CHAPTER 7

A MODEL OF PSYCHONEUROIMMUNOLOGICAL INTERACTION

This chapter illustrates the practical implications of the psychoneuroimmunological (PNI) interactions presented in previous chapters. It therefore demonstrates the mind-body link in PNI context. A model of sickness behaviour in PNI context is presented as a condition of adaptational mind-body homeostasis and it is argued that abnormalities in the regulatory feedback processes could potentially lead to psychological and other disturbances. It is shown that experiences during early life could predispose to abnormal feedback mechanisms and thus to increased vulnerability to stress-induced mental and physical problems. The hypothesis is put forward that uncontrolled sickness behaviour may lead to any of a number of mental disturbances. Scientific evidence is provided in support of the hypothesis.

Introduction

The previous chapters dealt with evidence of the pervasive interaction between the immune system and the behavioural functions, as well as the mechanisms through which the various communications occur. In this, the final chapter, the practical implications of the psychoneuroimmunological interactions will be demonstrated. Sickness behaviour will be presented as heuristic model to show the important role of the psychoneuroimmunological influence on psychological health.. The potential danger of deviations in the regulatory feedback mechanisms, as well as the role of predisposition by early life experiences and negative emotions will be illustrated by presenting sickness behaviour in psychoneuroimmunological context.

Psychoneuroimmunology is a young discipline in which most of the empirical evidence was initially derived from the biomedical sciences. However, in the last couple of years an increase was seen in the output of psychoneuroimmunological studies from researchers in the humanities and from cooperation between the humanities and the

biomedical sciences. These interdisciplinary efforts between the humanities and the biomedial sciences helped to decipher underlying mechanisms of a number of psychological phenomena and to understand the practical implications of some of the neuroimmunological interactions. The majority of the psychoneuroimmunological studies that were performed primarily from the psychological perspective focused on the influence of negative emotions and events on health.

The concept that emotions can influence physical and mental health is generally well accepted by most disciplines. Indications from psychoneuroimmunological studies are that negative emotions such as depression, anxiety, hostility and anger may be among those posing the worst threats to health and that they may significantly increase morbidity and mortality rates (1). It is a well-established fact that negative emotions can also indirectly influence health by promoting unhealthy life styles that include drug abuse, and a decline in attention to nutrition, exercise, sleep requirements and hygiene (2). The effects of these indirect effects on health would appear to speak for themselves, but the underlying mechanisms for the direct effects are less clear. For many years the focus has primarily been on the neuroendocrine system in trying to explain the adverse effects of negative emotions on health. However, these neuroendocrine mechanisms could only account for a minority of the direct pathways through which negative emotions can influence health. Recently, through psychoimmunological investigations, it has become clear that stressors like negative emotions can lead to immune dysregulation and in this way have a negative influence on health. This can lead to persistent increases in peripheral pro-inflammatory cytokine levels with, as shown in the previous chapter, a positive feedback to cerebral cytokine production and sustained negative emotions (1,3). A vicious cycle indeed. In addition to the role of the immune system in the direct pathways, it has further become clear that immunological processes are also involved in the indirect effects of negative emotions on health and that the effects of sleep deprivation, malnutrition, drug abuse and other life style factors are often partially mediated through their effects on the immune system (2, & Chapter 1). Immune dysregulation is, in fact, not only involved in mediating the effects of these life style factors but could, as will be seen later in this chapter, be instrumental in contributing to

the abnormal sleep patterns, poor eating habits, drug abuse and other "unhealthy" behaviours which may result from negative emotions.

