of chemotherapy (Pavol et al., 1995).

4) Several studies on depression associated with autoimmune diseases suggest that the depressive symptoms reflects the action of a basic physiological mechanism, such as immune activation, rather than a psychological reaction to the consequences of the disease (e.g. functional losses). Compared to patients with other neurological diseases, MS patients showed higher levels of depressive symptoms at the time of the diagnostic interview, and higher number of depressive episodes since their diagnosis had been made (Schiffer & Babigian, 1984; Whitlock & Siskind, 1980). Furthermore, depressed MS patients are frequently characterized by the presence of vegetative symptoms and diurnal variations in mood and energy (Whitlock & Siskind, 1980). This quality of depression may suggest an "organic" rather than a "reactive" depression. In many cases the onset of depression precedes the neurological diagnosis (Schiffer & Babigian, 1984). A prospective study of MS depressed patients revealed that immune dysregulation preceded the development of depression (Foley et al., 1992). Similarly, a study that addressed the relationship of helplessness and depression to disease activity in rheumatoid arthritis (RA) patients revealed that immunological activation might moderate this relationship (Parker et al., 1992). Studies in patients with systemic lupus erythematosus (SLE) are somewhat less supportive of the immune activation hypothesis, since no differences were found in the magnitude and quality of SLE-associated depression, compared to depression associated with other chronic medical conditions (Denburg et al., 1997; Hutchinson et al., 1996; Lim et al., 1988; Magner, 1991). The authors interpreted these results as indicating reactive depression (Denburg et al., 1997). However, since many of their control patients suffered from autoimmune diseases, the involvement of immune mechanisms cannot be ruled out, both in control and in SLE patients. In fact, one study found a direct relationship between depressive manifestations and autoantibodies to ribosomal P proteins in SLE patients (Schneebaom et al., 1991).

Together, these findings suggest that at least some of the depressive symptoms that accompany physical illness are not merely a reaction to the medical condition, but are at least partly produced by immune changes preceding and coincide with the appearance of clinical symptoms.

2.4.2. Immune Activation and Other Depressive Syndromes. Immune activation may be involved in depressive syndromes other than "depression due to a general medical condition." Although depression has traditionally been associated with suppression of specific immune functions (Herbert & Cohen, 1993), recent evidence indicates that several components of the immune system are activated in patients suffering from major depression (Connor & Leonard, 1998; Maes, 1995; Maes, Smith, & Scharpe, 1995c). Depression-associated immune activation includes: 1) Increased number of blood lymphocytes, neutrophils, monocytes, and activated T-cells (Maes, Lambrechts, Bosmans, Jacobs, Suy, Vandervorst, De Jockheere, Minner, & Raus, 1992a; Muller, Hofschuster, Ackenheil, Mempel, & Eckstein, 1993; Seidel, Arolt, Hunstiger, Rink, Behnisch, & Kirchner, 1996); 2) Increased serum levels of several soluble indicators of activated immune cells, including interleukin-2 receptor (Maes, Meltzer, Bosmans, Bergmans, Vandoolaeghe, Ranjan, & Desnyder, 1995a; Sluzewska,

Rybakowski, Bosmans, Sobieska, Berghmans, Maes, & Wiktorowicz, 1996), neopterin (Dunbar, Hill, Neale, & Mellsop, 1992; Maes, Scharpe, Meltzer, Okayli, D'Hondt, & Cosyns, 1994) and prostaglandin E2 (Lieb, & Karmali, 1983; Linnoila, Whorton, Rubinow, Cowdry, Ninan, & Waters, 1983); 3) Increased serum concentrations of positive acute phase proteins (APPs) and decreased levels of negative APPs (Maes, Scharpe, Neels, Wauters, Van Gastel, & Cosyns, 1995b; Maes, Scharpe, Van Grootel, Uyttenbroeck, Cooreman, Cosyns, & Suy, 1992b; Seidel, Arolt, Hunstiger, Rink, Behnisch, & Kirchner, 1995; Sluzewska et al., 1996; Song, Dinan, & Leonard, 1994); and 4) Increased secretion of cytokines, both *in vivo* (particularly IL-6) (Maes et al., 1995a; Maes, Bosmans, De Jongh, Kenis, Vandoolaeghe, & Neels, 1997a; Sluzewska, Rybakowski, Laciak, Mackiewicz, Sobieska, & Wiktorowicz, 1995; Sluzewska et al., 1996), and following *in vitro* induction by mitogens (particularly IL-1β, IL-6, and IFNγ) (Maes, Bosmans, Meltzer, Scharpe, & Suy, 1993; Maes et al., 1994; Seidel et al, 1995; Seidel et al., 1996).

Furthermore, immune activation is positively correlated with specific depressive symptoms and with the impaired feedback regulation of the HPA axis, found in major depression patients (Maes et al., 1993; Maes, 1995). Based on these findings, Maes and his colleagues hypothesized that production of interleukins contributes to the HPA hyperactivity and to the vegetative symptoms of severe major depression (Maes, 1995).

Clearly, immune activation and cytokine secretion do not account for all types of depressive disorders. However, immune factors may be involved in the pathophysiology of certain subtypes of depression (e.g., melancholia), characterized by a constellation of symptoms that are often found in virus-infected and cytokine-injected individuals. The source of immune activation in any depressive disorder other than "depression due to a general medical condition" has not been identified yet. It is possible, however, that subclinical infectious processes or viral reactivation induce immune reaction, which in turn contributes to the depressive symptomatology. This hypothesis is supported by studies reporting increased antibody titers to several viruses, particularly herpes simplex virus (HSV) in patients with major depression (Cappel, Gregoire, Thiry, & Sprecher, 1978; Lycke, Norrby, & Roos, 1974). Moreover, in a recent study (Zorzenon, Colle, Vecchio, Bertoli, Giavedoni, Degrassi, Lavaroni, & Aguglia, 1996) clear evidence was provided for active viral multiplication and elevated antibody titers to HSV in 41% of the patients with major depression. Similarly, higher serum antibodies to Borna disease virus, as well as isolation of this virus from patients with depression has been reported (Bode, Durrwald, Rantam, Ferszt, & Ludwig, 1996).

3. BEHAVIORAL EFFECTS OF INFECTIOUS DISEASES AND CYTOKINE ADMINISTRATION IN ANIMALS

In animals, the association between acute illness and suppression of general activity, appetite and grooming has been reported by animal handlers and veterinarians long ago. Experimental studies, using systemic protozoan, bacterial or viral infections, provided more conclusive evidence for sickness-induced behavioral changes (Hart, 1988). In addition, exogenous administration of proinflammatory cytokines produces sickness behavior, whereas cytokine antagonists, as well as cytokine synthesis blockers, attenuate the behavioral effects of pathogens. These findings indicate that sickness behavior

is mediated by immune-derived cytokines, rather than being produced by the pathogen itself. Several components of sickness behavior, which resemble the characteristics of depression, have been described in animal research:

3.1. Anorexia and Body Weight Loss

Anorexia and body weight loss are among the most robust effects of acute as well as chronic illness (Plata-Salaman, 1996). Such effects have been recently demonstrated in experimental models of disease, including influenza virus in-fection (Swiergiel, Smagin, & Dunn, 1996; Swiergiel, Smagin, Johnson, & Dunn, 1997), local inflammation induced by subcutaneous injection of turpentine (Kozac, Poli, Soszynski, Conn, Leon, & Kluger, 1996; Kozac, Soszynski, Rudolph, Conn, & Kluger, 1997), and exogenous administration of pathogen products, including LPS (Kozac et al., 1997; Yirmiya, 1996), and heat-inactivated *Mycoplasma fermentans* (Yirmiya, Barak, Avitsur, Galilly, & Weidenfeld, 1997). Several lines of evidence suggest that anorexia and body weight loss are mediated by cytokines: 1) Similar effects were observed following exogenous administration of cytokines, particularly IL-1β, TNFα, and IL-8, which act centrally and synergistically to suppress feeding (Plata-Salaman, 1998; Sonti, Ilyin, & Plata-Salaman, 1996); 2) The anorexic effects of influenza virus infection or LPS could be attenuated by pretreatment with IL-1ra (Swiergiel et al., 1997); 3) Increase in dietary N-3 fatty acids, which are known to reduce cytokine secretion, abolished the effects of local inflammation and LPS administration (Kozac et al., 1997); and 4) Mice deficient in IL-6 (IL-6 knockout) exhibited attenuated anorexia and weight loss following local inflammation or influenza pneumonitis (Kozac et al., 1996).

3.2. Hypersomnia

Sleepiness and altered sleep patterns are among the earliest signs of infection. Increased somnolence is produced by specific pathogen products, such as muramyl peptides, LPS, and viral double-stranded RNA (Krueger & Majde, 1994). Changes in sleep patterns are characterized by an increase in slow-wave sleep (SWS) and inhibition of rapid eye movement (REM) sleep. Exogenous administration of IL-1, TNFα or IFN-α, either peripherally or into the brain, also induce somnolence (Krueger, Takahashi, Kapas, Bredow, Roky, Fang, Floyd, Renegar, Guha-Thakurta, Novitsky, & Obal, 1995). Moreover, brain-derived IL-1 has recently been implicated in sleep responses following systemic, as well as central bacterial infection (Takahashi, Kapas, Fang, Seyer, Wang, & Krueger, 1996).

3.3. Psychomotor Retardation, Fatigue, and Reduced Exploratory Behavior

Psychomotor retardation, fatigue, and reduced exploratory behavior were found in various models of infectious disease, as well as following cytokine administration. For example, a decrease in locomotor and exploratory activity was produced by influenza pneumonitis, turpentine abscess (Kozac et al., 1996, 1997), *Mycoplasma fermentans* (Yirmiya et al., 1997), LPS (Dunn, Chapman, & Antoon, 1992; Yirmiya, 1996; Yirmiya, Rosen, Donchin, & Ovadia, 1994), IL-1 (Spadaro & Dunn, 1990), and

IFN-α (Segall & Crnic, 1990). Similar symptoms, as well as increased anxiety behavior were also reported, using a mouse model of autoimmune disease (systemic lupus erythematosus) (Schrott & Crnic, 1996), indicating that behavioral changes can also accompany non-infectious conditions.

3.4. Impaired Cognitive Abilities

The presence of IL-1 and IL-6 receptors in the hippocampus, and the findings that LPS, IL-1 and TNFα modulate neural processes thought to be involved in learning (including synaptic inhibition and long-term potentiation) (Cunningham, Murray, O'Neill, Lynch, & O'Connor, 1996; Katsuki, Nakai, Hirai, Akaji, Kiso, & Satoh, 1990), suggest a role for cytokines in cognitive functions. Such a role has recently been demonstrated by showing that bacterial, parasitic or viral infections, and LPS or IL-1 administration, impair learning in various paradigms, including autoshaping (Aubert, Vega, Dantzer, & Goodall, 1995), and spatial navigation learning in the Morris maze and radial arm maze (Beers, Henkel, Kesner, & Stroop, 1995; Gibertini, 1996; Gibertini, Newton, Friedman, & Klein, 1995; Kavaliers, Colwell, & Galea, 1995; Oitzl, van Oers, Schobitz, & de Kloet, 1993). These effects are not confounded by pyrogenic or general performance effects of immune challenges. These findings are particularly interesting because immune activation and cytokine release in the brain accompany many neurodegenerative disorders (Rothwell et al., 1996). A critical role for cytokines in cognitive deficits associated with neurodegenerative disorders was recently demonstrated in transgenic mice expressing interleukin-6 in the brain; inflammatory neurodegeneration was accompanied in these mice by progressive decline in avoidance learning (Heyser, Masliah, Samimi, Campbell, & Gold, 1997).

3.5. Impaired Social Behavior

The effect of immune activation on social behavior has been mainly studied using the behavioral test of olfactory exploration of a conspecific juvenile. The time spent by adult rats or mice in social exploration of a conspecific juvenile was profoundly reduced following systemic or intracerebral administration of LPS (Yirmiya, 1996; Johnson, Propes, & Shavit, 1996), *Mycoplasma fermentans* (Yirmiya et al., 1997), IL-1 (Bluthe, Dantzer, & Kelley, 1997; Kent, Bluthe, Dantzer, Hardwick, Kelley, Rothwell, & Vannice, 1992b), and TNFα (Bluthe, Dantzer, & Kelley, 1991). LPS administration also reduced aggressive attacks in mice selectively bred for high aggressive behavior (Granger, Hood, Ikeda, Reed, Jones, & Block, 1997).

3.6. Altered Pain Perception

Alterations in pain perception accompany inflammation, infection, autoimmune diseases and nerve injury. Proinflammatory cytokines, associated with these conditions, were found to activate neural circuits which modulate pain perception (Watkins, Maier, & Goehler, 1995b). Typically, cytokine secretion results in an immediate phase of hyperalgesia (increased responsiveness to painful stimuli) (Watkins et al., 1995b), which is later followed by a prolonged analgesic phase (Romanovsky, Kulchitsky, Akulich, Koulchitsky, Simons, Sessler, & Gourine, 1996; Yirmiya et al., 1994).

3.7. Anhedonia

Anhedonia means "without (an) pleasure (hedonia)" and can be defined as the diminished capacity to experience pleasure of any sort, i.e., activities that previously brought enjoyment, such as eating, sex, social, and recreational activities, provide little or no gratification in the depressed patient. Anhedonia is considered as one of the two essential features of a major depressive episode, and is even further emphasized in the subclassification criteria of a major depressive episode with melancholia (DSM-IV, 1994). The hypothesis that immune activation produces anhedonia has been studied in experimental animals using several paradigms, including the consumption of and preference for sweet solutions, intracranial electrical self stimulation (ICSS), and tests of libido and sexual activity.

