

# Cytokine-induced changes in mood and behaviour: implications for 'depression due to a general medical condition', immunotherapy and antidepressive treatment

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## Abstract

Several lines of evidence indicate that cytokine-mediated communication pathways between the immune system and the brain are involved in the pathophysiology of depression: (1) Depression is highly prevalent in various medical conditions, including infectious, autoimmune and neurodegenerative diseases. This clinical association cannot be attributed solely to psychological distress, and it probably reflects direct activation of illness-induced physiological processes. (2) Experiments in humans and in animals demonstrate that exposure to cytokines induces depressive-like mood and behavioural alterations. (3) Cytokine immunotherapy in cancer and hepatitis patients elicits a major depressive episode in a large percentage of the patients. (4) Several types of depression that are not directly associated with a physical disease (e.g. major depression, melancholia, dysthymia) were also associated with cytokine hypersecretion. (5) Antidepressant drugs possess anti-inflammatory characteristics, which may partly account for their therapeutic effect. Congruently, antidepressants were found to reverse cytokine-induced major depression in humans and depressive-like behaviours in animals. (6) Cytokines affect brain systems that were implicated in the aetiology of depression, including the hypothalamus–pituitary–adrenal axis and monoaminergic systems. These conclusions strongly suggest that during medical conditions elevated levels of cytokines directly contribute to the induction of depression. Therefore, illness-associated depression should not be underestimated (in terms of prevalence and severity), and should be treated with antidepressant drugs, which may act on the specific physiological mechanisms of this disorder.

Received 21 April 2002; Reviewed 13 May 2002; Revised 3 June 2002; Accepted 9 June 2002

**Key words:** Antidepressants, cytokines, illness-associated depression, immunotherapy.

## Introduction

Studies over the last decade revealed several humoral and neural communication pathways between the immune system and the brain (Dantzer et al., 2000; Watkins and Maier, 1999). This communication is mediated by immune-derived pro-inflammatory cytokines, particularly interleukin-1 $\beta$  (IL-1 $\beta$ ), tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and the interferons. Within the brain, immune-related information activates several areas, and induces glia cells and neurons to release the same cytokines, which serve as neurotransmitters and neuroregulators. Brain cytokines produce alterations in

several neurotransmitter, neuroendocrine and behavioural systems (Besedovsky and Del Rey, 1996; Maier and Watkins, 1998). In animal models, these behavioural changes include anhedonia (a reduced capacity to experience pleasure), reflected by reduced preference for sweet solutions, decreased intracranial self stimulation and suppressed libido and sexual behaviour, as well as anorexia and body weight loss, hypersomnia, psychomotor retardation, fatigue, and impaired cognitive abilities, exploration and social behaviour (Dantzer, 2001; Larson and Dunn, 2001; Yirmiya et al., 1999). The similarity between the behavioural effects of cytokines in animals and the symptoms of major depression in humans (APA, 1994) was observed first by Maes et al. (1993) and later by other researchers (Connor and Leonard, 1998; Dantzer et al., 1999; Leonard, 2001; Maes, 1995, 1999; Raison and Miller, 2001; Yirmiya, 1997, 2000; Yirmiya et al., 1999, 2000)

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who raised the hypothesis that cytokines are involved in the pathophysiology of depression. In the present paper we discuss the implications of this hypothesis to the co-morbidity of various physical diseases and depression, to cytokine immunotherapy and to the mechanism of action of antidepressants.

### **Co-morbidity of depression and non-psychiatric medical conditions**

The high prevalence of depression in general medical patients and among the elderly has been recognized as a major public health concern. The reported prevalence of major depressive episodes in physically ill patients varies from 5% to over 40% (Hosaka et al., 1999; Rodin and Voshart, 1986). Cross-regional studies of depression among old people revealed prevalence of 12.3–53%, depending on different diagnostic criteria (Benazzi, 2000; Cole et al., 1999). Depression in these populations is severe, very costly [e.g. the average hospital stay for a serious physical disease is 6–9 wk longer in depressed than in non-depressed patients (Hosaka et al., 1999)] and is associated with poorer prognosis (Black and Markides, 1999). However, illness-associated depression is often considered as a 'normal' side-effect of the disease process, attributed to medical and functional disability or to weakness of personality, and therefore its prevalence is usually underestimated and it is frequently not treated (Mills, 2001).

Recently, an attempt was made to identify particular diseases that are highly associated with depressive symptoms. Self-report studies of geriatric populations revealed that chronic digestive, arthritic, respiratory and heart diseases, migraine headaches, sinusitis and back pain were more related to depression than cancer, hypertension, diabetes and hearing or vision loss (Lee et al., 2001; Mills, 2001; Patten, 2001). In addition, depression was found to be related additively and synergistically to the number of chronic diseases afflicting the patient. These findings were interpreted as reflecting increased functional and social incapacitation, higher perceived or actual burden and lower illness controllability. The authors acknowledge, however, that the results were unanticipated with regard to some of the diseases that were less associated with depression 'since they are responsible for high rates of morbidity and/or mortality' (Mills, 2001).

Another interpretation of such findings is that depression associated with various medical conditions is not merely a psychological reaction to the incapacitation, pain, and losses that accompany the physical disease process, but may be directly caused by activation of the pathophysiological processes. This point

of view is reflected by the special psychiatric diagnostic entity of 'depression due to a general medical condition' (APA, 1994). To be diagnosed with this condition, 'the clinician should establish the presence of a general medical condition, and determine that the depression is aetiologically related to the general medical condition through a physiological mechanism' (APA, 1994). Several lines of evidence suggest that this physiological mechanism involves the immune system in general, and the inflammatory cytokines response in particular.

Congruent with the immunological hypothesis of depression, depressive symptoms are frequently associated with inflammatory diseases, both infectious and non-infectious. Infectious illnesses, such as influenza, gastroenteritis, hepatitis C, HIV and Epstein-Barr virus, are all associated with a range of depressive symptoms, including depressed mood, fatigue, psychomotor retardation, anorexia, as well as attention and memory impairments (Capuron et al., 1999; Dieperink et al., 2000; Maj, 1996). Depression is also highly prevalent in chronic inflammation associated with several types of non-infectious conditions, such as stroke (Robinson, 1997) or autoimmune diseases, e.g. diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, and particularly, multiple sclerosis (Gavard et al., 1993; Hutchinson et al., 1996; Pincus et al., 1996; Schiffer and Babigian, 1984; Schubert and Foliart, 1993). Importantly, several studies have revealed that immune deregulation and inflammatory activity preceded and coincided with multiple sclerosis-associated depression (Fassbender et al., 1998; Foley et al., 1992; Mohr et al., 2001).