As in several other approaches to health or stress, psychoneuroimmunological investigations on the effects of negative emotions have been far more intensively researched than that on positive emotions. The following quotation is a good assessment of the situation

Although it is clear that negative emotions can intensify a wide variety of health threats, positive emotions have received considerably less attention, perhaps related to the prevailing view of physical and mental health as the absence of disease and negative emotions, as well as the fact that positive emotions are fewer in number and less differentiated than negative emotions. Indeed, although a substantial empirical literature exists for depression and objective measure of health, almost none exists for happiness and health, ----

Kiecolt-Glaser *et al*, 2002 (1)

The pathogenic potential of stressors, independent of whether the stressor is primarily mental or physical, is fairly unpredictable and no linear relationship can summarily be assumed between the type, or intensity, of the stressor and the outcome. The main determinants of the outcome would appear to be the presence of vulnerability and resilience factors, as well as predisposition to stress vulnerability. Psychoneuroimmnological studies to date have identified a number of vulnerability and resilient factors that can influence the outcome - partially by altering immune function. These factors, recently reviewed by Kiecolt-Glaser *et al*, 2002 (1,3), include sociodemographic variables (age, gender, socio-economic status, culture, ethnic identity and minority status), social relationships (personal relationships, social support), as well as personality traits and coping styles. These studies, in general, showed high vulnerability and low resilience often to be accompanied by increases in pro-inflammatory cytokine production – especially IL-6.

The other main determinant of stress outcome, as mentioned in the previous paragraph, is predisposition, either genetic or as a result of early life experiences. The predisposition-stress model (4) explains why only some individuals develop psychopathology in reaction to stressors and why those who do develop psychopathology can develop different disorders in response to the same stressor. It distinguishes between *necessary* conditions, such as predispositioning by previous life experiences and genetics without which psychopatholgy cannot develop, and *sufficient* conditions, i.e., the interactive and cumulative effects of predispositioning and stressors, that will inevitably lead to the development of psychopathology (4).

It is thus fairly indisputable that negative emotions can influence mental as well as physical health and that the immune system forms part of the pathways involved. The question remains whether, and if so how, disturbances in health can lead to negative emotions and behavioural dysfunction. Behavioural reactions like reactive depression or anger in the face of pain or disability are well known and do not warrant any further discussion. It is, however, also becoming clear that infectious conditions can lead to behavioural changes through cerebral cytokine-induced alterations in neurohormonal activity. The underlying mechanisms of cytokines on the behavioural functions were discussed in Chapter 6.

In the remainder of this chapter sickness behaviour, not to be confused with illness behaviour, will be discussed as a condition where negative emotions, other than reactive in origin, can develop as a result of physical illness. It will be seen that the illness does not necessarily need to be primarily infection-related and that sickness behaviour can, in fact, also result from psychological stress. Cross-sensitisation between psychological and physical stressors will be shown to exacerbate the behavioural symptoms. A hypothesis, postulating that the neurobehavioural symptoms of sickness behaviour can, depending on predispositioning, become mental disturbances, will be presented and defended. In this presentation the disease process will be seen as the precipitating stressor and sickness behaviour as the adaptive homeostasis.

The layout of this chapter comprises

7.1 Sickness behaviour as model of the psychoneuroimmunological interaction

- 7.1.1 Behavioural symptoms of sickness behaviour
- 7.1.2 Underlying mechanisms of sickness behaviour
- 7.1.3 The value of sickness behaviour as state of adaptation
- 7.1.4 Control of sickness behaviour

7.2 The influence of early life experience – predisposition or stress resistance

- 7.2.1 The effects of early life experiences on the neuroendocrine systems involved in behaviour
- 7.2.2 The effects of early life experiences on the immune system
- 7.2.3 Mechanisms underlying the predisposition to stress hyperresponsiveness, hyporesponsiveness and stress resistance

7.3 Termination of the symptoms of sickness behaviour and failure to terminate the response

7.4 The Hypothesis: Uncontrolled sickness behaviour may lead to any of a number of mental disturbances – partially dependent on predisposition by early life experiences