3.7.1. Reduced Consumption of and Preference for Sweet Solutions. The consumption of and preference for sweet solutions can serve as a model for hedonic processes, because when presented with such solutions, animals will drink more fluid than they usually drink, and if given a choice, they will prefer these solutions over water. Moreover, non-hungry or thirsty animals will perform operant tasks to obtain sweet solutions as a rewarding stimulus, in the same way that they perform for ICSS and other rewards. Our studies demonstrated that various immune challenges attenuated the consumption of and preference for sweet solutions, while having minimal effects on water drinking (Table 1). LPS significantly decreased saccharin preference in fluid-deprived rats, and suppressed free consumption of saccharin solution in non-deprived rats; water consumption was not affected under these circumstances (Yirmiya, 1996). A similar decrease in saccharin-, but not water-consumption was demonstrated following intracerebral administration *of Mycoplasma fermentans* (Yirmiya et al., 1997) or HIV-1 gp120 (unpublished results). In addition, we have recently demonstrated decreased preference for a dilute sucrose solution in rats with experimental allergic encephalomyelitis (EAE), an established model of multiple sclerosis in humans.

Table 1. Effects of various immune challenges on the consumption of sweet solutions

Immune challenge	Sweet solution (ml)*	Water (ml)*
LPS (50μg/kg, i.p.)	25.3 (10.5)	17.5 (2.8)
Saline	55.6 (7.2)	21.9 (3.1)
IL-1 (50ng, i.c.v)	17.2 (7.0)	1.7 (0.5)
Saline	45.6 (7.9)	0.8 (0.3)
Mycoplasma fermentans (i.c.v.)	16.0 (6.9)	4.2 (1.4)
Saline	39.1 (4.6)	1.3 (0.5)
HIV gp120 (i.c.v.)	38.9 (5.1)	0.6 (0.3)
Saline	51.5 (3.1)	1.6 (1.1)
EAE	0.78 (0.20)	0.56 (0.10)
Control	12.26 (0.22)	0.54 (0.07)

*For each immune challenge, animals were presented with two graduated tubes containing the sweet solution or water. Data represents the mean (± S.E.M.) fluid consumption over a 24 hr period in non-deprived rats, following administration of LPS, IL-1β, *Mycoplasma fermentans* or gp120. Data for the acute immune challenges referes to the consumption of a 10 mM saccharin solution by rats. Data for the EAE model refers to the consumption of a dilute sucrose solution by SJL mice over a period of 6 hr (averge of 2 sessions).

Interestingly, the decrease in sucrose preference preceded the appearance of clinical symptoms in this model, demonstrating the independence of anhedonia from the physical disease symptoms (unpublished observation). Studies in other laboratories corroborate these findings, demonstrating that immune challenges reduced the intake of sweetened milk (Swiergiel et al., 1996, 1997), and abolished the reinforcing effect of cocaine (Suzuki, Funada, Sugano, Misawa, Okutomi, Soma, & Mizuno, 1994). Moreover, mice that spontaneously develop systemic autoimmune lupus-like disease, also show blunted sensitivity to sucrose, which can be reversed by an immunosuppressive treatment (Sakic, Denburg, Denburg, & Szechtman, 1996).

Several previous studies have used the consumption of sweet solutions as a model of anhedonia, describing a decrease in the consumption of and preference for sucrose and saccharin solutions in an animal model of depression (exposure to chronic mild unpredictable stress) (Willner, 1997). However, the use of consumption of sucrose or other calorie-rich highly palatable diets as a measure of cytokine-induced anhedonia is problematic, because of the marked anorexia and loss of body weight that accompany immune activation. Thus, a decrease in the total amount of sucrose or sweetened milk consumption may reflect either anhedonia and/or anorexia and reduced calorie intake. Because saccharin has a sweet taste but no calories, our findings that immune activation induced reduction in saccharin preference provide further support for the anhedonic effect of immune challenges.

It should be noted, however, that the validity of the saccharin preference test as a model of anhedonia is controversial. Previous research, demonstrated that although the major component of saccharin's taste is sweet, there is also an aversive, bitter-like component (Dess, 1993). Aubert & Dantzer (1998). have recently studied the effects of LPS on taste reactivity (TR) to saccharin, sucrose and quinine solutions. They showed that following LPS administration, TR to quinine and sucrose were unaltered, but the responses to saccharin or to a sucrose solution adulterated with quinine were changed, such that more aversive responses and less ingestive responses were exhibited by LPS-treated animals. These findings indicate that LPS accentuates the aversive component of the rewarding saccharin stimulus, suggesting that LPS produces increased finickiness rather than anhedonia. Nevertheless, it should be noted that changes in TR do not necessarily represent the overall hedonic response of the animal or its inclination to consume a palatable solution. TR responses are mediated by hedonic mechanisms in the lower brain stem taste centers, as evidenced by their preservation in decerebrate animals (Grill & Norgren, 1978). Hedonic evaluation assessed by the TR test can be at odds with consummatory or instrumental behavior. For example, in lines of rats that were genetically selected for high and low saccharin consumption, the high-consuming rats manifested more rejection responses to saccharin in the TR test (Badia-Elder, Kiefer, & Dess, 1996). Thus, it is possible that the effects of LPS and other immune challenges on saccharin preference is not solely explained by increased finickiness, but may be also related to their effects on incentive-motivational systems in brain centers higher than the brain stem. In conclusion, studies on the intake of and preference for palatable solutions as a model for anhedonia have some methodological problems, and therefore should employ both nutritive and non-nutritive solutions.

3.7.2. Decreased Responding for Rewarding Intracranial Self Stimulation. Further evidence for the anhedonic effects of immune activation is provided by investigation of the effects of immune challenges and cytokines on rewarding intracranial self stimulation (ICSS). Suppression of ICSS is a very useful animal model to study

anhedonia (Willner, 1994). Endotoxin-induced suppression of ICSS has been demonstrated more than 3 decades ago (Miller, 1964). This report was recently corroborated by the findings that exogenous administration of LPS (Borowski, Kokkinidis, Merali, & Anisman, 1997) or IL-2 (Anisman, Kokkinidis, Borowski, & Merali, 1998; Anisman, Kokkinidis, & Merali, 1996) produce a dramatic and long-lasting decrease in ICSS. Antigenic challenge with sheep red blood cells also reduced ICSS from rat nucleus accumbens at times that approximated the peak of immune response (Zacharko, Zalcman, Macneil, Andrews, Mendella, & Anisman, 1997). As shown in the above studies, the effects of immune challenges on ICSS represent a specific motivational change, rather than motoric, soporific, attentional or cognitive deficit.

In contrast to the effects of LPS and IL-2, administration of IL-1β had no clear effect on ICSS: No effect of IL-1β on ICSS was detected following administration of a dose comparable to an effective dose of IL-2 (1 μg/rat), whereas a higher dose (2 μg/rat), which induced overt signs of illness, attenuated ICSS (to a lesser extent than IL-2), with some of the animals ceasing responding almost completely and the others affected only slightly (Anisman et al., 1998). The authors conclude that whereas IL-2 reduce ICSS by producing anhedonia, the effects of IL-1 in this paradigm are secondary to illness. It should be noted, however, that these findings do not entirely rule out the possibility that IL-1 is involved in hedonic processes. It is possible that in contrast to the "pure" anhedonia produced by IL-2 (i.e., disruption of ICSS with no other signs of illness), illness and anhedonia are tightly coupled in IL-1-injected animals. The anhedonic effect of LPS is also coupled with sickness behavior; in fact, the dose of LPS (100 μg/kg), which was effective in decreasing ICSS, probably produced more illness than the ineffective dose of IL-1 (1 μg/rat). Thus, the possibility that IL-1 is at least partially involved in mediating the anhedonic effects of LPS can not be ruled out. Furthermore, several investigators have demonstrated that IL-1 acts synrgistically with other cytokines in producing sickness behavior symptoms. Thus, in future research the possibility that IL-1 influences hedonic processes via interactions with other cytokines should be examined.

3.7.3. Reduced Libido and Impaired Sexual Activity. A significant reduction in sexual interest or desire, as well as difficulties in sexual functioning are commonly associated features of depression (DSM-IV, 1994; Mathew & Weinman, 1982). These features are viewed as manifestation of the general loss of interest and pleasure in activities that were previously considered pleasurable (DSM-IV, 1994). Indeed, in animal studies, sexual contact has been shown to act as a reinforcing stimulus (Meyerson & Lindstrom, 1973), i.e., its motivational effects are similar to those of other reinforcing stimuli such as ICSS or palatable food. To further explore this anhedonic aspect of immune activation, we have recently examined the effects of LPS and IL-1β on sexual behavior in male and female rats, using various behavioral tests. Low doses of LPS, administered either peripherally or centrally, significantly reduced sexual motivation, proceptive (soliciting) behavior and receptivity in females. Higher doses of LPS completely abolished all aspects of female sexual behavior. In contrast, male sexual behavior was affected only by high doses of LPS (Avitsur, Pollak, & Yirmiya, 1997; Yirmiya, 1996) . Similarly, administration of IL-1β had no effect on any component of male sexual behavior, whereas even low doses of IL-1β, administered either peripherally or centrally, markedly decreased sexual motivation, proceptive behavior, receptivity, and attractivity in females (Avitsur et al., 1997; Avitsur, Cohen, & Yirmiya, 1998).

In conclusion, various immune challenges induce anhedonia as well as many behavioral alterations, which resemble the vegetative symptoms of depression. These findings suggest that immune activation produces a depression-like syndrome in animals.

4. IMMUNE ACTIVATION AND DEPRESSION ARE BOTH ASSOCIATED WITH SIMILAR NEUROENDOCRINE ALTERATIONS

Depression is characterized by marked alterations in neuroendocrine function. In particular, dysregulation of the HPA axis has been suggested as an important aspect of the pathophysiology of depression. Patients with major affective disorders exhibit elevated serum, urinary, and cerebrospinal fluid (CSF) levels of cortisol (Caroll, Curtis, & Mendels, 1976; Sachar, Hellman, Fukushima, & Gallaghaer, 1970; Traskman, Tybring, Asberg, Bertilsson, & Schalling, 1980), abnormal 24-hr cortisol secretory patterns (Linkowski, Mendlewicz, Leclercq, Brasseur, Hubain, Goldstein, Copinschi, & van Cauter, 1985), and non-suppression of serum cortisol following dexamethasone administration (Carroll, Martin, & Davies, 1968; Holsboer & Barden, 1996). The excessive adrenal cortisol secretion in depressed patients probably reflects abnormal limbic-hypothalamic activation, which results in increased production and secretion of corticotrpin-releasing hormone (CRH) (Gold, Chrousos, Kellner, Post, Roy, Auerginos, Schulte, Oldfield, & Loriaux, 1984; Holsboer & Barden, 1996; Yehuda & Nemeroff, 1994). This hypothesis is supported both by preclinical studies, demonstrating that intracerebroventricular administration of CRH induces behaviors in animals that resemble symptoms of depression (Owens & Nemeroff, 1993), and by clinical studies indicating that CRH concentrations in the CSF and CRH mRNA in the hypothalamus are increased in depressed patients (Holsboer & Barden, 1996; Owens & Nemeroff, 1993).

Immune activation produces neuroendocrine alterations, which are very similar to the alterations found in most depressed patients. Viral infection, *in vivo* antibody production, and direct administration of cytokines, including TNFα, IL-1β, and IL-6, have all been shown to activate the HPA axis (Besedovsky & Del Rey, 1996; Turnbull & Rivier, 1995). Such activation is mainly produced by the release of hypothalamic CRH (Rivier & Rivest, 1993; Tilders, Derijk, Van Dam, Vincent, Schotanus, & Persoons, 1994; Besedovsky & Del Rey, 1996).

The findings that increased production and release of CRH are concomitant of both depression and immune activation, and the increased production of cytokines in depressed patients (Maes, 1995; Maes et al., 1995c) suggest a role for cytokines in mediating HPA axis hyperactivity in depression. Support for this hypothesis was provided by Maes et al., (1993), who described a significant correlation between IL-1β production and post-dexamethasone (post-DEX) cortisol levels in depressed patients. According to this report, depressed patients who showed higher mitogen-induced *in vitro* production of IL-1β had higher post-DEX cortisol levels. This finding may be related to the results of two recent studies on the effects of immune challenges on glucocorticoid (GC) negative feedback regulation in animal models. In one study, endotoxin or IL-1 administration decreased the affinity of corticosteroid receptors, which mediate feedback inhibition of the HPA system (Schobitz, De Kloet, & Holsboer, 1994). In another study (Weidenfeld & Yirmiya,

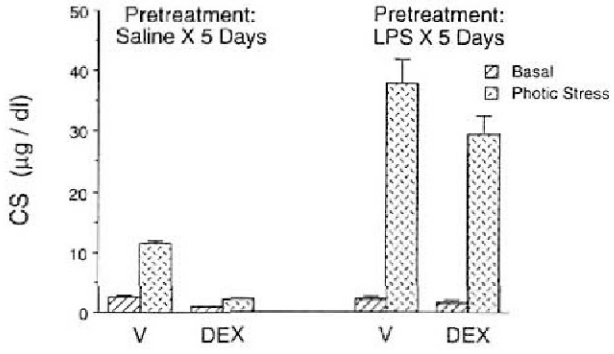

Figure 2. Effects of LPS on the glucocorticoid negative feedback regulation of the adrenocortical response.