The relationship between infection and depressive symptoms was also addressed experimentally. Despite the small number of studies, convincing data were collected indicating that induced infections with several viruses (e.g. common cold, influenza and rubella vaccination), but not others (e.g. cold viruses), produce depressive symptoms (Smith et al., 1992, 1993).

We have used a double-blind prospective design to investigate the immediate and prolonged psychological and physiological effects of a specific viral infection in humans (Morag et al., 1998). Subjects were teenage 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, comprised of subjects who were initially seronegative and were infected following vaccination, and a control group, comprised of subjects who were already immune to rubella before vaccination. Compared to control subjects, and to their own baseline, subjects from low, but not middle or high

socioeconomic status within the experimental group exhibited significantly higher levels of depressed mood, as well as significantly more social and attention problems and delinquent behaviour. The particular vulnerability to immunization-induced depression may be associated with several characteristics of low socioeconomic status, including higher incidence of stressful life events, and fewer sources of social support, which modulate the responsiveness to immune challenges. Thus, even a mild viral infection can produce a prolonged increase in depressive symptomatology in vulnerable individuals.

### Cytokine-induced depression

The best evidence for the involvement of cytokines in mediating the psychological effects of physical disease is that exogenous administration of cytokines to cancer or hepatitis-C patients produces marked psychological and neuroendocrine symptoms that are similar to those induced by viral infection. Administration of cytokines (IL-2, IFN- $\alpha$  or TNF- $\alpha$ ) causes influenza-like and depressive symptoms (Capuron et al., 2000; Meyers, 1999; Valentine et al., 1998). The fact that these symptoms appear almost immediately after cytokine administration, and usually disappear shortly after termination of the cytokine treatment, strongly suggests a causal role for cytokines in producing the depressive symptoms. Furthermore, immunotherapy-induced depression scores were significantly correlated with the increased production of IL-6, IL-8 and IL-10 and with decreased levels of serum dipeptidyl peptidase IV (a membrane-bound serine protease, which catalyses the cleavage of some cytokines and neuroactive peptides that modulate T-cell activity) (Bonaccorso et al., 2001; Capuron et al., 2001a; Maes et al., 2001a,b).

To further examine the role of cytokines in the psychological alterations that accompany infection and inflammation, we have recently studied the effects of lipopolysaccharides (LPS) on affective and cognitive variables in healthy volunteers (Reichenberg et al., 2001, In Press). Administration of a low dose of purified LPS (the major cell-wall component of Gram-negative bacteria) is the most established and frequently used experimental model for safe and accurate assessment of the acute host response to infection in humans. We used a cross-over design, in which each subject completed a battery of psychological and neuropsychological tests at various time-points following LPS injection on one day, and following saline on another day. A double-blind design was used, i.e. neither the experimenter nor the subject knew the group assignment. LPS had no effect on physical sickness symptoms, blood pressure,

or heart rate, but it caused a mild increase in rectal temperature, and markedly elevated the circulating levels of many cytokines and cortisol. Following LPS administration, the subjects showed a transient significant increase in levels of depressed mood, particularly at 3–4 h post-administration. This effect was reversed at 9 h post-administration, when inflammatory cytokine levels have subsided. LPS also produced significant anorexia, increased anxiety levels and impairments in verbal and non-verbal memory functions. Significant positive correlations were found between the secretion of specific cytokines (particularly IL-6 and TNF- $\alpha$ ) and LPS-induced depressed mood, anxiety, anorexia and the severity of memory impairments. The findings suggest that in humans, a mild stimulation of the primary host defence, even if it does not induce subjective physical sickness symptoms, is associated with emotional and cognitive disturbances, which may be caused by cytokine release.

### Immune activation markers in depressive disorders

Immune activation was reported to accompany depressive syndromes other than 'depression due to a general medical condition'. Major depression was associated with increased number of blood leucocytes, increased serum levels of several soluble indicators of activated immune cells, including IL-2 receptor (IL-2R), neopterin, prostaglandin E<sub>2</sub>, increased serum concentrations of complement proteins and of positive acute phase proteins (APPs) and decreased levels of negative APPs, increased secretion of cytokines, both in vivo (particularly IL-6) and following in-vitro induction by mitogens (particularly IL-1 $\beta$ , IL-6, TNF- $\alpha$  and IFN- $\gamma$ ) (Maes, 1995, 1999; Mikova et al., 2001; Zorrilla et al., 2001). However, these findings should be interpreted cautiously, because some studies reported no elevation in immune activation markers in depressed patients (Landmann et al., 1997; Natelson et al., 1999). Furthermore, other factors associated with depression, such as age, body mass index, gender, smoking habits, ongoing or recent infectious diseases, or prior medication, may all affect the results. In fact, a recent carefully controlled study in which all of these confounding factors were taken into account, reported no evidence for depression-related alterations in the levels of IL-1 receptor antagonist (IL-1Ra), soluble IL-2 receptor (sIL-2R), sTNF-R p75 and IL-6 (Haack et al., 1999). It may be argued that these negative results are attributed to concurrent medication of many of the patients (Natelson et al., 1999) or to limitations in detection of low cytokine (particularly IL-6 and TNF-levels (Haack et al., 1999).

Future studies should take these methodological issues into account.

Immune activation and cytokine secretion probably do not account for all types of depressive disorders. Rather, immune factors may be involved in the pathophysiology of certain subtypes of depression, characterized by a constellation of symptoms that are often found in virus-infected and cytokine-injected individuals. Indeed, several studies attempted to resolve the incongruent reports on immune patterns in depressed patients, by examining parameters of immune activation in separated subtypes of depression. Using this strategy, melancholic and non-melancholic depressed patients were found to show different immune patterns. Melancholic patients had normal leucocyte counts and decreased production of IL-2, IL-10 and IFN- $\gamma$ , whereas non-melancholic patients showed increased blood count and a normal cytokine profile. IL-1 $\beta$  production was unchanged in all groups (Rothermundt et al., 2001a,b). Other studies compared major depression and dysthymia patients, reporting that the levels of IL-6 were significantly increased in the two conditions, whereas the levels of IL-1 were increased only in the dysthymic patients (Schlatter et al., 2001), and that mitogen-stimulated lymphocyte proliferation was reduced to a greater extent among the dysthymic patients (Zaharia et al., 2000). Another study reported that seasonal affective disorder was associated with inflammatory activation, reflected by increased levels of circulating IL-6 (Leu et al., 2001). Late-onset depression was associated with elevated levels of intercellular adhesion molecule-1, a marker of ischaemia-induced inflammation (Thomas et al., 2000). Despite their attractiveness, these findings should be treated with caution until replicated in larger samples of patients.