- 7.4.1 Mental disorders as a continuation of sickness behaviour

7.5 Summary

7.1 Sickness behaviour as a model of the psychoneuroimmunological interaction

7.1.1 Behavioural symptoms of sickness behaviour

Sickness behaviour is generally defined as the coordinated set of behavioural changes that develop during infection. However, as will be discussed later in this chapter, sickness behaviour can also be initiated by other factors and conditions. The symptoms of sickness behaviour include disinterest in the physical and/or social environment (often transiently accompanied by a lethargic, depressive mood, anhedonia and sometimes irritability), decreased locomotor activity, loss of reproductive drive, a decrease in body-care activities, fever, sleepiness and a loss of appetite - despite increased metabolic needs for the fever response (5,6). What is seldom recorded and yet experienced by many who suffered prolonged periods of illness is that behavioural symptoms such as feelings of worthlessness, guilt, nihilism and even suicidal contemplations may occur. It is perhaps of interest to quote Charlton, 2000 (7) when he wrote

The state of malaise, which prevails in sickness behaviour interacts with memories of the past and anticipations of the future such that a demotivated exhausted and profoundly dysphoric state of malaise fills and colors past, present, and the anticipations of future mental life. Prolonged sickness behavior therefore creates a nihilistic mental state where life seems devoid of gratifying possibilities (i.e. pessimism) because feedback to the brain registers a physiological state (i.e. emotion) that is locked into sickness behavior, and unresponsiveness to the usual appetites (i.e. anhedonia). Another factor is that the sufferers from sickness behavior does not know that they are sick, and often interpret their lack of energy, lack of motivation and poor concentration as a moral failure – leading to feelings of guilt and unworthiness. Charlton, 2000 (7).

There may be much to criticise in the above description, especially the assumption that the emotional components are described as locked into sickness behaviour. This, as we are by now fully aware of the fact that the behavioural aspects constitute a major part of sickness behaviour. The description of Charlton does, however, verbalise those aspects of sickness behaviour that are hardly ever expressed in writing.

Despite the bleak picture painted above, sickness behaviour is, in fact, not primarily a sickness-induced weakness and debilitation, but intended as a new mind-body homeostasis meant to enable the individual to best counteract the infection or whatever other stressor initiated the process. Sickness behaviour has very eloquently been described as a central motivational state with selection of the appropriate strategy in response to the eliciting disease, in other words, a reorganisation of behavioural and other coping activities (5,6). There is ample evidence to show that, if any other factor is perceived to threaten the survival and wellbeing of the individual more than the infectious complication, it would override the sickness behaviour, e.g., the fear motivational state may take precedence over the sickness motivational state (5,8,9), and behaviour would be aimed at counteracting whatever elicited the fear. Sickness behaviour can thus be seen as a state of adaptive perceptions and reorganisation of coping responses. It therefore speaks for itself that the CNS must be signalled as to the severity of the peripheral infection or inflammatory activity and that sickness behaviour must be controlled from within the central nervous system.

The signalling process from the periphery to the brain occurs via the induction of cerebral cytokine production by inflammatory cytokines released in response to peripheral infectious or inflammatory conditions, while the brain signals and controls the sickness behaviour through neurohormonal mechanisms. The following short description briefly deals with the adaptational value of sickness behaviour, and the underlying processes.

7.1.2 Underlying mechanisms of sickness behaviour

Sickness behaviour is initiated by pro-inflammatory cytokines produced by activated monocytes and macrophages in response to infections. In addition, gram-negative bacteria-derived lipopolysaccharides (LPS) can also stimulate the process by binding to the CD14 receptor on these mononuclear phagocytes. The major pro-inflammatory cytokines involved in sickness behaviour are IL-1, IL-6 and TNFα (10), with IL-1 seen as the prototypical pro-inflammatory cytokine (11). T cell-derived IL-2, in addition to the pro-inflammatory cytokines from mononuclear cells, may also contribute to the symptoms of sickness behaviour. The role of the IL-1 family, i.e., IL-α, IL-1β, the

receptor antagonist cytokine IL-1ra, and the receptors involved in sickness behaviour is rather complicated and is not discussed in detail. Suffice to say that IL-1β is produced as precursor, that several factors are involved in controlling the conversion to the active cytokine and in controlling IL-1 activity at receptor level. At receptor level the actions of IL-1 are, for instance, regulated by the type I IL-1 receptor which, via nuclear transcription factor NFκB, functions as the signal transducer, while type II IL-1 receptor down-regulates IL-1 actions by acting as decoy receptor in binding excess IL-1. Receptor activation can further be downregulated by the receptor antagonist cytokine IL-lra, which prevents signal transduction (12).