1996), we examined the functional significance of this phenomenon. Rats were administered with either LPS or saline for 5 days. Two days following this treatment, rats were administered with either vehicle or dexamethasone, and 3.5 h later they were exposed to an acute stressful photic stimulation. In saline-pretreated rats, photic stimulation caused a marked elevation of serum corticosterone levels, and pretreatment with DEX completely abolished this response (Fig. 2). In LPS-pretreated animals, corticosterone levels following photic stimulation were significantly greater than in saline-treated animals, and DEX was ineffective. The effects on the negative feedback were specific to LPS, since other treatments, which mimic various aspects of prolonged LPS exposure, such as corticosterone administration or chronic stressful exposure, did not produce the same impairment of the GC negative feedback (Weidenfeld & Yirmiya, 1996). Together, these findings indicate that immune activation produces a neuroendocrine alteration, which is similar to one of the central abnormalities found in most depressed patients.

Serum corticosterone (CS) levels were measured under basal conditions and following exposure to stressful photic stimulation, in rats treated with either dexamethasone (DEX, 25 µg/Kg, i.p.) or vehicle, 3.5 hr prior to the onset of the stressor. The photic stimulation was applied 2 days following the 5th daily exposure to either saline or LPS. Pretreatment with LPS impaired the glucocorticoid negative feedback, reflected by elevated stress-induced CS secretion and insensitivity to DEX.

5. ADAPTIVE AND MALADAPTIVE ASPECTS OF IMMUNOLOGICALLY-INDUCED DEPRESSION

Immunologically-induced depression-like syndrome may be adaptive during acute, and possibly even chronic diseases. During infection, inflammation, or neurological disease processes, functioning of the organism is disturbed, and it may be advantageous for the organism to refrain from most activities, and postpone active coping until recuperation begins to take place. Thus, depression-like sickness behavior serves to "keep the organism out of troubles" during periods of high vulnerability. The behavioral effects of cytokines may serve several more specific functions: Psychomotor retardation serves to save body energy levels and maintain the highly

adaptive febrile response (Hart, 1988); Anorexia reduces the motivation of the organism to look for food, which may involve expenditure of energy. It also reduces the consumption of nutrients that are essential for the growth and proliferation of many pathogens (e.g., iron) (Hart, 1988); Anhedonia may further ensure the lack of motivation to engage in goal-directed behaviors, including social activity and sexual behavior; Finally, the inhibition of female sexual behavior following activation of the immune system may be adaptive in preventing conception when the animal is sick, thus reducing the risk of spontaneous abortion, prenatal infection and abnormal development (Avitsur et al., 1997; Avitsur et al., 1998; Yirmiya, Avitsur, Donchin, Cohen, 1995). A depressive-like response to infection in the same way that pain is adaptive in response to tissue injury. Whereas pain serves to protect and attend to a specific tissue or organ, which usually displays local inflammation, "depression due to a general medical condition" serves to protect the whole organism when the disease and inflammation are systemic, involving multiple sites and systems, and/or when the inflammatory processes occur within the brain.

It is also possible that many of the depressive symptoms associated with disease and immune activation are not adaptive in terms of the individual; rather, they are adaptive for the population. Sociobiologists argue that complex social behaviors may be selected for, in the course of evolution, even though the effect of the behavior on its bearer is to reduce its own personal fitness (Wilson, 1975). For example, an animal that utters a loud alarm call is drawing attention to itself, increasing the likelihood that it will be captured by the predator. Theories of inclusive fitness and kin selection provide convincing evidence for the adaptive value of such "altruistic" behaviors (Wilson, 1975). A similar phenomenon may explain the behavioral effects of infectious diseases, because such diseases may be transmitted from the individual to its kins and family members, thus reducing the individual's "inclusive fitness" (i.e., the net genetic representation in succeeding generations, including other relatives in addition to offspring). According to this view, the infected subject's withdrawal from regular activities, particularly those which involve social interactions, reduces the risk of infection spread in the population. This may be particularly important in species where the same food is shared by the whole group. In such a situation, transmission of pathogens is particularly likely, and immune-activation-induced anorexia and social withdrawal may be highly adaptive.

Obviously, adaptive immune-mediated depression-like syndrome should be transient and restricted to the time period in which the organism is sick. Indeed, many factors have been documented to tightly regulate and limit the behavioral, neural and neuroendocrine effects of cytokines, including glucocorticoids, vasopressin, and α-melanocyte stimulating hormone (α-MSH) (Dantzer et al., 1996). Disruption of these regulatory factors might lead to impairment in "shutting off" the immune and neural mechanisms underlying sickness behavior, thus resulting in maladaptive depressive symptomatology. This process may underlie the Chronic Fatigue Syndrome (CFS) and the Post-Viral Fatigue Syndrome (PVFS). Both syndromes are associated with psychological changes that persist long after recuperation from viral infection (Komaroff, Fagioli, Geiger, Doolittle, Lee, Kornish, Gleit, & Guerriero, 1996). They are mainly characterized by fatigue, which reduces patients' level of everyday activity by at least 50%. Additional symptoms are low fever, sore throat, enlargement, and/or pain of the lymph nodes, headaches, depression, anxiety, confusion, bad temper, and difficulties in concentration (Klonoff, 1992; Komaroff & Buchwald, 1991). Depression occurs in 70–85% of all CFS and PVFS patients (Abbey & Garfinkel, 1991; Komaroff

& Buchwald, 1991). Both syndromes are also associated with alterations in immune functions, including abnormal levels of lymphocytes, hyperactive immunological responses, high levels of antibodies to Epstein-Barr Virus, and other viruses, and impaired regulation of cytokine secretion (Buchwald & Komaroff, 1991; Komaroff & Buchwald, 1998). Blood levels of cortisol, which normally limits the extent of brain cytokine production and their behavioral impact (Goujon, Parnet, Laye, Combe, Kelley, & Dantzer, 1995; Johnson et al., 1996), are lower in these patients (Cleare, Bearn, Allain, McGregor, Wessely, Murray, & O'Keane, 1995). Thus, CFS and PVFS seem to involve impairment in at least one of the mechanisms responsible for down regulating the immune system, along with its psychological effects, following recuperation from a viral infection.

Other forms of depressive disorders are also associated with disruption of anti-inflammatory neuromediators. For example, the levels of vasopressin and α-MSH are lower in depressed patients, particularly those with melancholia (Laruelle, Seghers, Goffinet, Bouchez, & Legros, 1990; Maes, DeJonckheere, Vandervorst, Schotte, Cosyns, Raus, & Suy, 1991). Paradoxically, acute infection occurring during severe depression may produce (in addition to exacerbated depressive symptoms) a rebound activation of the anti-inflammatory system, which could temporarily attenuate the depressive symptomatology. The effects of acute endotoxin injection on depressed patients was recently examined (Bauer, Hohagen, Gimmel, Bruns, Lis, Krieger, Ambach, Guthmann, Grunze, Fritsch-Montero, Weissbach, Ganter, Frommnerger, Riemann, & Berger, 1995); as found, proinflammatory cytokines levels and body temperature were elevated during the first 6 hr following the injection, and the patients "exhibited pronounced apathy". However, 15 hr after endotoxin administration, when cytokine levels and fever subsided, the patients reported a significantly improved mood. This effect was transient and disappeared on the next day (Bauer et al., 1995). Thus, it is possible that activation of rebound "shutting off" mechanisms of immune activation in severely depressed patients can improved mood, at least transiently.

6. EFFECTS OF ANTIDEPRESSANTS ON DEPRESSION INDUCED BY IMMUNE ACTIVATION

Antidepressants have been used successfully in treating depressive symptoms associated with various medical conditions (Katon & Sullivan, 1990). Both tricyclic antidepressants (TCAs) (Schiffer & Wineman, 1990) and selective serotonin reuptake inhibitors (SSRIs) (Scott, Nussbaum, McConnell, & Brill, 1995) have been used successfully in the treatment of depression associated with multiple sclerosis, stroke (Lauritzen, Bjerg Bendsen, Vilmar, Bjerg Bendsen, Lunde, & Bech, 1994), Alzheimer's disease (Gottfries, 1997; Tueth, 1995), HIV infection (Ayuso, 1994; Rabkin, Wagner, & Rabkin, 1994), and depression induced by IFN administration (e.g., in hepatitis C or multiple sclerosis patients) (Levenson & Fallon, 1993; Mohr, Goodkin, Likosky, Gatto, Baumann, & Rudick, 1997).

To further elucidate the relationship between immune activation and depression, and explore the mechanisms underlying the therapeutic action of antidepressants, we employed an experimental animal model. Specifically, we examined the effects of antidepressants on LPS- or IL-1-induced behavioral and neuroendocrine alterations in rats.

6.1. Effects of Imipramine and Fluoxetin on LPS- and IL-1-Induced Sickness Behavior and Adrenocortical Activation

We first tested the effects of the tricyclic antidepressant imipramine on LPS-induced anhedonia, using the saccharin preference paradigm. Rats were habituated to a drinking deprivation schedule and to the taste of saccharin for several days before the experiment. On the first experiment day, rats were injected acutely with either imipramine or saline, immediately followed by an injection of either LPS or saline. Four hours later, animals were presented with two tubes containing either saccharin or water, and fluid consumption was measured over a priod of 20 minutes. For 3 weeks following this test, rats received only water, along with a daily injection of either imipramine or saline according to their respective group assignment during the first drinking test. On the last injection day (chronic imipramine test), the rats received either LPS or saline, according to their group assignment during the acute imipramine test, and the consumption of saccharin and water was measured 4 hours later. In the first expeimenal day, LPS significantly suppressed the consumption of saccharin, but not water, and this suppression was not attenuated by acute administration of imipramine. However, chronic imipraminetreatment, completely abolished the suppressive effect of LPS on saccharine consumption (Yirmiya, 1996).

Chronic administration of imipramine (daily injection for 5 weeks) attenuated many other behavioral effects of LPS. Imipramine-treated rats exhibited facilitated recovery from LPS-induced anorexia, body-weight loss, and reduced social activity. In addition, they did not demonstrate LPS-induced suppression of locomotor and exploratory behavior in the open field test. In another experiment, we showed that acute administration of imipramine did not have such effects, i.e., there was no effect of acute imipramine on LPS-induced reduction in food consumption, body weight, social exploration, and open-field activity. The dissociation between the effects of acute and chronic imipramine treatment is important, since in clinical settings, imipramine is also effective in alleviating depression only following chronic, but not acute administration (Montgomery, 1994).

In subsequent experiments we showed that chronic administration (daily injections, 5 weeks) of fluoxetin also affected some, but not all the alterations produced by LPS. Fluoxetin significantly attenuated LPS-induced reduction in food consumption and body weight, but did not affect LPS-induced decrease in social interaction and activity in the open-field test. Chronic fluoxetin treatment also attenuated LPS-induced secretion of corticosterone (Yirmiya, Weidenfeld, Pollak, Avitsur, Barak, & Ovadia, unpublished observation).

In contrast to the effects of antidepressants on the responsiveness to LPS, we found no evidence for an effect of imipramine on the behavioral and neuroendocrine changes induced by IL-1. Chronic treatment with imipramine had no significant effect on IL-1-induced reduction in food consumption, body weight, social exploration, open-field activity, and corticosterone secretion. This finding indicates that the behavioral response to IL-1 in imipramine-treated rats is normal. Thus, the effects of imipramine on LPS-induced behavioral changes are at least partly mediated by changes in immune reactivity to LPS (particularly reduced production of cytokines), and not by down-stream effects on IL-1-induced sickness behavior.

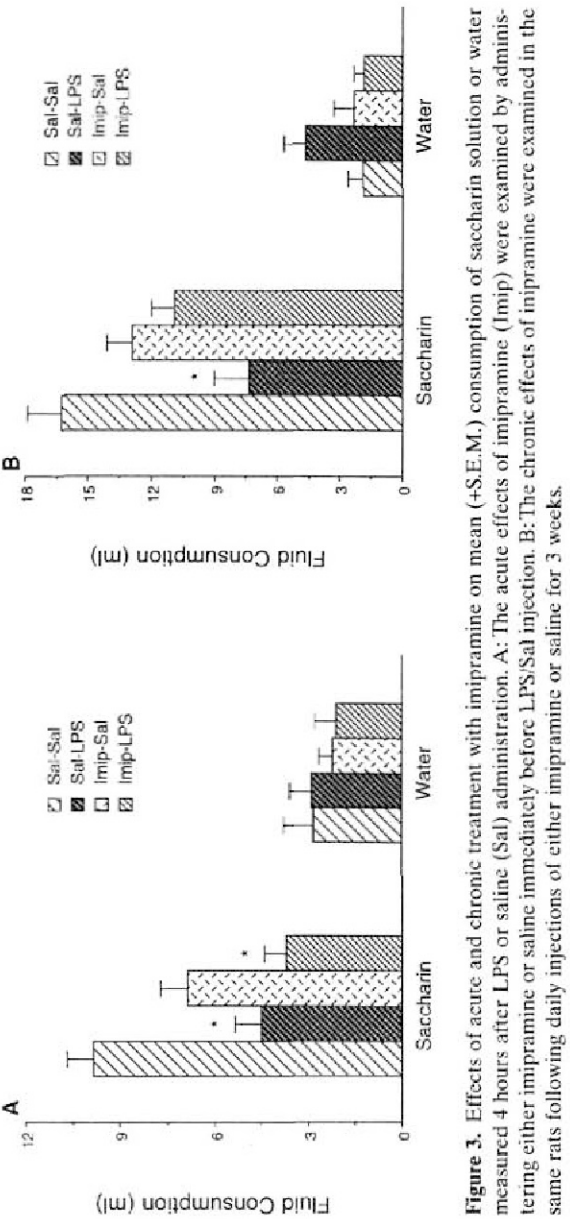

Figure 3. Effects of acute and chronic treatment with imipramine on mean (+S.E.M.) consumption of saccharin solution or water measured 4 hours after LPS or saline (Sal) administration. A: The acute effects of imipramine (Imip) were examined by administering either imipramine or saline immediately before LPS/Sal injection. B: The chronic effects of imipramine were examined in the same rats following daily injections of either imipramine or saline for 3 weeks.