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 reactions, which in turn contribute to the depressive symptomatology. This hypothesis is supported by studies reporting increased antibody titres to several viruses, particularly herpes simplex virus (HSV) in patients with major depression (Cappel et al., 1978; Lycke et al., 1974). Moreover, clear evidence was provided recently for active viral multiplication and elevated antibody titres to HSV in 41% of the patients with major depression (Zorzenon et al., 1996). Similarly, higher serum antibodies to Borna disease virus, as well as isolation of this virus from patients with depression have been reported (Bode et al., 1996). In contrast, prospective studies of infectious

mononucleosis patients provided no evidence for prolonged depressive episodes (for review see Peter and White, 1999).

Elevated stress levels may constitute another inducer of cytokine production and secretion in depressed patients. Several studies suggest that exposure to stress in both humans and animals results in increased production of pro-inflammatory cytokines (for review see Watkins et al., 1999). Stress has been suggested as an important risk factor for depression (Kendler et al., 1999). Thus, it is possible that at least in some incidences of depression that are not preceded by an inflammatory condition, increased cytokine production is a result of exposure to stress.

### The anti-inflammatory effects of antidepressant drugs

Another line of evidence for the relation between depression and immune activation derives from studies that examined the effects of antidepressants on immune processes and inflammation-related behavioural alterations.

In-vitro studies indicated that antidepressants can have direct effects on immune cells. Tricyclic antidepressants (TCAs) were found to induce apoptosis (Xia et al., 1997) and to inhibit spontaneous secretion of IL-2 and IFN- $\gamma$  from T cells, as well as spontaneous and LPS-induced secretion of IL-1, IL-6 and TNF- $\alpha$  from monocytes (Xia et al., 1996). Similarly, the antidepressant rolipram was found to suppress TNF- $\alpha$  and also, to a lesser extent, IFN- $\gamma$  secretion by human and rat autoreactive T cells (Sommer et al., 1995). Seven antidepressant drugs [2 tricyclic, 2 selective serotonin (5-HT) reuptake inhibitors (SSRIs), a 5-HT-noradrenaline reuptake inhibitor, a heterocyclic and the immediate precursor of 5-HT] have been found to suppress the IFN- $\gamma$ /IL-10 production ratio in diluted whole-blood samples of treatment-resistant depression patients and normal controls (Kubera et al., 2001a; Maes et al., 1999), whereas joint application of imipramine and thyrotropin-releasing hormone, which is known to accelerate the antidepressive effect, decreased the production of both IL-10 and IFN- $\gamma$  (Kubera et al., 2000a). Antidepressants may exert their effect on non-cytokine inflammatory mediators. Over 20 years ago it was suggested that antidepressants might inhibit the synthesis of PGE<sub>2</sub> (Mtabaji et al., 1977). A recent in-vitro study has shown that both TCAs and SSRIs attenuated cytokine-induced PGE<sub>2</sub> and nitric oxide production by inflammatory cells from synovial tissue (Yaron et al., 1999).

In living animals, antidepressant treatment 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 and Leonard, 1994), reduced IL-1 and IL-2 production and increased IL-10 production in the chronic mild stress model of depression (Kubera et al., 1996, 2001b), and inhibited immune activation in rats with experimental allergic neuritis (Zhu et al., 1994). Anti-inflammatory properties were demonstrated for both fluoxetine and clomipramine in carrageenin or brewers' yeast-induced inflammation (Bianchi and Panerai, 1996). Repeated (1–4 wk) administration of desipramine and amitriptyline to mice enhanced biochemical and proliferative activities of splenocytes and increased both pro- and anti-inflammatory cytokine production, depending on the drugs used and on the duration of administration (Kubera et al., 2000b). Acute and chronic administration of desipramine increased total hippocampal TNF- $\alpha$  levels (estimated by ELISA analysis) and decreased neuronal-associated TNF- $\alpha$  (estimated by immunohistochemistry). These findings were interpreted as reflective of increased protein generation and also increased release or redistribution within the cell (Ignatowski et al., 1997; Nickola et al., 2001).

In depressed patients, the effects of antidepressants are less consistent. When depression was associated with immune activation, antidepressants suppressed immune function and cytokine secretion in many, but not all, studies. For example, the increased plasma levels of IL-6 during acute depression were normalized by 8-wk treatment with fluoxetine (Sluzewska et al., 1995), the increased monocyte counts in depressed patients were reduced following 6 wk treatment with TCAs (Seidel et al., 1996), and the increased numbers of leucocytes and neutrophils were also reduced by antidepressant treatment (Maes et al., 1997). In multiple sclerosis, depressed patients, subjected to either individual cognitive behavioural therapy, group psychotherapy or sertraline therapy, the antidepressive effect was accompanied by decreased IFN- $\gamma$  production by peripheral blood mononuclear cells (PBMC), stimulated by OKT 3 (non-specifically) or myelin oligodendrocyte glycoprotein (MOG) (antigen-specifically) (Mohr et al., 2001). On the other hand, antidepressant treatment, though effectively ameliorated depressive symptoms, had no effect on major depression-associated up-regulation of sIL-2R, IL-6, sIL-6R, IL-10 and IL-1Ra and dysthymia-associated up-regulation of IL-1 (Anisman et al., 1999; Kubera et al., 2000c). Similarly, successful light therapy did not alter the elevated levels of IL-6 and sIL-2R in patients with seasonal

affective disorder (Leu et al., 2001). These findings suggest that acute phase dysfunction may be a trait, rather than a state marker of depression. When immune functions in depressed patients were found to be normal, antidepressants had no effects on immune parameters, e.g. chronic moclobemide treatment had no effect on monocytes functions, TNF- $\alpha$  production or IFN- $\gamma$  levels (Landmann et al., 1997). Moreover, in a study of depressed patients who exhibited immune suppression before treatment, the TCA clomipramine increased the production of IL-1 $\beta$ , IL-2, and IL-3 (Weizman et al., 1994).

### Effects of antidepressants on illness- and cytokine-induced depression

Antidepressants have been used successfully in treating depressive symptoms associated with medical illness. Both TCAs and SSRIs are of proven value in treating depression associated with a wide range of conditions (Gottfries, 1997; Lauritzen et al., 1994; Rabkin et al., 1994; Schiffer and Wineman, 1990; Van Heeringen and Zivkov, 1996).