Cytokines, produced by peripheral immune cells, can signal the brain to up-regulate cerebral cytokine synthesis and release. The way the signal reaches the brain targets and the subsequent signal transduction were discussed in the previous chapter.

The intracerebral effects of pro-inflammatory cytokines can directly as well as indirectly cause all symptoms of sickness behaviour. The direct mechanisms involve alteration of the basal activity of neurohormonal systems like the hypothalamo-pituitary-adrenocortical axis, the central noradrenergic system and the central serotonergic systems (13). Cytokines may in addition act in synergism with the HPA-axis to change tryptophan, and by implication, serotonin (5-HT) metabolism. Tryptophan in being transported from the circulation to the brain is converted to 5-hydroxytryptophan and then to serotonin. However, immunological factors may stimulate the enzyme indoleamine 2,3-dioxygenase and glucocorticoids may stimulate the enzyme tryptophan 2,3-dioxygenase which will switch tryptophan metabolism away from serotonin in favour of the production of kynurenine with a subsequent decrease in tryptophan availability for serotonin synthesis (14). Indirect mechanisms involve activation of intermediates such as prostaglandin synthesis and nitric oxide (NO) release through intracerebral cytokine-induced COX-2 and inducible nitric oxide synthase (iNOS) activation. These intermediates are implicated in the alteration of neural pathways involved in several symptoms of the sickness behaviour, including somnolence, fever, as well as those physiological and behavioural symptoms mediated through activation of the central CRH

system and HPA-axis (5,15,16,17). For more detail on the contribution of specific cytokines on individual components of sickness behaviour the reader is referred to an overview by Dantzer *et al,* 1999 (18).

7.1.3 The value of sickness behaviour as state of adaptation

The value of fever during infection is still strongly debated. However, several arguments favour fever as an essential component of the host response to infection, including a) the argument that it is unlikely that a process as costly, in terms of energy expenditure, would have persisted throughout evolution if it did not have a function, b) the results of many studies which show that fever during bacterial infections is associated with a better prognosis, c) the increase in morbidity and mortality in animal studies on the use of antipyretics to attenuate fever, d) experimental evidence from hyperthermia and hypothermia studies which showed an adaptive function for hyperthermia and e) the highly regulated nature of fever which implies that fever must have developed as a host defense mechanism (19). Fever is further known to play a role in the suppression of microbial growth in iron-poor environments. It is also known to enhance a number of facets of the immune response such as stimulation of the expression of adhesion molecules that enhances leukocyte migration, proliferation of T cells, bactericidal activity of neutrophils and the pro-inflammatory cytokine profile (19,20,21). In addition, it is said to protect against the infection-induced disturbance of membrane lipids by phospholipase, and in so doing protect the integrity of membranes with regard to signal transduction and receptor expression (22).

The value of somnolence, another well-recognised characteristic of infectious diseases, is generally accepted, but poorly investigated. There are numerous studies to support the assumption of a negative effect of sleep deprivation on immunity, on neurohormonal activities and on behaviour. There is, however, very little research on the direct positive effects of sleep. One of the very few studies on the effects of excessive sleep showed increased NREM sleep to positively correlate with survival (23).