6.2. Mechanisms of the Effects of Antidepressants on Immune Activation-Induced Depressive Symptoms

6.2.1. Alterations in Cytokine Production. The effects of antidepressants on immune functions, including cytokine production, have been assessed both in depressed patients, and in experimental animal models. In depressed patients, the effects of antidepressants seem to be related to the immune status of the patients at the initiation of the treatment. When depression was associated with immune activation, antidepressants suppressed immune function and cytokine secretion. For example, the increased plasma levels of IL-6 during acute depression were normalized by 8-week treatment with fluoxetin (Sluzewska et al., 1995), the increased monocyte counts in depressed patients were reduced following 6-weeks treatment with tricyclic antidepressants (Seidel et al., 1996), and the increased numbers of leukcytes and neutrophils were also reduced by antidepressant treatment (Maes, Vandoolaeghe, Van Hunsel, Bril, Demedts, Wauters, & Neels, 1997b). On the other hand, when immune functions were found to be normal, antidepressants had no effects, e.g., chronic moclobemide treatment had no effect on monocytes functions, TNFα production or IFNγ levels (Landmann, Schaub, Link, & Wacker 1997). Moreover, in a study of depressed patients who exhibited immune suppression before treatment, the tricyclic antidepressant clomipramine increased the production of IL-1β, IL-2, and IL-3 (Weizman, Laor, Podliszewski, Notti, Djaldetti, & Bessler, 1994).

In experimental animals, antidepressants (both TCAs and SSRIs) produce mainly immune suppression and anti-inflammatory effects (Albrecht, Helderman, Schlesser, & Rush, 1985; Audus & Gordon, 1982; Eisen, Irwin, Quay, & Livnat, 1989; Miller, Asnis, van Praag, Norin, 1986; Xiao & Eneroth, 1996). Antidepressant treatment *in vivo* was found to reduce immune activation in several models: it inhibited the increased acute phase response in olfactory bulbectomized rats, a useful animal model of depression (Song & Leonard, 1994), reduced IL-1 and IL-2 production in a chronic mild stress model of depression (Kubera, Symbirtsev, Basta-Kaim, Borycz, Roman, Papp, & Claesson, 1996), and inhibited immune activation in rats with experimental allergic neuritis (Zhu, Bengtsson, Mix, Thorell, Olsson, & Link, 1994). Anti-inflammatory properties were demonstrated for both fluoxetin and clomipramine in carrageenin or brewer's yeast-induced inflammation (Bianchi, Rossoni, Sacerdote, Panerai, & Berti, 1995; Bianchi, Sacerdote, & Panerai, 1994a, b). Some of the effects of antidepressants are probably mediated by a direct action on immune cells; TCAs were found to inhibit spontaneous secretion of IL-2 and IFNγ form T-cells, as well as spontaneous and LPS-induced secretion of IL-1 and IL-6 and TNFα from monocytes (Xia, DePierre, & Nassberger, 1996). Similarly, the antidepressant rolipram was found to suppress TNFα and (to a lesser extent) also IFNγ secretion by human and rat auto-reactive T-cells (Sommer, Loschmann, Northoff, Weller, Steinbrecher, Steinbach, Lichtenfels, Meyermann, Riethmuller, Fontana, Dichgans, & Martin, 1995).

These findings suggest that the effects of antidepressants on LPS-induced sickness behavior and corticosterone secretion, found in our studies, are mediated by changes in immune reactivity to LPS (particularly reduced production of cytokines). To elucidate these mechanisms we have recently examined the effects of chronic fluoxetin on the expression of TNFα and iNOS mRNA following LPS administration. Preliminary evidence suggests that LPS-induced TNFα mRNA in splenocytes was attenuated in fluoxetin-treated rats. Furthermore, LPS-induced expression of iNOS was

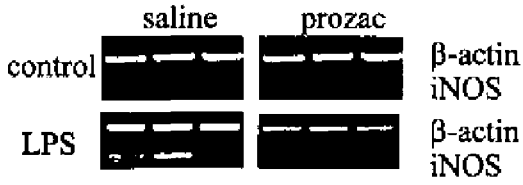

Figure 4. Effects of chronic treatment with fluoxetin on LPS-induced expression of iNOS and β-actin (as control) mRNA in the spleen.

also markedly attenuated (Fig. 4), suggesting that the immune-suppressive effect of chronic fluoxetin treatment on splenocytes is general, and not specific to TNFα.

Following chronic treatment with either saline (Sal) or fluoxetin (Prozac, 10 mg/kg injected daily for 5 weeks), rats were injected acutely with either saline or LPS (100 μg/kg). Spleens were removed 2 hr post-injection and iNOS mRNA levels assessed by RT-PCR analysis. The results represent data from individual spleens, obtained during one replication of this experiment.

Previous studies have clearly demonstrated that TNFα is involved in mediating the effects of various immune challenges on food consumption, body weight and HPA axis activation. Exogenous administration of TNFα produced anorexia, body weight loss, and pituitary-adrenal activation (Plata-Salaman, 1998; Sonti et al., 1996; Van der Meer, Fred Sweep, Pesman, Borm, & Hermus, 1995; Warren, Finck, Arkins, Kelley, Scamurra, Murtaugh, & Johnson, 1997). Moreover, TNFα synthesis blockers or antibodies to TNFα suppressed the anorexia, body weight loss, and adrenocortical activation produced by various immune challenges (Breuille, Farge, Rose, Arnel, Attaix, & Obled, 1993; Smith, & Kluger, 1993; Wohlman, Gallily, Yirmiya, & Weidenfeld, 1997). Thus, the attenuation of LPS-induced TNFα expression in fluoxetin-treated rats may explain at least some of the reduction of anorexia, body-weight loss, and adrenocortical activation in these rats.

6.2.2. Alteration in Monoaminergic Systems. In addition to their direct effects on cytokines, antidepressants may suppress the behavioral and neuroendocrine effects of LPS by modulating monoaminergic neurotransmission.

Both imipramine and fluoxetin are monoamine reuptake inhibitors (imipramine inhibits the reuptake of both norepinephrine and serotonin, whereas fluoxetin is an SSRI) (Montgomery, 1994). The basis for the therapeutic effects of these drugs is not clear. Chronic, but not acute, treatment produces adaptive changes in several neural systems, particularly monoaminergic systems and the HPA axis. For example, animal studies demonstrated that chronic imipramine reduces the number and function of β-adrenergic and serotonergic (5-HT_2) receptors (Burnet, Michelson, Smith, Gold, & Sternberg, 1994), and decreases tyrosine hydroxylase and CRH mRNA levels (Brady, Whitfield, Fox, Gold, & Herkenham, 1991). Chronic administration of fluoxetin was also found to down regulate serotonergic receptors functions (Leonard, 1994; Newman, Shapira, & Lerer, 1992). These changes may be relevant to the effects of LPS observed in our study, since LPS administration has been found to increase the turnover of norepinephrine and serotonin in several brain areas (Dunn & Welch, 1991; Dunn & Wang, 1995; Linthorst, Flachskamm, Holsboer, & Reul, 1995a; Linthorst, Flackskmann, Muller-Preuss, Holsboer, & Reul, 1995b). Although there is no direct evidence for the involvement of monoamines in mediating LPS-induced sickness behavior symptoms,

we have recently found that pretreatment with the α1 adrenoreceptor antagonists prazosin and urapidil significantly attenuated IL-1-induced sickness behavior (Pollak, Avitsur, Canaan, & Yirmiya, 1998). Similarly, pretreatment with the serotonin "synthesis blocker PCPA attenuated several sickness behavior symptoms (Zubareva, Abdurasulova, Bluthe, Dantzer, & Klimenko, 1998). Thus, it is possible that following chronic treatment with antidepressants, the activation of monoaminergic systems by LPS is reduced, and this reduction may be responsible for the attenuation of the behavioral anhedonia and sickness behavior.

6.3.3. Alterations in the HPA Axis. Chronic treatment with antidepressants also alters the functioning and regulation of the HPA axis (Holsboer & Barden, 1996). Chronic, but not acute, administration of imipramine (Barden, Reul & Holsboer, 1995) or fluoxetin (Brady, Gold, Herkenham, Lynn, & Whitfield, 1992) were found to increase the levels of glucocorticoids receptors in the hippocampus (Brady et al., 1992), which normally mediate the negative feedback response to LPS-induced activation of the HPA axis (e.g., Weidenfeld & Yirmiya, 1996). In experimental animals, long term administration of fluoxetin, as well as tricyclic antidepressants, inhibits the pituitary-adrenal response to various challenges (Li, Levy, Cabrera, Brownfield, Battaglia, & Van de Kar, 1993; Reul, Stec, Soder, & Holsboer, 1993). Similarly, chronic imipramine treatment was found to normalize the hyperactive HPA axis in successfully treated depressed patients (Holsboer, Liebel, & Hofschuster, 1982). Finally, following long (8 weeks), but not short (2 weeks) treatment with Fluoxetin, CRH mRNA was decreased by 30–48% in the hypothalamic PVN (Brady et al., 1992).

CRH within the brain mediates many of the behavioral and neuroendocrine effects of immune challenges (e.g., Bluthe, Crestani, Kelley, & Dantzer, 1992; Uehara, Sekiya, Takasugi, Namiki, & Arimura, 1989; Tilders et al., 1994; Turnbull & Rivier, 1995). Thus, it may be suggested that the attenuation of CRH system induced by antidepressants is also involved in the reduction of the behavioral and neuroendocrine depressive-like symptoms induced by immune activation.

7. CONCLUSIONS

Accumulating evidence indicates that immune activation during various medical conditions is associated with a depressive syndrome in both humans and experimental animals. Taken together with the reports that brain cytokines influence the neurochemical systems involved in depression, these findings support the hypothesis that immune activation, via the release of peripheral and brain cytokines, might be involved in the etiology and symptomatology of "depression due to a general medical condition" and some other specific depressive syndromes (Fig. 5).

Many medical conditions involve the activation of the immune system and the release of cytokines, particularly within the brain. These conditions include acute and chronic peripheral infections, the post-partum period, exposure to stressful stimuli, autoimmune diseases, such as multiple sclerosis (MS) and rheumatoid arthritis (RA), neurodegenerative diseases, such as Alzheimer's disease, stroke, and other brain traumas, and intracerebral infections with pathogens such as Borna Disease virus, herpes simplex virus (HSV), human immunodeficiency virus (HIV) *and mycoplasma fermentans*. All of these conditions are also associated with a high prevalence of depressive syndromes. Cytokine release within the brain can affect the neural substrate

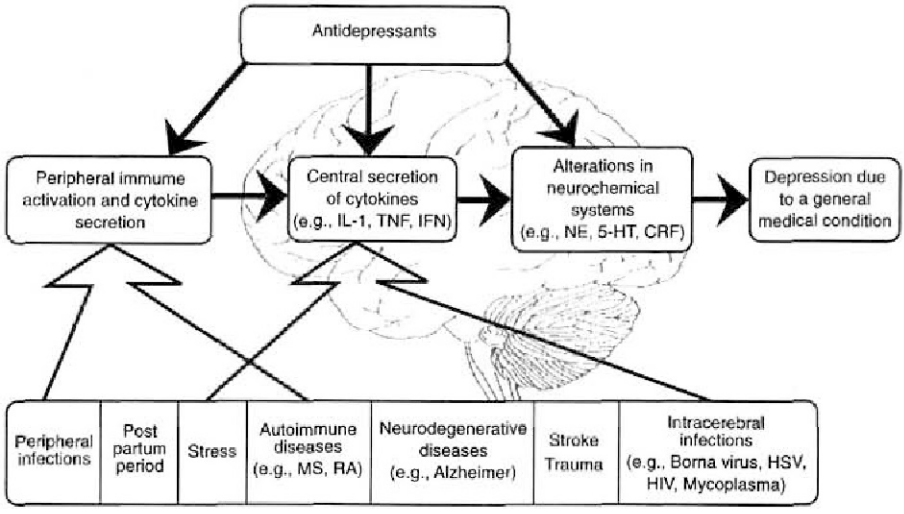

Figure 5. Immune activation and depression due to a general medical condition: Possible mechanisms for modulation by antidepressants.

of depressive symptomatology and thus can serve as the physiological mechanism of "depression due to a general medical condition". Effective treatment of cytokine-induced depressive symptoms may be based on the ability of antidepressant drugs to interfere with the production and secretion of cytokines, either in the periphery or within the brain. In addition, antidepressants may prevent the neurochemical alterations that underlie cytokine-mediated depression.

This hypothesis has direct implications for antidepressant therapy. In previous research it has been demonstrated that 1) Antidepressants can be used successfully for treating depression associated with medical conditions, as well as cytokine-induced depression in humans; 2) Antidepressants inhibit the increased immune reactivity and cytokine responses exhibited by some depressed patients; 3) Antidepressants have anti-inflammatory properties in experimental animal models; and 4) Antidepressants suppress the secretion of proinflammatory cytokines following various *in vitro* challenges. Based on these findings and on our recent demonstration that chronic treatment with antidepressant drugs attenuated endotoxin-induced anhedonia, sickness behavior, adrenocortical activation, and expression of TNFα mRNA, we have recently suggested that some of the therapeutic effects of antidepressants can be attributed to their suppressing effects on the synthesis and/or activity of cytokines (Yirmiya, 1997). Within the brain, cytokines released by activated immune cells, glia cells or neurons have been documented to affect all of the neurochemical and neuroendocrine systems which have been implicated in depressive symptomatology. In particular, alterations in norepinephrine and serotonin neurotransmission and dysregulation of the HPA axis have been reported in various medical conditions or following cytokine administration. Thus, in addition to direct effects of antidepressants on immune activation and cytokine secretion within the brain, these drugs may influence the cytokine-induced alterations in the neurochemical substrate of depression (Fig. 5). Future research should examine the effects of antidepressant drugs on immune functions and cytokine secretion, as well as the effects of cytokine synthesis-blockers and antagonists on depressive disorders associated with medical conditions.