To further elucidate the relationship between immune activation and depression, and explore the mechanisms underlying the therapeutic action of antidepressants, experimental animal models have been used. Specifically, we, as well as several other laboratories, examined the effects of antidepressants on LPS-induced behavioural and neuroendocrine alterations in rats. Chronic, but not acute administration with antidepressants from several groups (i.e. imipramine, desipramine, fluoxetine and tianeptine) attenuated LPS-induced sickness behaviour, as well as some of the physiological and neuroendocrine effects of LPS in rats (Castanon et al., 2001; Shen et al., 1999; Yirmiya, 1996; Yirmiya et al., 2001). In contrast, treating mice with similar protocols had no effect on LPS-induced reduction in appetitive-hedonic behaviour (Dunn and Swiergiel, 2001).

In a recent study, this procedure has been adopted for the treatment of cytokine-induced depression in humans. Using a double-blind, placebo-controlled design, patients were pretreated with the antidepressant paroxetine or placebo for 2 wk prior to the initiation of chronic administration of high-dose interferon therapy for malignant melanoma (Musselman et al., 2001). Most patients on placebo met the criteria for major depression or had to discontinue interferon due to toxicity before 3 months. In contrast, less than a third of the patients on paroxetine developed depression and no patients on paroxetine had dropped out of treatment, reflected by a statistically significant

improvement in morbidity and compliance. Together, these data indicate that antidepressants provide useful treatment and prophylaxis against the development of illness-associated mood disorders.

### **Mechanisms underlying cytokine-induced depression**

Several mechanisms may underlie the relationships between cytokines and depression.

#### *Activation of the hypothalamic–pituitary–adrenal (HPA) axis*

This has been implicated in the aetiology of depression (Holsboer, 2000; Plotsky et al., 1998). Pro-inflammatory cytokines are potent activators of the HPA axis, inducing the production and secretion of corticotropin-releasing hormone and glucocorticoids, and it is reasonable to hypothesize that HPA activation mediates at least some cytokine-induced depressive symptoms. Furthermore, a correlation was found between immune function and cortisol levels in depressed patients (Maes et al., 1995). Confirming this suggestion, imipramine, fluoxetine and tianeptine were all found to attenuate LPS-induced corticosterone secretion (Castanon et al., In Press; Yirmiya, 1996; Yirmiya et al., 2001).

#### *Alterations in monoaminergic systems*

According to the monoamine theory, depression is caused by alterations in the noradrenergic and serotonergic systems (Charney, 1998; Delgado, 2000). Many studies have demonstrated bidirectional relationships between cytokines and monoaminergic systems, some of which may be directly relevant for the pathophysiology of depression and the mechanism of action of antidepressant drugs.

Most studies on the acute effects of cytokines on norepinephrine and 5-HT secretion report increased, rather than decreased neurotransmission. For example, exogenous administration of IL-1 $\beta$ , or elevation of endogenous pro-inflammatory cytokine levels by immune challenges such as LPS, produce an increase in the turnover and extracellular concentrations of norepinephrine and 5-HT or their metabolites, in several brain areas (Dunn et al., 1999; Linthorst and Reul, 1998). The effects of chronic exposure to cytokines are less clear, but may also produce similar effects, e.g. repeated IL-2 administration was found to increase 5-HT and norepinephrine turnover (Lacosta et al., 2000). These findings seem less compatible with the monoaminergic hypothesis of depression. However, it is still possible that chronic cytokine exposure increases the utilization

of monoamines to levels that exceed the capacity for their synthesis, resulting in reduced monoamine levels. The results of studies on the effects of cytokines on other components of the monoaminergic systems (particularly the regulation of receptor expression and sensitivity) may be more congruent with this hypothesis (e.g. desensitization of receptors following over-activation). To examine the effects of antidepressant treatment on serotonergic neurotransmission, we recently tested the effects of chronic treatment with the TCA clomipramine on LPS-induced secretion of brain 5-HT (Yirmiya et al., 2000). On the last day of antidepressant treatment, rats were implanted with a dialysis probe into the hypothalamus, and the effect of LPS on 5-HT concentrations was assessed 24 h later in freely moving rats. In rats that were chronically treated with saline, LPS produced a significant elevation in hypothalamic 5-HT concentration. This effect was completely abolished by chronic clomipramine treatment, suggesting that antidepressants can attenuate the serotonergic activation induced by an immune challenge.

The effects of cytokines on monoaminergic neurotransmission may be indirect, via the metabolism of monoamines precursors. A particularly attractive hypothesis implicates the enzyme indoleamine 2,3-dioxygenase (IDO) as the target for the involvement of cytokines in serotonergic neurotransmission and possibly in depression. IDO is the first rate-limiting enzyme of the catabolism pathway of the 5-HT precursor tryptophan, and its induction by cytokines such as IFN- $\gamma$  enhances the catabolism of tryptophan (Konan and Taylor, 1996). The involvement of IDO in cytokine-induced depression was first suggested by Maes et al. (1993) and is supported by a study reporting that cancer patients with depression and cachexia exhibited significantly elevated levels of serum neopterin (a marker of endogenous IFN- $\gamma$ ), along with decreased 5-HT and tryptophan levels (Iwagaki et al., 1997). Furthermore, systemic immune activation with LPS was recently found to stimulate IDO activity in the rodent brain (Lestage et al., In Press). Finally, patients receiving immunotherapy showed reduced levels of tryptophan and 5-HT (Bonaccorso et al., 2002; Capuron et al., 2001b). It can, therefore, be hypothesized that the reduced availability of brain tryptophan, the precursor of 5-HT, resulting from cytokine-induced IDO activation, alters 5-HT synthesis.

Cytokines may alter the availability of tryptophan via other mechanisms: The tryptophan/cerebral amino-acid ratio is reduced in pregnant women before and after delivery, and is inversely correlated with the production of IL-6, IL-1Ra and leukaemia inhibitory

factor (LIF) receptor (Maes et al., 2001c). Furthermore, IL-1, TNF- $\alpha$  and IFN- $\gamma$  were all found to up-regulate the 5-HT transporter (5-HTT), whereas IL-4 was found to downregulate the 5-HTT (Morikawa et al., 1998; Mossner et al., 1998, 2001; Ramamoorthy et al., 1995). Accordingly, pro-inflammatory cytokines can serve as 5-HT antagonists, resulting in 5-HT hypoactivity.

Another finding that may be relevant to cytokine-induced monoaminergic hypoactivity is that TNF- $\alpha$  inhibits noradrenergic neurotransmission in the rat hippocampus. This inhibition is mediated via activation of  $\alpha_2$  adrenergic receptors (Ignatowski et al., 1997), resulting in NE hypoactivity. Interestingly, this noradrenergic inhibition by TNF- $\alpha$  is transformed into potentiation following antidepressant treatment.