The behavioural effects of sickness behaviour largely correspond to those of depression. Similarities include fatigue, psychomotor slowing, anorexia, lethargy, suppression of certain cognitive abilities such as thinking and concentration, low interest in socializing and reproductive activities, as well as anhedonia. It is therefore not surprising to learn that the same cytokine profile is seen in the majority of patients with severe depression. In fact, the immunological profile of severe depression would further appear to be similar to that of the acute phase reaction, including the increases in plasma complement factors, increases in positive acute phase proteins, decreases in negative acute phase proteins, changes in T-cell numbers and activity, the release of inflammatory mediators, and many other similarities (24.25). The adaptive advantage of cytokine-induced depression during infectious disorders probably lies in the fact that it forces the individual not to get involved in activities which will test his or her coping abilities, to slow down, and to conserve energy expenditure for the adaptive febrile response and for immunological activity (26,27). The suppression of eating and reproductive behaviours are said to reduce the intake of nutrients (especially iron) necessary for the proliferation of the pathogen, and to prevent conception in the sick female individual – a risk factor for abortion and abnormal development (27). It should be stressed that cytokine-induced sickness behaviour is not only initiated by infectious conditions, but can develop in many non-infectious general medical conditions. Cytokine-induced sickness behaviour is for instance known to manifest in some cases of chronic inflammatory and autoimmune diseases, neurodegenerative conditions and post-partum (27). It may even be initiated by psychological stressors, as will be seen later in this chapter.

The symptoms of sickness behaviour may very well underlie some of the neuro-behavioural changes seen as poor patient compliance or illness behaviour - a personality and culture-dependent behavioural when ill. It is, however, important to remember that sickness behaviour and illness behaviour are two separate, albeit interacting, entities.

7.1.4 Control of sickness behaviour

Cytokine-induced sickness behaviour is of significant adaptational value, but unwarranted continuation of this syndrome has a serious down side. It is therefore of great importance that infection-induced synthesis and activity of pro-inflammatory

cytokines be strictly controlled and limited to the period of the disease. The short-term effects of severe, uncontrolled activity on multiple organ functions are well known. However, mild to moderately increased pro-inflammatory cytokine activity after recuperation from the infectious condition has its own problems. Such continued activity of the pro-inflammatory cytokine response can lead to cognitive and emotional problems, as well as to other psychological and physical symptoms that can impair the quality of life. Cognitive and emotional effects include the inability to concentrate, irritability, bad temper, anhedonia, apathy, or even anxiety and depression, while physical signs include symptoms like fatigue, headaches, swollen lymph nodes and sore throat (27,28). During prolonged severe sickness the behavioural patterns may turn into feelings of worthlessness, guilt and helplessness. Prolonged continuation of the symptoms of sickness behaviour has on occasion been implicated in the post-viral fatigue and chronic fatigue syndromes (27,29) and many sufferers would support the idea of the presence of feelings of worthlessness and helplessness in these conditions. More severe psychiatric/psychological effects of cytokines have been described in the previous chapter and it is thus theoretically possible that a continued high level of cytokines as a result of non-termination of sickness behaviour may have similar effects. The importance of termination of the inflammatory response upon recovery from the initiating disturbance is therefore abundantly clear.

Several substances are involved in the control of pro-inflammatory activity, including the anti-inflammatory cytokines, glucocorticosteroids, ADH, α-melanocyte stimulating hormone, the SAM-axis and certain members of the interleukin-1 family (5,30,31). The molecular mechanisms involved in containment of the sickness response are sometimes referred to as the cryogens (32). The role of the glucocorticosteroids are generally that of normal negative feedback. The HPA-axis, as previously mentioned, is stimulated by pro-inflammatory cytokines. The glucocorticoids thus secreted can in turn control the cytokine-induced effects a) by down-regulation of pro-inflammatory cytokine synthesis and release through inhibition of transcriptional and post-transcriptional expression of the IL-1β gene and decreasing the stability of the IL-1β mRNA, b) by decreasing the ratio of type I IL-1 to type II IL-1 receptors, and c) by suppressing the conversion of proIL-1β to

its biological active form through inhibition of the IL-1β converting enzyme (30, 33,34,35). ADH, a substance that acts in synergism with CRH, as shown in Chapter 5, is also involved. Fever-induced ADH secretion has, for instance, been shown to limit the suppressive effect of IL-1β on the behavioural functions (33).