ACKNOWLEDGMENTS

Supported by grant no. 97–204 from the United States—Israel Binational Science Foundation and by a grant from the German-Israeli Foundation for Scientific research and Development.

REFERENCES

Abbey, S. E. & Garfinkel, P. E. (1991). Chronic fatigue syndrome and depression: Cause, effect or covariate. *Reviews of Infectious Diseases, 13*, S73–83.

Abramowitz, E. S., Baker, A. H., & Fleischer, S. F. (1982). Onset of depressive psychiatric crises and the menstrual cycle. *American Journal of Psychiatry, 139*(4), 475–478.

Adler, N. E., Boyce, T., Chesney, M. A., Cohen, S., Folkman, S., Khan, R. L., & Syme, S. L. (1994). Socioeconomic status and health. *American Psychologist, 49*(1), 15–24.

Albrecht, J., Helderman, J. H., Schlesser, M. A., & Rush, A. J. (1985). A controlled study of cellular immune function in affective disorders before and during somatic therapy. *Psychiatry Research, 15*, 185–193.

Anderson, N. B. & Armstead, C. A. (1995). Toward understanding the association of socioeconomic status and health: A new challenge for the biopsychosocial approach. *Psychosomatic Medicine, 57*, 213–225.

Anisman, H., Kokkinidis, L., & Merali, A. (1996). Interleukin-2 decreases accumbal dopamine efflux and responding for rewarding lateral hypothalamic stimulation. *Brain Research, 731*, 1–11.

Anisman, H., Kokkinidis, L., Borowski, T., & Merali, A. (1998). Differential effects of interleukin (IL)-1, IL-2, and IL-6 on responding for rewarding lateral hypothalamic stimulation. *Brain Research, 779*, 177–187.

Arenzana-Seisdedos, F. & Virelizer, J. L. (1983). Interferons as macrophage-activating factors. II. Enhanced secretion of interleukin-1 by lipopolysaccharide-stimulated human monocytes. *European Journal of Immunology, 13*, 437–440.

Arvin, B., Neville, L. F., Barone, F. C., & Feuerstein, G. Z. (1996). The role of inflammation and cytokines in brain injury. *Neuroscience and Biobehavioral Reviews, 20*, 445–452.

Aubert, A., Vega, C., Dantzer, R., & Goodall, G. (1995). Pyrogens specifically disrupt the acquisition of a task involving cognitive processing in the rat. *Brain Behavior and Immunity, 9*, 129–148.

Aubert, A. & Dantzer, R. (1998). Effects of lipopolysaccharide on taste reactivity in rats. *Neuroimmunomodulation, 5*, 3.

Audus, K. L. & Gordon, M. A. (1982). Tricyclic antidepressant effects on the murine lymphocyte mitogen response. *Journal of Immunopharmacology, 4*, 13–27.

Avitsur, R., Pollak, Y., & Yirmiya, R. (1997). Different receptor mechanisms mediate the effects of endotoxin and interleukin-1 on female sexual behavior. *Brain Research, 773*, 149–161.

Avitsur, R., Cohen, E., & Yirmiya, R. (1998). Effects of interleukin-1 on sexual attractivity in a model of sickness behavior. *Physiology and Behavior, 63*, 25–30.

Ayuso, J. L. (1994). Use of psychotropic drugs in patients with HIV infection. *Drugs, 47*(4), 599–610.

Badia-Elder, N., Kiefer, S. W., & Dess, N. K. (1996). Taste reactivity in rats selectively bred for high vs. low saccharin consumption. *Physiology and Behavior, 59*, 749–755.

Barden, N., Reul, J. M. H. M., & Holsboer, F. (1995). Do antidepressants stabilize mood through actions on the hypothalamic-pituitary-adrenocortical system? *Trends in Neurosciences, 18*, 6–11.

Bauer, J., Hohagen, F., Gimmel, E., Bruns, F., Lis, S., Krieger, S., Ambach, W., Guthmann, A., Grunze, H., Fritsch-Montero, R., Weissbach, A., Ganter, U., Frommnerger, U., Riemann, D., & Berger, M. (1995). Induction of cytokines synthesis and fever suppresses REM sleep and improves mood in patients with major depression. *Biological Psychiatry, 38*, 611–621.

Beers, D. R., Henkel, J. S., Kesner, R. P., & Stroop, W. G. (1995). Spatial recognition memory deficits without notable CNS pathology in rats following herpes simplex encephalitis. *Journal of the Neurological Sciences, 131*, 119–127.

Besedovsky, H. O. & Del-Rey, A. (1996). Immune-neuro-endocrine interactions: facts and hypotheses. *Endocrine Reviews, 17*, 64–102.

Bianchi, M., Sacerdote, P., & Panerai, A. E. (1994a). Fluoxetin reduces inflammatory edema in the rat: Involvement of the pituitary-adrenal axis. *European Journal of Pharmacology, 263*, 81–84.

Bianchi, M., Sacerdote, P., & Panerai, A. E. (1994b). Chlomipramine differentially affects inflammatory edema and pain in the rat. *Pharmacology, Biochemistry, and Behavior, 4*, 1037–1040.

Bianchi, M., Rossoni, G., Sacerdote, P., Panerai, A. E., & Berti, F. (1995). Effects of clomipramine and fluoxetin on subcutaneous carrageenin-induced inflammation in the rat. *Inflammation Research, 44*, 466–469.

Bluthe, R. M., Dantzer, R., & Kelley, K. W. (1991). Interleukin-1 mediates behavioral but not metabolic effects of tumor necrosis factor alpha in mice. *European Journal of Pharmacology, 209*, 281–283.

Bluthe, R. M., Crestani, F., Kelley, K. W., & Dantzer, R. (1992). Mechanisms of the behavioral effects of interleukin 1. Role of prostaglandins and CRF. *Annals of The New York Academy of Sciences, 650*, 268–275.

Bluthe, R. M., Dantzer, R., & Kelley, K. W. (1997). Central mediation of the effects of interleukin-1 on social exploration and body weight in mice. *Psychoneuroendocrinology, 22*, 1–11.

Bode, L., Zimmerman, W., Ferszt, R., Steinbach, F., & Ludwig, H. (1995). Borna disease virus genome transcribed and expressed in psychiatric patients. *Nature Medicine, 1*, 232–236.

Bode, L., Durrwald, R., Rantam, F. A., Ferszt, R., & Ludwig, H. (1996). First isolation of infectious human Borna disease virus from patients with mood disorders. *Molecular Psychiatry, 1*, 200–212.

Borowski, T., Kokkinidis, L., Merali, A., & Anisman, H. (1997). Behavioral and central monoamine alterations induced by interleukin-1, interleukin-6, and lipopolysaccharide. *Society for Neuroscience Abstracts, 23*, 1508.

Brady, L. S., Whitfield, H. J., Fox, R. J., Gold, P. W., & Herkenham, M. (1991). Long-term antidepressant administration alters corticotropin-releasing hormone, tyrosine hydroxylase, and mineralocorticoid receptor gene expression in rat brain. *Journal of Clinical Investigation, 87*, 831–837.

Brady, L. S., Gold, P. W., Herkenham, M., Lynn, A. B., & Whitfield, H. J. (1992). The antidepressants fluoxetine, idazoxan, and phenelzine alter corticotropin-releasing hormone and tyrosine hydroxylase mRNA levels in rat brain: therapeutic implications. *Brain Research, 572*, 117–125.

Breuille, D., Farge, M. C., Rose, F., Arnel, M., Attaix, D., & Obled, C. (1993). Pentoxifylline decreases body weight loss and muscle protein wasting characteristics of sepsis. *American Journal of Physiology, 265*, E660–E666.

Brown, S. L., Steinberg, R. L., & van Praag, H. M. (1994). The pathogenesis of depression: reconsideration of neurotransmitter data. In J. A. Den Boer & J. M. Sitsen (Eds.), *Handbook of Depression and Anxiety: A Biological Approach* (pp. 529–542). New York: Marcel Dekker, Inc.

Bruce, M. L., Takeuchi, D. T., & Leaf, P. J. (1991). Poverty and psychiatric status. *Archives of General Psychiatry, 48*, 470–474.

Buchwald, D. & Komaroff, A. L. (1991). Review of laboratory findings for patients with chronic fatigue syndrome. *Reviews of Infectious Diseases, 13*, 12–18.

Burnet, P. W. J., Michelson, D., Smith, M. A., Gold, P. W., & Sternberg, E. M. (1994). The effect of chronic imipramine administration on the densities of 5-HT1A and 5-HT2 receptors and the abundances of 5-HT receptor and transporter mRNA in the cortex, hippocampus, and dorsal raphe of three strains of rat. *Brain Research, 638*, 311–324.

Cannon, J. G. & Dinarello, C. A. (1985). Increased plasma interleukin-1 activity in woman after ovulation. *Science, 227*, 1247–1249.

Cappel, R., Gregoire, E., Thiry, L., & Sprecher, S. (1978). Antibody and cell-mediated immunity to herpes simplex virus in psychotic depression. *Journal of Clinical Psychiatry, 39*, 266–268.

Carroll, B. J., Martin, F. I. R., & Davies, B. (1968). Resistance to suppression by dexamethasone of plasma 11-hydroxycorticosterone levels in severe depressive illness. *British Medical Journal, 3*, 285–287.

Carroll, B. J., Curtis, G. C., & Mendels, J. (1976). Neuroendocrine regulation in depression. I. Limbic system adrenocortical dysfunction. *Archives of General Psychiatry, 33*, 1039–1044.

Cavallo, M. G., Pozzini, P., & Thorpe, R. (1993). Cytokines and autoimmunity. *Clinical and Experimental Immunology, 96*, 1–7.

Chochinov, H. M., Wilson, K. G., Enns, M., & Lander, S. (1994). Prevalence of depression in the terminally ill: Effects of diagnostic criteria and symptom threshold judgments. *American Journal of Psychiatry, 4*, 537–540.

Cleare, A. J., Bearn, J., Allain, T., McGregor, A., Wessely, S., Murray, R. M., & O'Keane, V. (1995). Contrasting neuroendocrine responses in depression and chronic fatigue syndrome. *Journal of Affective Disorders, 34*, 283–289.

Cohen, S. (1995). Psychological stress and susceptibility to upper respiratory infections. *American Journal of Respiratory and Critical Care Medicine, 152*, 53–58.

Connor, T. J. & Leonard, B. E. (1998). Depression, stress and immunological activation: the role of cytokines in depressive disorders. *Life Sciences, 62*, 583–606.

Cox, S. M., King, M. R., Casey, M. L., & Macdonald, P. C. (1993). Interleukin-1β, -1α, and -6 and prostaglandins

in vaginal cervical fluids of pregnant women before and during labor. *Journal of Clinical Endocrinology and Metabolism*, *77*, 805–815.

Cunningham, A. J., Murray, C. A., O'Neill, L. A. J., Lynch, M. A., & O'Connor, J. J. (1996). Interleukin-1β (IL-1β) and tumour necrosis factor (TNF) inhibit long-term potentiation in the rat dentate gyrus *in vitro*. *Neuroscience Letters*, *203*, 17–20.

Dantzer, R., Bluthe, R. M., Aubert, A., Goodall, G., Bret-Dibat, J. L., Kent, S., Goujon, E., Laye, S., Parnet, P., & Kelley, K. W. (1996). Cytokine actions on behavior. In N. J. Rothwell (Ed.), *Cytokines in the nervous system* (pp. 117–144). New York: R. G. Landes Company and Chapman & Hall.

Day, H. E. W. & Akil, H. (1996). Differential pattern of c-fos mRNA in rat brain following central and systemic administration of interleukin-1 beta: Implications for mechanisms of action. *Neuroendocrinology*, *63*, 207–218.

Denburg, S. D., Carbotte, R. M., & Denburg, J. A. (1997). Psychological aspects of systemic lupus erythematosus: Cognitive Function, mood, and self-report. *Journal of Rheumatology*, *24*, 998–1003.

Dess, N. K. (1993). Saccharin's aversive taste in rats: Evidence and implications. *Neuroscience and Biobehavioral Reviews*, *17*, 359–372.

Dinarello, C. A. & Wolff, S. M. (1993). The role of interleukin-1 in disease. *New England Journal of Medicine*, *328*, 106–113.

Dohrenwend, B. P. (1973). Social status and stressful life events. *Journal of Personality and Social Psychology*, *28*, 225–235.

DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)*. (1994). Washington, DC: American Psychiatric Association.

Dunbar, P. R., Hill, J., Neale, T. J., & Mellsop, G. W. (1992). Neopterin measurement provides evidence of altered cell-mediated immunity in patients with depression, but not with schizophrenia. *Psychological Medicine*, *22*, 1051–1057.

Dunn, A. J. & Welch, J. (1991). Stress- and endotoxin-induced increases in brain tryptophan and serotonin metabolism depend on sympathetic nervous system activity. *Journal of Neurochemistry*, *57*, 1615–1622.

Dunn, A. J. & Wang, J. (1995). Cytokine effects on CNS biogenic amines. *Neuroimmunomodulation*, *2*, 319–328.

Dunn, A. J., Chapman, Y., & Antoon, M. (1993). Endotoxin-induced behavioral changes of mice in the multicompartment chamber are distinct from those of interleukin-1. *Neuroscience Research Communications*, *10*, 63–69.

Eisen, J. N., Irwin, J., Quay, J., & Livnat, S. (1989). The effect of antidepressants on immune function in mice. *Biological Psychiatry*, *26*, 805–817.