### Summary and conclusions

The 'inflammatory response system hypothesis of depression', first proposed by Smith (1991) and Maes (1995), suggests that activation of immune activation plays a role in the aetiology of depression. Most literature on this topic consists of correlative studies, suggesting that at least some components of the immune system are activated in some depressive disorder patients, and demonstrating unequivocal co-morbidity of medical conditions and depression. However, leaning on non-experimental data raises two methodological problems. First, non-random assignment allows many confounding factors to interfere, which may result in fortuitous association between immunity and depression. Indeed, a recent controlled study based on a large sample of psychiatric patients on admission, found no evidence for depression-associated rise in plasma cytokines, after covarying confounding factors (Haack et al., 1999). The second problem is the inability to deduce causal relationship between immune activation and depression symptomatology from correlative studies. The only quasi-experimental paradigms of cytokine-induced depression in humans, which is observed in cancer and hepatitis patients undergoing immunotherapy, suffer three methodological disadvantages. (1) There is a large difference between the relatively low levels of endogenous cytokines measured in depressed patients and the therapeutic large doses of exogenous cytokines that are used in immunotherapy. (2) The number of cytokines that are used in immunotherapy is limited (predominantly IFN- $\alpha$  and IL-2), and does not include the pro-inflammatory cytokines (e.g. IL-1, TNF- $\alpha$  and IL-6), which are presumed to play an important role in immune-to-brain communication and cytokine-induced depressive symptoms. (3) The subjects in these studies

constitute a unique population, with a serious, life-threatening disease. The only experimental data that is available (i.e. using the paradigms of experimental virus inoculation or endotoxin administration) demonstrates temporary cytokine-induced negative mood alterations and depressive-like symptoms, rather than a full-blown major depressive episode. Some investigators attempted to overcome the methodological limitations of human studies by using animal models. Although these studies provide abundant data on the depressive-like effects of cytokines, indicating that depressive symptoms can be directly produced by immune activation, the obvious difficulty in establishing an animal model for mood disorder precludes easy generalization to humans.

It may be concluded, therefore, that there is convincing evidence that (1) medical conditions are frequently associated with depression; (2) cytokines induce mood alterations, and (3) in the context of serious diseases, high doses of cytokines can also cause major depression episodes. These conclusions have several important clinical implications. Since immune activation alters mood in the negative direction, medical conditions, associated with immune activation, should be regarded as risk factors for the establishment of mood disorders. Moreover, due to the inflammatory mediation of these mood alterations, it could be hypothesized that anti-inflammatory treatment will have an antidepressive effect. Thus, in addition to the ample literature on the anti-inflammatory characteristics of antidepressant drugs (for review see Bianchi and Panerai, 1996), more research is needed on the antidepressive effects of anti-inflammatory drugs.

### Acknowledgements

The paper was supported by a grant from the Israel Science Foundation (No. 820/00-1). R.Y. is a member of the Eric Roland Center for Neurodegenerative Diseases at the Hebrew University of Jerusalem.

### References

- Anisman H, Ravindran AV, Griffith J, Merali Z (1999). Interleukin-1 $\beta$  production in dysthymia before and after pharmacotherapy. *Biological Psychiatry* 46, 1649-1655.
- APA (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th edn). Washington, DC: American Psychiatric Association.
- Benazzi F (2000). Late-life chronic depression: a 399-case study in private practice. *International Journal of Geriatric Psychiatry* 15, 1-6.
- Besedovsky HO, Del Rey A (1996). Immune-neuro-endocrine interactions: facts and hypotheses. *Endocrine Reviews* 17, 64-102.

- Bianchi M, Panerai AE (1996). Antidepressant drugs and experimental inflammation. *Pharmacological Research* 33, 235–238.
- Black SA, Markides KS (1999). Depressive symptoms and mortality in older Mexican Americans. *Annals of Epidemiology* 9, 45–52.
- Bode L, Durrwald R, Rantam FA, Ferszt R, Ludwig H (1996). First isolation of infectious human Borna disease virus from patients with mood disorders. *Molecular Psychiatry* 1, 200–212.
- Bonaccorso S, Marino V, Puzella A, Pasquini M, Biondi M, Artini M, Almerighi C, Verkerk R, Meltzer HY, Maes M (2002). Increased depressive ratings in patients with hepatitis C receiving interferon- $\alpha$ -based immunotherapy are related to interferon- $\alpha$ -induced changes in the serotonergic system. *Journal of Clinical Psychopharmacology* 22, 86–90.
- Bonaccorso S, Puzella A, Marino V, Pasquini M, Biondi M, Artini M, Almerighi C, Levero M, Egyed B, Bosmans E, Meltzer HY, Maes M (2001). Immunotherapy with interferon- $\alpha$  in patients affected by chronic hepatitis C induces an intercorrelated stimulation of the cytokine network and an increase in depressive and anxiety symptoms. *Psychiatry Research* 15, 45–55.
- 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.
- Capuron L, Lamarque D, Dantzer R, Goodall G (1999). Attentional and mnemonic deficits associated with infectious disease in humans. *Psychological Medicine* 29, 291–297.
- Capuron L, Miller AH, Ravaud A, Neveu PJ, Maes M, Dantzer R (2001b). *Brain, Behavior and Immunity* 15, 139–140.
- Capuron L, Ravaud A, Dantzer R (2000). Early depressive symptoms in cancer patients receiving interleukin2 and/or interferon  $\alpha$ -2b therapy. *Journal of Clinical Oncology* 18, 2143–2151.
- Capuron L, Ravaud A, Gualde N, Bosmans E, Dantzer R, Maes M, Neveu PJ (2001a). Association between immune activation and early depressive symptoms in cancer patients treated with interleukin-2-based therapy. *Psychoneuroendocrinology* 26, 797–808.
- Castanon N, Bluthé RM, Dantzer R (2001). Chronic treatment with the atypical antidepressant tianeptine attenuates sickness behavior induced by peripheral but not central lipopolysaccharide and interleukin-1 $\beta$  in the rat. *Psychopharmacology* 154, 50–60.
- Castanon N, Médina C, Mormède C, Dantzer R (In Press). Chronic treatment with the antidepressant tianeptine attenuates splenic and brain expression of pro-inflammatory cytokines. *Brain, Behavior and Immunity*.
- Charney DS (1998). Monoamine dysfunction and the pathophysiology and treatment of depression. *Journal of Clinical Psychiatry* 59, S11–S14.
- Cole MG, Bellvance F, Mansour A (1999). Prognosis of depression in elderly community and primary care populations: a systematic review and meta-analysis. *American Journal of Psychiatry* 156, 1182–1189.
- Connor TJ, Leonard BE (1998). Depression, stress and immunological activation: the role of cytokines in depressive disorders. *Life Science* 62, 583–606.
- Dantzer R (2001). Cytokine-induced sickness behavior: where do we stand? *Brain Behavior and Immunity* 15, 7–24.
- Dantzer R, Konsman JP, Bluthé RM, Kelley KW (2000). Neural and humoral pathways of communication from the immune system to the brain: parallel or convergent? *Autonomic Neuroscience* 20, 60–65.
- Dantzer R, Wollman EE, Vitkovic L, Yirmiya R (1999). Cytokines and depression: fortuitous or causative associations? *Molecular Psychiatry* 4, 328–332.
- Delgado PL (2000). Depression: the case for a monoamine deficiency. *Journal of Clinical Psychiatry* 61, S7–S11.
- Dieperink E, Willenbring M, Ho SB (2000). Neuropsychiatric symptoms associated with hepatitis C and interferon  $\alpha$ : a review. *American Journal of Psychiatry* 157, 867–876.
- Dunn AJ, Swiergiel AH (2001). The reductions in sweetened milk intake induced by interleukin-1 and endotoxin are not prevented by chronic antidepressant treatment. *Neuroimmunomodulation* 9, 163–169.
- Dunn AJ, Wang J, Ando T (1999). Effects of cytokines on cerebral neurotransmission. Comparison with the effects of stress. *Advances in Experimental Medicine and Biology* 461, 117–127.
- Fassbender K, Schmidt R, Mossner R, Kischka U, Kuhnen J, Schwartz A, Hennerici M (1998). Mood disorders and dysfunction of the hypothalamic–pituitary–adrenal axis in multiple sclerosis: association with cerebral inflammation. *Archives of Neurology* 55, 66–72.
- Foley FW, Traugott U, LaRocca NG, Smith CR, Perlman KR, Caruso LS, Scheinberg LC (1992). A prospective study of depression and immune dysregulation in multiple sclerosis. *Archives of Neurology* 49, 238–244.
- Gavard JA, Lustman PJ, Clouse RE (1993). Prevalence of depression in adults with diabetes. *Diabetes Care* 16, 1167–1178.
- Gottfries CG (1997). Recognition and management of depression in the elderly. *International Clinical Psychopharmacology* 12, S31–S36.
- Haack M, Hinze Selch D, Fenzel T, Kraus T, Kuhn M, Schuld A, Pollmächer T (1999). Plasma levels of cytokines and soluble cytokine receptors in psychiatric patients upon hospital admission: effects of confounding factors and diagnosis. *Journal of Psychiatric Research* 33, 407–418.
- Holsboer F (2000). The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology* 23, 477–501.
- Hosaka T, Aoki T, Watanabe T, Okuyama T, Kurosawa H (1999). Comorbidity of depression among physically ill patients and its effect of hospital stay. *Psychiatry and Clinical Neuroscience* 53, 491–495.
- Hutchinson GA, Nehall JE, Simeon DT (1996). Psychiatric disorders in systemic lupus erythematosus. *West Indian Medical Journal* 45, 48–50.
- Ignatowski TA, Noble BK, Wright JR, Gorfien JL, Heffner RR, Spengler RN (1997). Neuronal-associated tumor necrosis