Failure of any one of the factors involved in terminating the inflammatory process can contribute to the continuation of the sickness behaviour. An interesting phenomenon is the fact that the pro-inflammatory cytokines themselves can contribute to the continuation by inducing glucocorticoid resistance. Interleukin-1α was, for instance, shown to suppress glucocorticoid translocation and glucocorticoid-mediated gene transcription (36) and consequently inhibit the negative feedback on the production of pro-inflammatory cytokines.

There are indications that some antidepressant drugs may be successful in the treatment of the cytokine-induced depression (27,36). Whether this is mediated through a suppression of the induction of pro-inflammatory cytokines by activated immune cells, glial cells or neurons, or through their effects on the cytokine-induced changes in the neurohormonal activity is, in many cases, still under investigation. This aspect will be returned to at a later stage.

To summarise this writing on sickness behaviour, it can be said that sickness behaviour is a good practical example of the psychoneuroimmunological interaction. It should be seen as a new mind-body homeostasis – a functional homeostatic adaptation caused by the induction of pro-inflammatory cytokine production in the brain, rather than a debilitating side effect of infectious diseases. However, if this pro-inflammatory activity is not terminated after recuperation from the infectious condition it may lead to emotional, cognitive and physical problems that can impair the quality of life.

In the previous chapter it was shown how peripheral immunological events can stimulate central nervous system cytokine production with subsequent changes in the neuroendocrine systems and an eventual new mind-body homeostasis in which the

physical and psychological changes are intended to aid in coping with the stressor – the stressor in this case being the infectious condition (Figure 6.1, Chapter 6). This diagram can now, based on the discussion of sickness behaviour, be extented into a schematic presentation of sickness behaviour in psychoneuroimmunological context (Figure 7.1). Figure 7.1 shows how infection can, through the induction of cerebral cytokine production, lead to changes in central nervous system activity and alterations in stress system set points. This could then shift the total mind-body homeostasis to a sickness behaviour homeostasis, which includes adaptations in neurohormonal functioning, behaviour, metabolic and motor function, as well as adaptive immunological alterations. Upon recuperation from the infectious affliction, anti-inflammatory cytokines, glucocorticoids, ADH and several other factors are involved in the termination of the immunologically induced stress response, and return to the original homeostasis should occur. The symptoms of sickness behaviour can be seen at the bottom of the diagram. It is also indicated that once the stimulus is gone, i.e., the infection is cleared, factors that counteract the sickness behaviour symptoms by returning the neuroendocrine homeostasis to normal must come into action. Failure to do so may have serious physical and mental implications.