Fent, K. & Zbinden, G. (1987). Toxicity of interferon and interleukin. *Trends in Pharmacological Sciences*, *8*, 101–105.

Foley, F. W., Traugott, U., LaRocca, N. G., Smith, C. R., Perlman, K. R., Caruso, L. S., & Scheinberg, L. C. (1992). A prospective study of depression and immune dysregulation in multiple sclerosis. *Archives of Neurology*, *49*, 238–244.

Gibertini, M. (1996). IL-1 beta impairs relational but not procedural rodent learning in a water maze task. *Advances in Experimental Medicine and Biology*, *402*, 207–217.

Gibertini, M., Newton, C., Friedman, H., & Klein, T. W. (1995). Spatial learning impairment in mice with legionella pneumophila or administered exogenous interleukin-1-beta. *Brain, Behavior, and Immunity*, *9*, 113–128.

Gold, P. W., Chrousos, G., Kellner, C., Post, R., Roy, A., Auerginos, P., Schulte, H., Oldfield, E., & Loriaux, D. L. (1984). Psychiatric implications of basic and clinical studies with corticotropin releasing factor. *American Journal of Psychiatry*, *141*, 619–627.

Gottfries, C. G. (1997). Recognition and management of depression in the elderly. *International Clinical Psychopharmacology*, *12*(7), S31–S36.

Goujon, E., Parnet, P., Laye, S., Combe, C., Kelley, K. W., & Dantzer, R. (1995). Stress downregulates lipopolysaccharide-induced expression of proinflammatory cytokines in the spleen, pituitary, and brain of mice. *Brain, Behavior, and Immunity*, *9*, 292–303.

Granger, D. A., Hood, K. E., Ikeda, S. C., Reed, C. L., Jones, B. C., & Block, M. L. (1997). Effects of peripheral immune activation on social behavior and adrenocortical activity in aggressive mice: genotype environment interactions. *Aggressive Behavior*, *23*, 93–105.

Greenwood, R. (1987). Residual mental disorders after herpesvirus infections. In E. Kurstak, Z. J. Lipowski, & P. V. Morozov (Eds.), *Viruses, Immunity, and Mental Disorders* (pp. 65–80). New York: Plenum.

Grill, J. J. & Norgren, R. (1978). The taste reactivity test. II. Mimetic responses to gustatory stimuli in chronic thalamic and chronic decerebrate rats. *Brain Research, 143*, 281–297.

Grossman, C. J. (1985). Interactions between the gonadal steroids and the immune system. *Science, 227*, 257–261.

Hall, S. & Smith, A. P. (1996a). Investigating the effects and aftereffects of naturally occurring upper respiratory tract illnesses on mood and performance. *Physiology and Behavior, 59*, 569–577.

Hall, S. & Smith, A. P. (1996b). Behavioral effects of infectious mononucleosis. *Neuropsychobiology, 33*, 202–209.

Hart, B. (1988). Biological basis of the behavior of sick animals. *Neuroscience and Biobehavioral Reviews, 12*, 123–37.

Hendler, N. (1987). Infectious mononucleosis and psychiatric disorders. In E. Kurstak, Z. J. Lipowski, & P. V. Morozov (Eds.), *Viruses, Immunity, and Mental Disorders* (pp. 81–94). New York: Plenum.

Herbert, T. B. & Cohen, S. (1993). Depression and immunity: A meta-analytic review. *Psychological Bulletin, 3*, 472–486.

Heyser, C. J., Masliah, E., Samimi, A., Campbell, I. L., & Gold, L. H. (1997). Progressive decline in avoidance learning paralleled by inflammatory neurodegeneration in transgenic mice expressing interleukin-6 in the brain. *Proceedings of the National Academy of Sciences of the United States of America, 94*, 1500–1505.

Hickie, I. & Lloyd, A. (1995). Are cytokines associated with neuropsychiatric syndromes in humans? *International Journal of Immunopharmacology, 17*, 677–683.

Holsboer, F. (1995). Neuroendocrinology of mood disorders. In F. E. Bloom & D. J. Kupfer (Eds.), *Psychopharmacology: The Fourth Generation of Progress* (pp. 957–969). New York: Raven Press.

Holsboer, F. & Barden, N. (1996). Antidepressants and hypothalamic-pituitary-adrenocortical regulation. *Endocrine Reviews, 17*, 187–205.

Holsboer, F., Liebel, R., & Hofschuster, E. (1982). Repeated dexamethasone test during depressive illness: normalization of test result compared with clinical improvement. *Journal of Affective Disorders, 4*, 93–101.

Hutchinson, G. A., Nehall, J. E., & Simeon, D. T. (1996). Psychiatric disorders in systemic lupus erythematosus. *West Indian Medical Journal, 45*, 48–50.

Isometsa, E. T., Aro, H. M., Henriksson, M. M., Heikkinen, M. E., & Lonnqvist, J. K. (1994). Suicide and major depression in different treatment settings. *Journal of Clinical Psychiatry, 55*, 523–527.

Joffe, R. T., Lippert, G. P., Gray, T. A., Sawa, G., & Horvath, A. (1987). Mood disorder and multiple sclerosis. *Archives of Neurology, 44*, 376–378.

Johnson, R. W., Propes, M. J., & Shavit, Y. (1996). Corticosterone modulates the behavioral and metabolic effects of lipopolysaccharide. *American Journal of Physiology, 270*, R192–R198.

Katon, W. & Sullivan, M. D. (1990). Depression and chronic medical illness. *Journal of Clinical Psychiatry, 51*, 3–11.

Katsuki, H., Nakai, S., Hirai, Y., Akaji, K., Kiso, Y., & Satoh, M. (1990). Interleukin-1β inhibits long-term potentiation in the CA3 region of mouse hippocampal slices. *European Journal of Pharmacology, 191*, 323–326.

Kavaliers, M., Colwell, D. D., & Galea, L. A. M. (1995). Parasitic infection impairs spatial learning in mice. *Animal Behaviour, 50*, 223–229.

Kent, S., Bluthe, R. M., Kelley, K. W., & Dantzer, R. (1992a). Sickness behavior as a new target for drug development. *Trends in Pharmacological Sciences, 13*, 24–28.

Kent, S., Bluthe, R. M., Dantzer, R., Hardwick, A. J., Kelley, K. W., Rothwell, N. J., & Vannice, J. L. (1992b). Different receptor mechanisms mediate the pyrogenic and behavioral effects of interleukin-1. *Proceedings of the National Academy of Sciences of the United States of America, 89*, 9117–9120.

Kiecolt-Glaser, J. K. & Glaser, R. (1991). Stress and immune function in humans. In R. Ader, D. L. Felten, & N. Cohen (Eds.), *Psychoneroimmunology* (pp. 849–867). San Diego: Academic Press.

Klonoff, D. C. (1992). Chronic fatigue syndrome. *Clinical infectious diseases, 15*, 812–823.

Komaroff, A. L. & Buchwald, D. S. (1991). Symptoms and signs of chronic fatigue syndrome. *Reviews of Infectious Diseases, 13*, 8–11.

Komaroff, A. L. & Buchwald, D. S. (1998). Chronic fatigue syndrome: an update. *Annual Review of Medicine, 49*, 1–13.

Komaroff, A. L., Fagioli, L. R., Geiger, A. M., Doolittle, T. H., Lee, J., Kornish, J., Gleit, M. A., & Guerriero, R. T. (1996). An examination of the working case definition of chronic fatigue syndrome. *American Journal of Medicine, 100*, 56–64.

Kozak, W., Poli, V., Soszynski, D., Conn, C. A., Leon, L. R., & Kluger, M. (1996). Sickness behavior in mice

deficient in interleukin-6 during turpentine abscess and influenza pneumonitis. *American Journal of Physiology, 272*, R621–R630.

Kozak, W., Soszynski, D., Rudolph, K., Conn, C. A., & Kluger, M. (1997). Dietary n-3 fatty acids differentially affect sickness behavior in mice during local and systemic inflammation. *American Journal of Physiology, 272*, R1298–R1307.

Krueger, J. M. & Majde, J. A. (1994). Microbial products and cytokines in sleep and fever regulation. *Critical Reviews in Immunology, 14*, 355–379.

Krueger, J. M., Takahashi, S., Kapas, L., Bredow, S., Roky, R., Fang, J., Floyd, R., Renegar, K. B., Guha-Thakurta, N., Novitsky, S., & Obal, F. (1995). Cytokines in sleep regulation. *Advances in Neuroimmunology, 5*, 171–188.

Kubera, M., Symbirtsev, A., Basta-Kaim, A., Borycz, J., Roman, A., Papp, M., & Claesson, M. (1996). Effect of chronic treatment with imipramine on interleukin-1 and interleukin-2 production by splenocytes obtained from rats subjected to chronic mild stress model of depression. *Polish Journal of Pharmacology, 48*, 503–506.

Laghrissi-Thode, F., Pollock, B. G., Szanto, K., & Reynolds, C. F. (1996). Depression and suicide in medically ill patients. *Current Opinion in Psychiatry, 9*, 137–140.

Landmann, R., Schaub, B., Link, S., & Wacker, H. R. (1997). Unaltered monocyte function in patients with major depression before and after three months of antidepressive therapy. *Biological Psychiatry, 41*, 675–681.

Laruelle, M., Seghers, A., Goffinet, S., Bouchez, S., & Legros, J. J. (1990). Plasmatic vasopressin neurophysin in depression: Basic levels and relations with HPA axis. *Biological Psychiatry, 27*, 1249–1263.

Lauritzen, L., Bjerg Bendsen, B., Vilmar, T., Bjerg Bendsen, E., Lunde, M., & Bech, P. (1994). Post-stroke depression: combined treatment with imipramine or desipramine and mianserin. *Psychopharmacology, 114*, 119–122.

Leonard, B. E. (1994). Effect of antidepressants on specific neurotransmitters: Are such effects relevant to the therapeutic actions? In J. A. den Boer & J. M. Siten (Eds.), *Handbook of depression and anxiety: A biological approach* (pp. 379–404). New York: Marcel Dekker, Inc.

Levenson, J. L. & Fallon, H. J. (1993). Fluoxetine treatment of depression caused by interferon-alpha. *American Journal of Gastroenterology, 88*(5), 760–761.

Li, Q., Levy, A. D., Cabrera, T. M., Brownfield, M. S., Battaglia, G., & Van de Kar, L. D. (1993). Long-term fluoxetine, but not desipramine, inhibits the ACTH and oxytocin responses to the 5-HT 1A agonist, 8-OH-DPAT, in male rats. *Brain Research, 630*, 148–156.

Licinio, J., Kling, M. A., & Hauser, P. (1998). Cytokines and brain function: relevance to interferon-alpha-induced mood and cognitive changes. *Seminars in Oncology, 25*(1), 30–38.

Lieb, J. & Karmali, R. (1983). Elevated levels of prostaglandin E2 and thromboxane B2 in depression. *Prostaglandins and Leukotrienes in Medicine, 10*, 361–368.

Lim, L., Ron, M. A., Ormerod, I. E., David, J., Miller, D. H., Logsdail, S. J., Walport, M. J., & Harding, A. E. (1988). Psychiatric and neurological manifestations in systemic lupus erythematosus. *Quarterly Journal of Medicine, 66*, 27–38.

Linkowski, P., Mendlewicz, J., Leclercq, R., Brasseur, M., Hubain, P., Goldstein, J., Copinschi, G., & van Cauter, E. (1985). The 24-hr profile of adrenocorticotropin and cortisol in major depressive illness. *Journal of Clinical Endocrinology and Metabolism, 61*, 429–438.

Linnoila, M., Whorton, R., Rubinow, D. R., Cowdry, R. W., Ninan, P. T., & Waters, R. N. (1983). CSF prostaglandin levels in depressed and schizophrenic patients. *Archives of General Psychiatry, 40*, 405–406.

Linthorst, A. C. E., Flachskamm, C., Holsboer, F., & Reul, J. M. H. M. (1995a). Intraperitoneal administration of bacterial endotoxin enhances noradrenergic neurotransmission in the rat preoptic area: relationship with body temperature and hypothalamic-pituitary-adrenocortical axis activity. *European Journal of Neuroscience, 7*, 2418–2430.

Linthorst, A. C. E., Flachskamm, C., Muller-Preuss, P., Holsboer, F., & Reul, J. M. H. M. (1995b). Effect of bacterial endotoxin and interleukin-1 beta on hippocampal serotonergic neurotransmission, behavioral activity, and free corticosterone levels: an *in vivo* microdialysis study. *Journal of Neuroscience, 15*, 2920–2934.

Lycke, E., Norrby, R., & Roos, B. E. (1974). A serological study on mentally ill patients with particular reference to prevalence of herpes simplex virus infections. *British Journal of Psychiatry, 124*, 273.

Lyketsos, C. G., Steele, C., Baker, L., Galik, E., Kopunek, S., Steinberg, M., & Warren, A. (1997). Major and minor depression in Alzheimer's disease: prevalence and impact. *Journal of Neuropsychiatry and Clinical Neurosciences, 9*(4), 556–561.

Lynch, E. A., Dinarello, C. A., & Cannon, J. G. (1994). Gender differences in IL-1α, IL-1β, and IL-1

receptor antagonist secretion from mononuclear cells and urinary excretion. *Journal of Immunology, 153*, 300–306.

Maes, M. (1995). Evidence for an immune response in major depression: A review and hypothesis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 19*, 11–38.

Maes, M., DeJonckheere, C., Vandervorst, C., Schotte, C., Cosyns, P., Raus, J., & Suy, E. (1991). Abnormal pituitary function during melancholia: Reduced alpha melanocyte stimulating hormone secretion and increased intact ACTH non-suppression. *Journal of Affective Diseases, 22*, 149–157.