- factor (TNF- $\alpha$ ): its role in noradrenergic functioning and modification of its expression following antidepressant drug administration. *Journal of Neuroimmunology* 79, 84–90.
- Iwagaki H, Hizuta A, Uomoto M, Takeuchi Y, Saito S, Tanaka N (1997). Cancer cachexia and depressive states: a neuroendocrine-immunological disease? *Acta Medica Okayama* 51, 233–236.
- Kendler KS, Karkowsky LM, Prescott CA (1999). Causal relationship between stressful life events and the onset of major depression. *American Journal of Psychiatry* 156, 837–841.
- Konan KW, Taylor MW (1996). Importance of the two interferon-stimulated response element (ISRE) sequences in the regulation of the human indoleamine 2,3-dioxygenase gene. *Journal of Biological Chemistry* 271, 19140–19145.
- Kubera M, Holan V, Mathison R, Maes M (2000b). The effect of repeated amitriptyline and desipramine administration on cytokine release in C57BL/6 mice. *Psychoneuroendocrinology* 25, 785–797.
- Kubera M, Kenis G, Bosmans E, Jaworska-Feil L, Lason W, Scharpe S, Maes M (2000a). Suppressive effect of TRH and imipramine on human interferon- $\gamma$  and interleukin-10 production in vitro. *Polish Journal of Pharmacology* 52, 481–486.
- Kubera M, Kenis G, Bosmans E, Zieba A, Dudek D, Nowak G, Maes M (2000c). Plasma levels of interleukin-6, interleukin-10, and interleukin-1 receptor antagonist in depression: comparison between the acute state and after remission. *Polish Journal of Pharmacology* 52, 237–241.
- Kubera M, Lin AH, Kenis G, Bosmans E, Van-Bockstaele D, Maes M (2001a). Anti-inflammatory effects of antidepressants through suppression of the interferon- $\gamma$ /interleukin-10 production ratio. *Journal of Clinical Psychopharmacology* 21, 199–206.
- Kubera M, Maes M, Holan V, Basta Kaim A, Roman A, Shani J (2001b). Prolonged desipramine treatment increases the production of interleukin-10, an anti-inflammatory cytokine, in C57BL/6 mice subjected to the chronic mild stress model of depression. *Journal of Affective Disorders* 63, 171–178.
- 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.
- Lacosta S, Merali Z, Anisman H (2000). Central monoamine activity following acute and repeated systemic interleukin-2 administration. *Neuroimmunomodulation* 8, 83–90.
- Landmann R, Schaub B, Link S, Wacker HR (1997). Unaltered monocyte function in patients with major depression before and after three months of antidepressive therapy. *Biological Psychiatry* 41, 675–681.
- Larson SJ, Dunn AJ (2001). Behavioral effects of cytokines. *Brain, Behavior and Immunity* 15, 371–387.
- Lauritzen L, Bendtsen BB, Vilmar T, Bendtsen EB, Lunde M, Bech P (1994). Post-stroke depression: combined treatment with imipramine or desipramine and mianserin. *Psychopharmacology* 114, 119–122.
- Lee Y, Choi K, Lee YK (2001). Association of comorbidity with depressive symptoms in community-dwelling older persons. *Gerontology* 47, 254–262.
- Leonard B (2001). The immune system, depression and the action of antidepressants. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 25, 767–780.
- Lestage J, Gaunt D, Pehourcq F, Dantzer R (In Press). Evidence for induction of IDO in the brain in response to peripheral immune stimuli. *Brain, Behavior and Immunity*.
- Leu SJ, Shiah IS, Yatham LN, Cheu YM, Lam RW (2001). Immune-inflammatory markers in patients with seasonal affective disorder: effects of light therapy. *Journal of Affective Disorders* 63, 27–34.
- Linthorst AC, Reul JM (1998). Brain neurotransmission during peripheral inflammation. *Annals of New York Academy of Sciences* 840, 139–152.
- Lycke E, Norrby R, Roos BE (1974). A serological study on mentally ill patients with particular reference to prevalence of herpes simplex virus infections. *British Journal of Psychiatry* 124, 273.
- 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 (1999). Major depression and activation of the inflammatory response system. *Advances in Experimental Medicine and Biology* 461, 25–46.
- Maes M, Bonaccorso S, Marino V, Puzella A, Pasquini M, Biondi M, Artini M, Almerighi C, Meltzer H (2001b). Treatment with interferon- $\alpha$  (IFN- $\alpha$ ) of hepatitis C patients induces lower serum dipeptidyl peptidase IV activity, which is related to IFN- $\alpha$ -induced depressive and anxiety symptoms and immune activation. *Molecular Psychiatry* 6, 475–480.
- Maes M, Bosmans E, Meltzer HY (1995). Immunoendocrine aspects of major depression. Relationships between plasma interleukin-6 and soluble interleukin-2 receptor, prolactin and cortisol. *European Archives of Psychiatry and Clinical Neuroscience* 245, 172–178.
- Maes M, Capuron L, Ravaut A, Gualde N, Bosmans E, Egyed B, Dantzer R, Neveu PJ (2001a). Lowered serum dipeptidyl peptidase IV activity is associated with depressive symptoms and cytokine production in cancer patients receiving interleukin-2-based immunotherapy. *Neuropsychopharmacology* 24, 130–140.
- Maes M, Meltzer HY, Scharpe S, Cooreman W, Uyttenbroeck W, Suy E, Vandervorst C, Calabrese J, Raus J, Cosyns P (1993). Psychomotor retardation, anorexia, weight loss, sleep disturbances, and loss of energy: psychopathological correlates of hyperhaptoglobinemia during major depression. *Psychiatry Research* 47, 229–241.
- Maes M, Ombelet W, Verkerk R, Bosmans E, Scharpe S (2001c). Effects of pregnancy and delivery on the availability of plasma tryptophan to the brain: relationships to delivery-induced immune activation and early post-partum anxiety and depression. *Psychological Medicine* 31, 847–858.