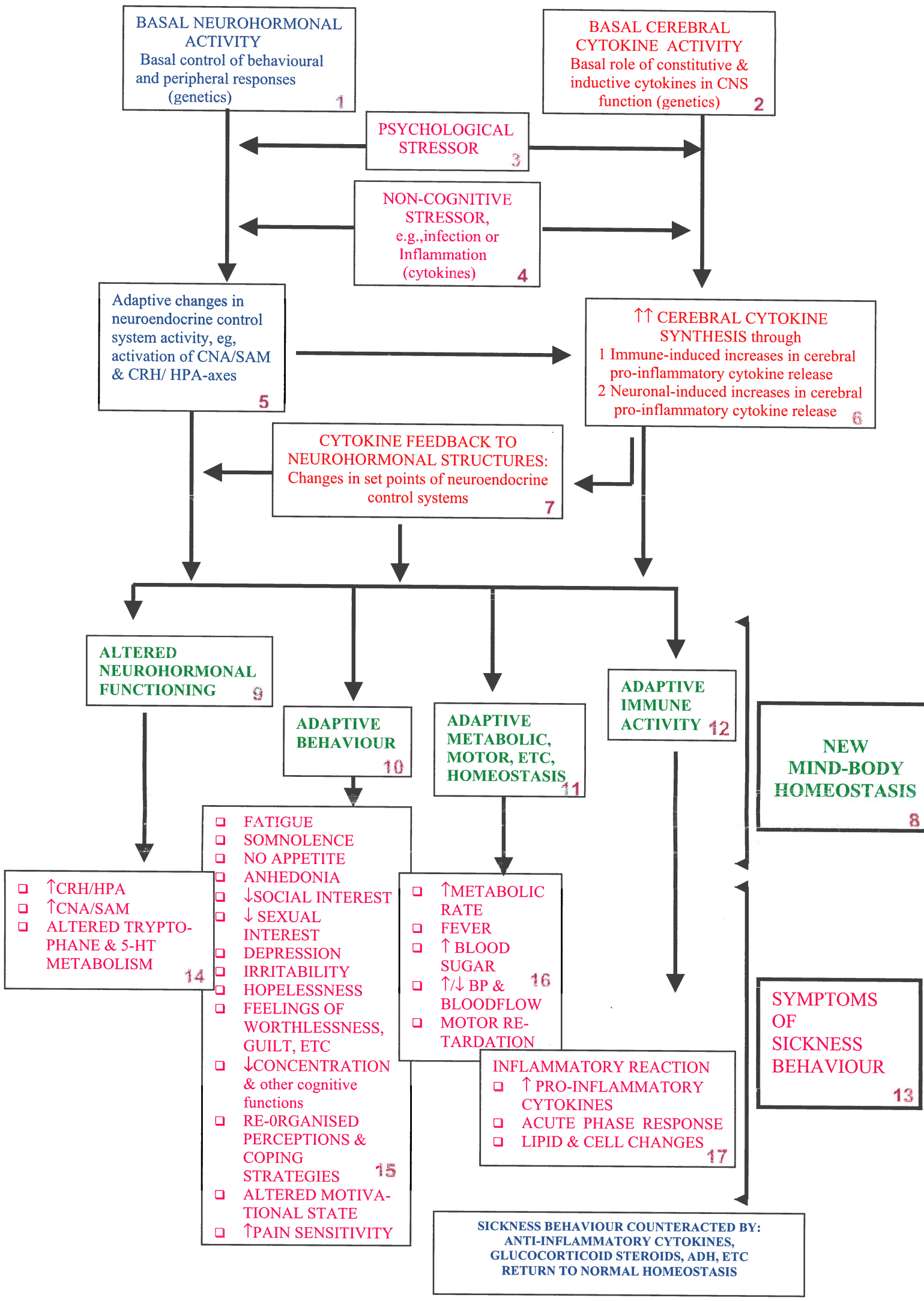

Figure 7.1: Sickness behaviour in psychoneuroimmunological perspective.

[1 and 2 represent the basal neurohormonal and basal immunological activity of the brain.These basal activities can be stimulated both by psychological sressors (3) and, as the case of infections, trauma and inflammatory conditions, by peripherally derived cytokines (4). The increase in basal neurologicical activity (5) would induce further cerebral cytokine production. Cerebral cytokine production is thus increased (6) as a result of peripheral immune activity as well as the increased neuronal activity. The marked increase in cerebral cytokine activity (6) can in turn feedback to the neurohormonal systems to bring about changes in their set points (7). The altered cerebral neurohormonal and cytokine activity will lead to a new adaptive mind-body homeostasis (8) intended to help cope with the stressor. Components of the new adaptive homeostasis include altered neurohormonal functioning (9), adaptive behavioural functions (10), adaptive metabolic and motor function (11) and adaptive immunological activity (12). The symptoms specific for the adaptive homeostasis of sickness behaviour (13) are shown in 14, 15, 16 and 17.]