Maes, M., Lambrechts, J., Bosmans, E., Jacobs, J., Suy, E., Vandervorst, C., De Jockheere, C., Minner, B., & Raus, J. (1992a). Evidence for systemic immune activation during depression: results of leukocyte enumeration by flow cytometry in conjunction with monoclonal antibody staining. *Psychological Medicine, 22*, 45–53.

Maes, M., Scharpe, S., Van Grootel, L., Uyttenbroeck, W., Cooreman, W., Cosyns, P., & Suy, E. (1992b). Higher alpha-1-antitrypsin, haptoglobin, ceruloplasmin, and lower retinol binding protein plasma levels during depression: further evidence for the existence of an inflammatory response during that illness. *Journal of Affective Disorders, 24*, 183–192.

Maes, M., Bosmans, E., Meltzer, H. Y., Scharpe, S., & Suy, E. (1993). Interleukin-1β—A Putative Mediator of HPA Axis Hyperactivity in Major Depression. *American Journal of Psychiatry, 150*, 1189–1193.

Maes, M., Scharpe, S., Meltzer, H. Y., Okayli, G., D'Hondt, P., & Cosyns, P. (1994). Increased neopterin and interferon gamma secretion and lower L-tryptophan levels in major depression: further evidence for immune activation in severe depression. *Psychiatry Research, 54*, 143–160.

Maes, M., Meltzer, H. Y., Bosmans, E., Bergmans, R., Vandoolaeghe, E., Ranjan, R., & Desnyder, R. (1995a). Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2, and transferrin receptor in major depression. *Journal of Affective Disorders, 34*, 301–309.

Maes, M., Scharpe, S., Neels, H., Wauters, A., Van Gastel, A., & Cosyns, P. (1995b). Total serum protein and serum protein fractions in major depression. *Journal of Affective Disorders, 34*, 61–69.

Maes, M., Smith, R., & Scharpe, S. (1995c). The monocyte T-lymphocyte hypothesis of major depression. *Psychoneuroendocrinology, 20*, 111–116.

Maes, M., Bosmans, E., De Jongh, R., Kenis, G., Vandoolaeghe, E., & Neels, H. (1997a). Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokine, 9*, 853–858.

Maes, M., Vandoolaeghe, E., Van Hunsel, F., Bril, T., Demedts, P., Wauters, A., & Neels, H. (1997b). Immune disturbances in treatment-resistant depression: modulation by antidepressive treatment. *Human Psychopharmacology, 12*, 153–162.

Magner, M. B. (1991). Psychiatric morbidity in outpatients with systemic lupus erythematosus. *South African Medical Journal, 80*, 291–293.

Maier, S. F. & Watkins, L. R. (1998). Cytokines for psychologists: Implications of bi-directional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychological Review, 105*, 83–107.

Maj, M. (1996). Depressive syndromes and symptoms in subjects with human immunodefficiency virus (HIV) infection. *British Journal of Psychiatry, 168*, 117–122.

Marshal, P. S. (1993). Allergy and depression: A neurochemical threshold model of the relation between the illnesses. *Psychological Bulletin, 113*, 23–43.

Mathew, R. J. & Weinman, M. L. (1982). Sexual dysfunctions in depression. *Archives of Sexual Behavior, 11*, 323–328.

McDonald, E. M., Mann, A. H., & Thomas, H. C. (1987). Interferons as mediators of psychiatric morbidity: An investigation in a trial of recombinant α-interferon in hepatitis-B carriers. *Lancet, 2*, 1175–1179.

McGeer, P. L. & McGeer, E. G. (1995). The inflammatory response system of brain: implications for therapy of Alzheimer and other neurodegenerative diseases. *Brain Research Reviews, 21*, 195–218.

Meijer, A., Zakay-Rones, Z., & Morag, A. (1988). Post-influenzal psychiatric disorder in adolescents. *Acta Psychiatrica Scandinavica, 78*, 176–181.

Mendez, M. F., Martin, R. J., Smyth, K. A., & Whitehouse, P. J. (1990). Psychiatric symptoms associated with Alzheimer's disease. *Journal of Neuropsychiatry and Clinical Neurosciences, 2*(1), 28–33.

Meyers, C. A. & Valentine, A. D. (1995). Neurologic and psychiatric adverse effects of immunological therapy. *CNS Drugs, 3*, 56–68.

Meyers, C. A., Valentine, A. D., Wong, F. C. L., & Leeds, N. E. (1994). Reversible neurotoxicity of interleukin-2 and tumor necrosis factor: Correlation of SPECT with neurophysiological testing. *Journal of Neuropsychiatry and Clinical Neurosciences, 6*, 285–288.

Meyerson, B. J. & Lindstrom, L. H. (1973). Sexual motivation in the female rat. *Acta Physiologica Scandinavica, 389*, 1–80.

Miller, N. E. (1964). Some psychophysiological studies of motivation and of the behavioral effects of illness. *Bulletin of the British Psychological Society, 17*, 1–20.

Miller, A. H., Asnis, G. M., Van Praag, H. M., & Norin, A. J. (1986). Influence of desmethylimipramine on natural killer cell activity. *Psychiatry Research, 19*, 9–15.

Minden, S. L. & Schiffer, R. B. (1990). Affective disorders in multiple sclerosis: Review and recommendations for clinical research. *Archives of Neurology, 47*, 98–104.

Minden, S. L., Orav, J., & Reich, P. (1987). Depression in multiple sclerosis. *General Hospital Psychiatry, 9*, 426–434.

Mohr, D. C., Goodkin, D. E., Likosky, W., Gatto, N., Baumann, K. A., & Rudick, R. A. (1997). Treatment of depression improves adherence to interferon β -1b therapy for multiple sclerosis. *Archives of Neurology, 54(5)*, 531–533.

Montgomery, S. A. (1994). Antidepressants in long-term treatment. *Annual Review of Medicine, 45*, 447–457.

Morag, M., Yirmiya, R., Lerer, B., & Morag, A. (in press). Influence of socioeconomic status on behavioral, emotional, and cognitive effects of rubella vaccination: A prospective, double blind sudy. *Psychoneuroendocrinology.*

Mrak, R. E., Sheng, J. G., & Griffin, S. T. (1995). Glial cytokines in Alzheimer's disease: review and pathogenic implications. *Human Pathology, 26*(8), 816–823.

Muller, N., Hofschuster, E., Ackenheil, M., Mempel, W., & Eckstein, R. (1993). Investigations of the cellular immunity during depression and the free interval: evidence for an immune activation in affective psychosis. *Progress in Neuropsychopharmacology and Biological Psychiatry, 17*, 713–730.

Murphy, J. M., Olivier, D. C., Monson, R. R., Sobol, A. M., Federman, E. B., & Leighton, A. H. (1991). Depression and anxiety in relation to social status. *Archives of General Psychiatry, 48*, 223–229.

Newman, M. E., Shapira, B., & Lerer, B. (1992). Regulation of 5-hydroxytryptamine 1A receptor function in rat hippocampus by short- and long-term administration of 5-hydroxytryptamine agonist and antidepressants. *Journal of Pharmacology and Experimental Therapeutics, 260*, 16–20.

Niiranen, A., Laaksonen, R., Iivanainen, M., Mattson, K., Fakkila, M., & Cantell, K. (1988). Behavioral assessment of patients treated with alpha-interferon. *Acta Psychiatrica Scandinavica, 78*, 622–626.

Oitzl, M. S., van Oers, H., Schobitz, B., & de Kloet, E. R. (1993). Interleukin-1β, but not interleukin-6, impairs spatial navigation learning. *Brain Research, 613*, 160–163.

Okanoue, T., Sakamoto, S., Itoh, Y., Minami, M., Yasui, K., Sakamoto, M., Nishioji, K., Katagishi, T., Nakagawa, Y., Tada, H., Sawa, Y., Mizuno, M., Kagawa, K., & Kashima, K. (1996). Side effects of high-dose interferon therapy for chronic hepatitis C. *Journal of Hepatology, 25*, 283–291.

Owens, M. J. & Nemeroff, C. B. (1993). The role of CRF in the pathophysiology of affective disorders: laboratory and clinical studies. In W. W. Vale (Ed.), *Ciba Foundation Symposium on Corticotropin Releasing Factor*, 172 (pp. 193–316). New York: John Wiley.

Parker, J., Smarr, K., Anderson, S., Hewett, J., Walker, S., Bridges, A., & Caldwell, W. (1992). Relationship of changes in helplessness and depression to disease activity in rheumatoid arthritis. *Journal of Rheumatology, 19*, 1901–1905.

Parry, B. L. (1995). Mood disorders linked to the reproductive cycle in women. In F. E. Bloom & D. J. Kupfer (Eds.), *Psychopharmacology: The fourth Generation of Progress* (pp. 1029–1042). New York: Raven Press.

Pavol, M. A., Meyers, C. A., Rexer, J. L., Valentine, A. D., Mattis, P. J., & Talpaz, M. (1995). Pattern of neurobehavioral deficits associated with interferon α therapy for leukemia. *Neurology, 45*, 947–950.

Pincus, T., Griffith, J., Pearce, S., & Isenberg, D. (1996). Prevalence of self-reported depression in patients with rheumatoid arthritis. *British Journal of Rheumatology, 35*, 879–883.

Plata-Salaman, C. R. (1996). Anorexia during acute and chronic disease. *Nutrition, 12*, 69–78.

Plata-Salaman, C. R. (1998). Cytokines and anorexia: a brief overview. *Seminars in Oncology, 25*(1), 64–72.

Pollak, Y., Avitsur, R., Canaan, R., & Yirmiya, R. (1998). Central α1 adrenergic receptors are involved in mediating IL-1 induced sickness behavior. *NeuroImmunoModulation, 5*, 38.

Rabkin, J. G., Wagner, G., & Rabkin, R. (1994). Effects of setraline on mood and immune status in patients with major depression and HIV illness: an open trial. *Journal of Clinical Psychiatry, 55*, 433–439.

Ranchor, A. V., Bouma, J., & Sanderman, R. (1996). Vulnerability and social class: Differential patterns of personality and social support over the social classes. *Personality and Individual Differences, 20*(2), 229–237.

Renault, P. F., Hoofnagle, J. H., Park, Y., Mullen, K. D., Peters, M., Jones, D. B., Rustgi, V., & Jones, E. A. (1989). Psychiatric complications of long-term interferon alpha therapy. *Archives of Internal Medicine, 147*, 1577–1580.

Reul, J. M. H. M., Stec, I., Soder, M., & Holsboer, F. (1993). Chronic treatment of rats with antidepressant

amitriptyline attenuates the activity of the hypothalamic-pituitary-adrenocortical system. *Endocrinology, 133*, 312–320.

Rivier, C. & Rivest, S. (1993). Mechanisms mediating the effects of cytokines on neuroendocrine functions in the rat. In D. J. Chadwick, J. Marsh, & K. Ackrill (Eds.), *Corticotropin-Releasing Factor* (pp. 204–225). New York: John Weily & Sons.

Robinson, R. G. (1997). Neuropsychiatric consequences of stroke. *Annual Review of Medicine, 48*, 217–229.

Rodin, G. & Voshart, K. (1986). Depression in the medically ill: An overview. *American Journal of Psychiatry, 143*, 696–705.

Romanovsky, A. A., Kulchitsky, V. A., Akulich, N. V., Koulchitsky, S. V., Simons, C. T., Sessler, D. I., & Gourine, V. N. (1996). First and second phases of biphasic fever: two sequential stages of the sickness syndrome. *American Journal of Physiology, 271*, R244–R253.

Rothwell, N. J., Luheshi, G., & Toulmond, S. (1996). Cytokines and their receptors in the central nervous system: Physiology, pharmacology, and pathology. *Pharmacology and Therapeutics, 69*, 85–95.

Sachar, E. J., Hellman, L., Fukushima, D. K., & Gallaghaer, T. F. (1970). Cortisol production in depressive illness: a clinical and biochemical clarification. *Archives of General Psychiatry, 23*, 289–298.

Sadovnick, A. D., Remick, R. A., Allen, J., Swartz, E., Lee, I. M. L., Eisen, K., Farquhar, R., Hashimoto, S. A., Hooge, J., Kastrukoff, L. F., Morrison, W., Nelson, J., Ogar, J., & Paty, D. W. (1996). Depression and multiple sclerosis. *Neurology, 46*, 628–632.

Sakic, B., Denburg, J. A., Denburg, S. D., & Szechtman, H. (1996). Blunted sensitivity to sucrose in autoimmune MRL-lpr mice: A curve shift study. *Brain Research Bulletin, 41*, 305–311.

Schiffer, R. B. & Babigian, H. M. (1984). Behavioral disorders in multiple sclerosis, temporal lobe epilepsy, and amyotrophic lateral sclerosis: An epidemiological study. *Archives of Neurolology, 41*, 1067–1069.

Schiffer, R. B. & Wineman, N. M. (1990). Antidepressant pharmacotherapy of depression associated with multiple sclerosis. *American Journal of Psychiatry, 147*, 1493–1497.

Schneebaom, A. B., Singleton, J. D., & West, S. G. (1991). Association of psychiatric manifestations with antibodies to ribosomal P proteins in systemic lupus erythematosus. *American Journal of Medicine, 90*, 54–62.

Schobitz, B., De Kloet, E. R., & Holsboer, F. (1994). Gene expression and function of interleukin 1, interleukin 6, and tumor necrosis factor in the brain. *Progress in Neurobiology, 44*, 397–432.

Schrott, L. M. & Crnic, L. S. (1996). Anxiety behavior, exploratory behavior, and activity in NZB X NZW F1 hybrid mice: role of genotype and autoimmune disease progression. *Brain, Behavior, and Immunity, 10*, 260–274.