- Maes M, Song C, Lin A-h, Bonaccorso S, Kenis G, De Jongh R, Bosmans E, Scharpe S (1999). Negative immunoregulatory effects of antidepressants: inhibition of interferon- $\gamma$  and stimulation of interleukin-10 secretion. *Neuropsychopharmacology* 20, 370–379.
- Maes M, Vandoolaeghe E, Van Hunsel F, Bril T, Demedts P, Wauters A, Neels H (1997). Immune disturbances in treatment-resistant depression: modulation by antidepressive treatment. *Human Psychopharmacology* 12, 153–162.
- Maier SF, Watkins LR (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 immunodeficiency virus (HIV) infection. *British Journal of Psychiatry* 168, 117–122.
- Meyers CA (1999). Mood and cognitive disorders in cancer patients receiving cytokine therapy. *Advances in Experimental Medicine and Biology* 461, 75–81.
- Mikova O, Yakimova R, Bosmans E, Kenis G, Maes M (2001). Increased serum tumor necrosis factor alpha concentrations in major depression and multiple sclerosis. *European Neuropsychopharmacology* 11, 203–208.
- Mills TL (2001). Comorbid depressive symptomatology: isolating the effects of chronic medical conditions on self-reported depressive symptoms among community-dwelling older adults. *Social Science and Medicine* 53, 569–578.
- Mohr DC, Goodkin DE, Islar J, Hauser SL, Genain CP (2001). Treatment of depression is associated with suppression of nonspecific and antigen-specific T(H)1 responses in multiple sclerosis. *Archives of Neurology* 58, 1081–1086.
- Morag M, Yirmiya R, Lerer B, Morag A (1998). Influence of socioeconomic status on behavioral, emotional, and cognitive effects of rubella vaccination: a prospective, double blind study. *Psychoneuroendocrinology* 23, 337–351.
- Morikawa O, Sakai N, Obara H, Saito N (1998). Effects of interferon- $\alpha$ , interferon- $\gamma$  and cAMP on the transcriptional regulation of the serotonin transporter. *European Journal of Pharmacology* 348, 317–324.
- Mossner R, Daniel S, Schmitt A, Albert D, Lesch KP (2001). Modulation of serotonin transporter function by interleukin-4. *Life Science* 68, 873–880.
- Mossner R, Heils A, Stober G, Okaldnova O, Daniel S, Lesch KP (1998). Enhancement of serotonin transporter function by tumor necrosis  $\alpha$  but not by interleukin-6. *Neurochemistry International* 33, 251–254.
- Mtabaji JP, Manku MS, Horrobin DS (1977). Actions of the tricyclic antidepressant clomipramine on responses to pressor agents: interactions with prostaglandin E<sub>2</sub>. *Prostaglandins* 4, 25–132.
- Musselman DL, Lawson DH, Gumnick JF, Manatunga AK, Penna S, Goodkin RS, Greiner K, Nemeroff CB, Miller AH (2001). Paroxetine for the prevention of depression induced by high dose interferon alpha. *New England Journal of Medicine* 344, 961–969.
- Natelson BH, Denny T, Zhou XD, LaManca JJ, Ottenweller LE, Tiersky L, DeLuca J, Gause WC (1999). Is depression associated with immune activation? *Journal of Affective Disorders* 53, 179–184.
- Nickola TJ, Ignatowski TA, Reynolds JL, Spengler RN (2001). Antidepressant drug-induced alterations in neuron-localized tumor necrosis factor- $\alpha$  mRNA and  $\alpha$ (2)-adrenergic receptor sensitivity. *Journal of Pharmacology and Experimental Therapeutics* 297, 680–687.
- Patten SB (2001). Long-term medical conditions and major depression in a Canadian population study at waves 1 and 2. *Journal of Affective Disorders* 63, 35–41.
- Peter D, White MD (1999). Do viruses cause depressive illness? *General Hospital Psychiatry* 21, 18–20.
- 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.
- Plotsky PM, Owens MJ, Nemeroff CB (1998). Psychoneuroendocrinology of depression. Hypothalamic–pituitary–adrenal axis. *Psychiatric Clinics of North America* 21, 293–307.
- Rabkin JG, Wagner G, Rabkin R (1994). Effects of sertraline on mood and immune status in patients with major depression and HIV illness: an open trial. *Journal of Clinical Psychiatry* 55, 433–439.
- Raison CL, Miller AH (2001). The neuroimmunology of stress and depression. *Seminars in Clinical Neuropsychiatry* 6, 277–294.
- Ramamoorthy S, Ramamoorthy JD, Prasad PD, Bhat GK, Mahesh VB, Leibach FH, Ganapathy V (1995). Regulation of the human serotonin transporter by interleukin-1 $\beta$ . *Biochemical and Biophysical Research Communications* 216, 560–567.
- Reichenberg A, Schuld A, Kraus T, Haack M, Pollmächer T, Yirmiya R (In Press). Endotoxin-induced anorexia in healthy human volunteers is mediated by cytokine secretion. *Psychoneuroendocrinology*.
- Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Pollmächer T (2001). Endotoxin-induced emotional and cognitive disturbances in healthy volunteers are associated with increased plasma levels of cytokines and cortisol. *Archives of General Psychiatry* 58, 445–452.
- Robinson RG (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.
- Rothermundt M, Arolt V, Fenker J, Gutbrodt H, Peters M, Kersting A, Kirchner H (2001b). Inflammatory markers in major depression and melancholia. *Journal of Affective Disorders* 63, 93–102.
- Rothermundt M, Arolt V, Fenker J, Gutbrodt H, Peters M, Kirchner H (2001a). Different immune patterns in melancholic and non-melancholic major depression. *European Archives of Psychiatry and Clinical Neuroscience* 251, 90–97.
- Schiffer RB, Babigian HM (1984). Behavioral disorders in multiple sclerosis, temporal lobe epilepsy, and amyotrophic