Schubert, D. S. P. & Foliart, R. H. (1993). Increased depression in multiple sclerosis patients: A meta analysis. *Psychosomatics, 34*, 124–130.

Schwartz, J. A., Speed, N. M., Brunberg, J. A., Brewe, T. L., Brown, M., & Greden, J. F. (1993). Depression in stroke rehabilitation. *Biological Psychiatry, 33*, 694–699.

Scott, T. F., Nussbaum, P., McConnell, H., & Brill, P. (1995). Measurement of treatment response to sertraline in depressed multiple sclerosis patients using the Carroll scale. *Neurological Research, 17*, 421–422.

Segall, M. A. & Crnic, L. S. (1990). An animal model for the behavioral effects of interferon. *Behavioral Neuroscience, 4*, 612–618.

Seidel, A., Arolt, V., Hunstiger, M., Rink, L., Behnisch, A., & Kirchner, H. (1995). Cytokine production and serum proteins in depression. *Scandinavian Journal of Immunology, 41*, 534–538.

Seidel, A., Arolt, V., Hunstiger, M., Rink, L., Behnisch, A., & Kirchner, H. (1996). Major depressive disorder is associated with elevated monocyte counts. *Acta Psychiatrica Scandinavica, 94*, 198–204.

Seilhean, D., Kobayashi, K., He, Y., Uchihara, T., Rosenblum, O., Katlama, C., Bricaire, F., Duyckaerts, C., & Hauw, J. J. (1997). Tumor necrosis factor-alpha, microglia, and astrocytes in AIDS dementia complex. *Acta Neuropathologica, 93*, 508–517.

Sluzewska, A., Rybakowski, J., Laciak, M., Mackiewicz, A., Sobieska, M., & Wiktorowicz, K. (1995). Interleukin-6 serum levels in depressed patients before and after treatment with fluoxetine. *Annals of the New York Academy of Sciences, 762*, 474–476.

Sluzewska, A., Rybakowski, J., Bosmans, E., Sobieska, M., Berghmans, R., Maes, M., & Wiktorowicz, K. (1996). Indicators of immune activation in major depression. *Psychiatry Research, 64*, 161–167.

Smith, B. K. & Kluger, M. J. (1993). Anti-TNF-alpha Antibodies Normalized Body Temperature and Enhanced Food Intake in Tumor-Bearing Rats. *American Journal of Physiology, 265*, R615–R619.

Smith, A. P., Tyrrell, D. A. J., Al-Nakib, W., Coyle, K. B., Donovan, C. B., Higgins, P. G., & Willman, J. S. (1987).

Effects of experimentally induced respiratory virus infections and illness on psychomotor performance. *Neurosychobiology, 18*, 144–148.

Smith, A. P., Tyrrell, D. A. J., Al-Nakib, W., Coyle, K. B., Donovan, C. B., Higgins, P. G., & Willman, J. S. (1988). The effects of experimentally induced respiratory virus infections on performance. *Psychological Medicine, 18*, 65–71.

Smith, A. P., Tyrrell, D. A. J., & Barrow, G. I. (1992). Mood and experimentally induced respiratory virus infections and illness. *Psychology and Health, 6*, 205–212.

Smith, A. P., Thomas, M., Brockman, P., Kent, J., & Nicholson, K. G. (1993). Effect of Influenza B Virus Infection on Human Performance. *British Medical Journal, 306*, 760–761.

Sommer, N., Loschmann, P. A., Northoff, G. H., Weller, M., Steinbrecher, A., Steinbach, J. P., Lichtenfels, R., Meyermann, R., Riethmuller, A., Fontana, A., Dichgans, J., & Martin, R. (1995). The antidepressant rolipram suppresses cytokine production and prevents autoimmune encephalomyelitis. *Nature Medicine, 1*, 244–248.

Song, C. & Leonard, B. E. (1994). An acute phase protein response in the olfactory bulbectomized rat: Effect of sertraline treatment. *Medical Science Research, 22*, 313–314.

Song, C., Dinan, T., & Leonard, B. E. (1994). Changes in immunoglobulin, complement and acute phase protein levels in depressed patients, and normal controls. *Journal of Affective Disorders, 30*, 283–288.

Sonti, G., Ilyin, S. E., & Plata-Salaman, C. R. (1996). Anorexia induced by cytokine interactions at pathophysiological concentrations. *American Journal of Physiology, 270*, R1394–R1402.

Spadaro, F. & Dunn, A. J. (1990). Intracerebroventricular administration of interleukin-1 to mice alters investigation of stimuli in a novel environment. *Brain, Behavior, and Immunity, 4*, 308–322.

Spriggs, D. R., Sherman, M. L., Michie, H., Arthur, K. A., Imamura, K., Wilmore, D., Frei, E., & Kufe, D. W. (1988). Recombinant human tumor necrosis factor administration as a 24-hr intravenous infusion. A phase I and pharmacologic study. *Journal of National Cancer Institute, 80*, 1039–1044.

Suzuki, T., Funada, M., Sugano, Y., Misawa, M., Okutomi, T., Soma, G. I., & Mizuno, D. (1994). Effects of a lipopolysaccharide from pantoea agglomerans on the cocaine-induced place preference. *Life Sciences, 54*, PL75–PL80.

Swiergiel, A. H., Smagin, G. N., & Dunn, A. J. (1996). Influenza virus infection of mice induces anorexia: Comparison with endotoxin and interleukin-1 and the effects of indomethacin. *Pharmacology, Biochemistry, and Behavior, 57*, 389–396.

Swiergiel, A. H., Smagin, G. N., Johnson, L. J., & Dunn, A. J. (1997). The role of cytokines in the behavioral responses to endotoxin and influenza virus infection in mice: effects of acute and chronic administration of the interleukin-1-receptor antagonist (IL-1ra). *Brain Research, 77*, 696–104.

Takahashi, S., Kapas, L., Fang, J., Seyer, J. M., Wang, Y., & Krueger, J. M. (1996). An interleukin-1 receptor fragment inhibits spontaneous sleep and muramyl dipeptide-induced sleep in rabbits. *American Journal of Physiology, 271*, R101–R108.

Tilders, F. J. H., Derijk, R. H., Van Dam, A. M., Vincent, V. A. M., Schotanus, K., & Persoons, J. H. A. (1994). Activation of the Hypothalamus-Pituitary-Adrenal Axis by Bacterial Endotoxins—Routes and Intermediates. *Psychoneuroendocrinology, 19*, 209–232.

Traskman, L., Tybring, G., Asberg, M., Bertilsson, L., & Schalling, D. (1980). Cortisol in the CSF of depressed and suicidal patients. *Archives of General Psychiatry, 37*, 761–767.

Tueth, M. J. (1995). How to manage depression and psychosis in Alzheimer's disease. *Geriatrics, 50*(1), 43–46, 49.

Turnbull, A. V. & Rivier, C. (1995). Regulation of the HPA axis by cytokines. *Brain, Behavior, and Immunity, 9*, 253–275.

Uehara, A., Sekiya, C., Takasugi, Y., Namiki, M., & Arimura, A. (1989). Anorexia induced by interleukin 1: involvement of corticotropin-releasing factor. *American Journal of Phsyiology, 257*, R613–R617.

Valentine, A. D., Meyers, C. A., Kling, M. A., Richelson, E., & Hauser, P. (1998). Mood and cognitive side effects in interferon-alpha therapy. *Seminars in Oncology, 25*(1), 39–47.

Van der Meer, M. J. M., Fred Sweep, C. G. J., Pesman, G. J., Borm, G. F., & Hermus, A. R. M. M. (1995). Synergism between IL-1β and TNF-α on the activity of the pituitary-adrenal axis and on food intake in rats. *American Journal of Physiology, 268*, E551–E557.

Walker, L. G., Wesnes, K. P., Heys, S. D., Walker, M. B., Lolley, J., & Eremin, O. (1996). The cognitive effects of recombinant interleukin-2 (rIL-2) therapy: a controlled clinical trial using computerised assessments. *European journal of Cancer, 13*, 2275–2283.

Walker, L. G., Walker, M. B., Heys, S. D., Lolley, J., Wesnes, K. P., & Eremin, O. (1997). The psychological and psychiatric effects of rIL-2 therapy: a controlled clinical trial. *Psychooncology, 6*(4), 290–301.

Warren, E. J., Finck, B. N., Arkins, S., Kelley, K. W., Scamurra, R. W., Murtaugh, M. P., & Johnson, R. W. (1997). Coincidental changes in behavior and plasma cortisol in unrestrained pigs after intracerebroventricular injection of tumor necrosis factor-α. *Endocrinology*, *138*, 2365–2371.

Watkins, L. R., Maier, S. F., & Goehler, L. E. (1995a). Cytokine-to-brain communication: A review and analysis of alternative mechanisms. *Life Sciences*, *57*, 1011–1026.

Watkins, L. R., Maier, S. F., & Goehler, L. E. (1995b). Immune activation: the role of pro-inflammatory cytokines in inflammation, illness responses, and pathological pain states. *Pain*, *63*, 289–302.

Weidenfeld, J. & Yirmiya, R. (1996). Effect of bacterial endotoxin on the glucocorticoid feedback regulation of adrenocortical response to stress, *Neuroimmunomodulation*, *3*, 352–357.

Weizman, R., Laor, N., Podliszewski, E., Notti, I., Djaldetti, M., & Bessler, H. (1994). Cytokine Production in Major Depressed Patients Before and After Clomipramine Treatment. *Biological Psychiatry*, *35*, 42–47.

Whitlock, F. A. & Siskind, M. M. (1980). Depression as a major symptom of multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, *43*, 861–865.

Willner, P. (1994). Animal models of depression. In J. A. den Boer & J. M. Sitsen (Eds.), *Handbook of depression and anxiety* (pp. 291–316). New York: Marcel Dekker, Inc.

Willner, P. (1997). Validity, reliability, and utility of the chronic mild stress model of depression: A 10-year review and evaluation. *Psychopharmacology*, *134*, 319–329.

Wilson, E. O. (1975). *Sociobiology: The new synthesis*. Cambridge: Harvard University Press.

Wohlman, A., Gallily, R., Yirmiya, R., & Weidenfeld, J. (1997). Characterization of the effect of *Mycoplasma fermentans* on the hypothalamo-pituitary-adrenal axis. *Neuroendocrinology*, *66*, 221–228.

Wong, M. L., Bongiorno, P. B., Rettori, V., McCann, S. M., & Licinio, J. (1997). Interleukin (IL) 1β, IL-1 receptor antagonist, IL-10, and IL-13 gene expression in the central nervous system and anterior pituitary during systemic inflammation: Pathophysiological implications. *Proceedings of the National Academy of Sciences of the United States of America*, *94*, 227–232.

Xia, Z., DePierre, J. W., & Nassberger, L. (1996). Tricyclic antidepressants inhibit IL-6, IL-1β, and TNF-α release in human blood monocytes and IL-2 and interferon-γ in T-cells. *Immunobiology*, *34*, 27–37.

Xiao, L. & Eneroth, P. (1996). Tricyclic antidepressants inhibit human natural killer cells. *Toxicology and Applied Pharmacology*, *137*, 157–162.

Yamada, T. & Yamanaka, I. (1995). Microglial localization of alpha interferon receptor in human brain tissues. *Neuroscience Letters*, *189*, 73–76.

Yehuda, R. & Nemeroff, C. B. (1994). Neuropeptide alterations in affective and anxiety disorders. In J. A. den Boer & J. M. Sitsen (Eds.), *Handbook of depression and anxiaty* (pp. 543–571). New York: Marcel Dekker, Inc.

Yirmiya, R. (1996). Endotoxin produces a depressive-like syndrome in rats. *Brain Research*, *711*, 163–174.

Yirmiya, R. (1997). Behavioral and psychological effects of immune activation: Implications for "depression due to a general medical condition". *Current Opinion in Psychiatry*, *10*, 470–476.

Yirmiya, R., Rosen, H., Donchin, O., & Ovadia, H. (1994). Behavioral effects of lipopolysaccharide in rats: Involvement of endogenous opioids. *Brain Research*, *648*, 80–86.

Yirmiya, R., Avitsur, R., Donchin, O., & Cohen, E. (1995). Interleukin-1 inhibits sexual behavior in female but not in male rats. *Brain, Behavior, and Immunity*, *9*, 220–33.

Yirmiya, R., Barak, O., Avitsur, R., Gallily, R., & Weidenfeld, J. (1997). Intracerebral administration of *Mycoplsma fermentans* produces sickness behavior: role of prostaglandins. *Brain Research*, *749*, 71–81.

Zacharko, R. M., Zalcman, S., Macneil, G., Andrews, M., Mendella, P. D., & Anisman, H. (1997). Differential effects of immunologic challenge on self-stimulation from the nucleus accumbens and the substantia nigra. *Pharmacology, Biochemistry, and Behavior*, *58*, 881–886.

Zhu, J., Bengtsson, B. O., Mix, E., Thorell, L. H., Olsson, T., & Link, H. (1994). Effect of monoamine reuptake inhibiting antidepressants on major histocompatibility complex expression on macrophages in normal rats and rats with experimental allergic neuritis (EAN). *Immunopharmacology*, *27*(3), 225–244.

Zorzenon, M., Colle, R., Vecchio, D., Bertoli, M., Giavedoni, A., Degrassi, A., Lavaroni, S., & Aguglia, E. (1996). Major depression, viral reactivation, and immune system. *European Psychiatry*, *11*, 332.

Zubareva, O. E., Abdurasulova, I. N., Bluthe, R. M., Dantzer, R., & Klimenko, V. M. (1998). Effects of serotonin synthesis blockade on IL-1 beta actions in the brain of rats. *NeuroImmunoModulation*, *5*, 56.