- lateral sclerosis: an epidemiological study. *Archives of Neurology* 41, 1067–1069.
- Schiffer RB, Wineman NM (1990). Antidepressant pharmacotherapy of depression associated with multiple sclerosis. *American Journal of Psychiatry* 147, 1493–1497.
- Schlatter J, Ortuno F, Cervera-Enguix S (2001). Differences in interleukins' patterns between dysthymia and major depression. *European Psychiatry* 16, 317–319.
- Schubert DSP, Foliart RH (1993). Increased depression in multiple sclerosis patients: a meta analysis. *Psychosomatics* 34, 124–130.
- 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.
- Shen Y, Connor TJ, Nolan Y, Kelly JP, Leonard BE (1999). Differential effect of chronic antidepressant treatments on lipopolysaccharide-induced depressive-like behavioural symptoms in the rat. *Life Science* 17, 1773–1786.
- 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.
- Smith AP, Thomas M, Brockman P, Kent J, Nicholson KG (1993). Effect of influenza B virus infection on human performance. *British Medical Journal* 306, 760–761.
- Smith AP, Tyrrell DAJ, Barrow GI (1992). Mood and experimentally induced respiratory virus infections and illness. *Psychology and Health* 6, 205–212.
- Smith RS (1991). The macrophage theory of depression. *Medical Hypotheses* 35, 298–306.
- Sommer N, Loschmann PA, Northoff GH, Weller M, Steinbrecher A, Steinbach JP, 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 BE (1994). An acute phase protein response in the olfactory bulbectomized rat: effect of sertraline treatment. *Medical Science Research* 22, 313–314.
- Thomas AJ, Ferrier IN, Kalaria RN, Woodward SA, Ballard C, Oakley A, Perry RH, O'Brien JT (2000). Elevation in late-life depression of intercellular adhesion molecule-1 expression in the dorsolateral prefrontal cortex. *American Journal of Psychiatry* 157, 1682–1684.
- Valentine AD, Meyers CA, Kling MA, Richelson E, Hauser P (1998). Mood and cognitive side effects on interferon-alpha therapy. *Seminars in Oncology* 25, 39–47.
- Van Heeringen K, Zivkov M (1996). Pharmacological treatment of depression in cancer patients. A placebo-controlled study of mianserin. *British Journal of Psychiatry* 169, 440–443.
- Watkins LR, Maier SF (1999). Implications of immune-to-brain communication for sickness and pain. *Proceedings of the National Academy of Sciences USA* 6, 7710–7713.
- Watkins LR, Nguyen KT, Lee JE, Maier S (1999). Dynamic regulation of proinflammatory cytokines. *Advances in Experimental Medicine and Biology* 461, 153–178.
- 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.
- Xia Z, DePierre JW, Nassberger L (1996). Tricyclic antidepressants inhibit IL-6, IL-1 $\beta$  and TNF- $\alpha$  release in human blood monocytes and IL-2 and interferon- $\gamma$  in T-cells. *Immunopharmacology* 34, 27–37.
- Xia Z, Karlsson H, DePierre JW, Nassberger L (1997). Tricyclic antidepressant induce apoptosis in human T lymphocytes. *International Journal of Immunopharmacology* 19, 645–654.
- Yaron I, Shirazi I, Judovich R, Levartovsky D, Caspi D, Yaron M (1999). Fluoxetine and amitriptyline inhibit nitric oxide, prostaglandin E<sub>2</sub>, and hyaluronic acid production in human synovial cells and synovial tissue cultures. *Arthritis and Rheumatism* 42, 2561–2568.
- 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 (2000). Depression in medical illness: the role of the immune system. *Western Journal of Medicine* 173, 333–336.
- Yirmiya R, Pollak Y, Barak O, Avitsur R, Ovadia H, Bette M, Weihe E, Weidenfeld J (2001). Effects of antidepressant drugs on the behavioral and psychological responses to lipopolysaccharide (LPS) in rodents. *Neuropsychopharmacology* 24, 531–544.
- Yirmiya R, Pollak Y, Morag M, Reichenberg A, Barak O, Avitsur R, Shavit Y, Ovadia H, Weidenfeld J, Morag A, Newman ME, Pollmacher T (2000). Illness, cytokines and depression. *Annals of the New York Academy of Sciences* 917, 478–487.
- Yirmiya R, Weidenfeld J, Pollak Y, Morag M, Morag A, Avitsur R, Barak O, Reichenberg A, Cohen E, Shavit Y, Ovadia H (1999). Cytokines, 'depression due to a general medical condition', and antidepressant drugs. *Advances in Experimental Medicine and Biology* 461, 283–316.
- Zaharia MD, Ravindran AV, Griffiths J, Merali Z, Anisman H (2000). Lymphocyte proliferation among major depressive and dysthymic patients with typical or atypical features. *Journal of Affective Disorders* 58, 1–10.
- Zhu J, Bengtsson BO, Mix E, Thorell LH, 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, 225–244.
- Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, McCorkle R, Seligman DA, Schmidt K (2001). The relationship of depression and stressors to immunological assays: a meta-analytic study. *Brain, Behavior and Immunity* 15, 199–226.
- 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.