Legend to Figure 7.1

Figure 7.1: Sickness behaviour in psychoneuroimmunological perspective

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It is, as previously mentioned, essential that sickness behaviour be terminated at the appropriate time in order to prevent secondary behavioural effects. Before addressing the consequences of a failure in the correct negative feedback mechanisms for mental health we must first ask whether the vulnerability of the CNS cytokine-neuroendocrine mechanisms responsible for the sickness behaviour is dependent merely on the qualities of the initiating stressor and the genetic disposition or whether predisposition to either the development or inappropriate continuation may occur as a result of previous life experiences. These aspects will be addressed in the following sections.

7.2 The influence of early life experience

In Chapters 4, 5 and 6 it was shown that a bidirectional influence exists between the basal neuroendocrine and the basal immunological activities of the brain. Should either of these basal processes be altered by early life experiences, or rather by previous life experiences, it speaks for itself that deviations from the norm could develop and that it may even predispose to what is artificially separated into physical and behavioural disorders. In Figure 7.2 it is asked whether such changes can indeed develop.

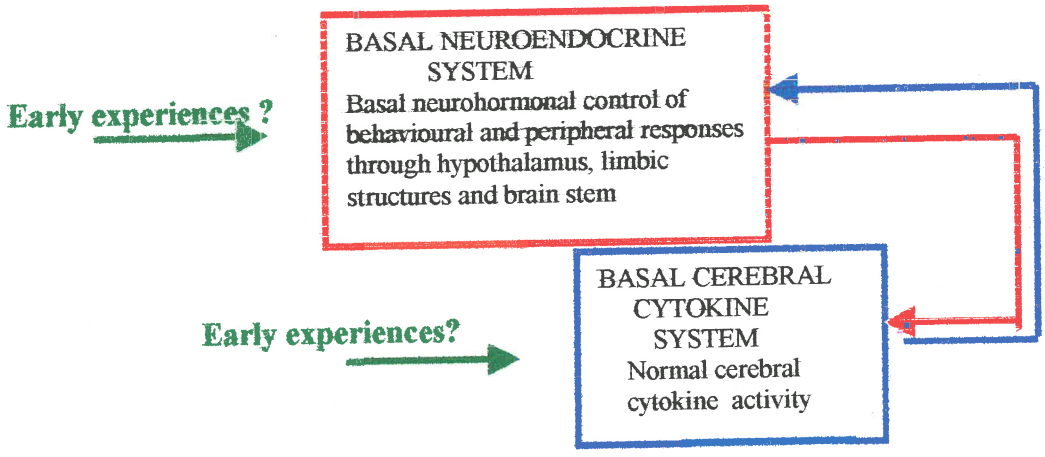

Figure 7.2: Can changes in the basal responsiveness of the neuroendocrine or cerebral cytokine systems predispose to mental and physical disorders?

The next two sections will show that early life experiences can change the basal neuroendocrine activity of the two main stress axes as well as the basal activity of the immune system and by implication predispose to physical and psychological abnormalities.

7.2.1 The effects of early life experiences on the neuroendocrine systems involved in behaviour

Genetics are known to have an influence on behaviour, but it is also widely accepted that early psychosocial life experiences can have a marked impact on the psychological wellbeing of adulthood. The latter is sometimes referred to as the non-genetic transfer of behavioural characteristics. The influence of early life experiences on the stress axes-related neuroendocrine systems involved in behaviour were already touched upon in previous chapters where the psychoneurological interactions were discussed in terms of the two main stress axes. The emphasis was, however, to some degree on the structural changes of the brain as a result of unfavourable environmental conditions rather than on the long-term implications for psychological and physical health. In general there can be no doubt that adverse psychosocial experiences during early life will have negative effects on both the physical and the psychological adaptations and health. These negative consequences are largely the reflections of alterations in the neuroendocrine structure and function. In short, one can say that infants are born with a genetic predisposition (37), which will partly determine their adult behavioural responses as well as the type of pathology they may develop when under severe or continuous stress (38,39). However, in addition to the genetic-make-up, early rearing experiences fundamentally influence the outcome by priming the individual to react in certain ways in the face of a stressor. The next couple of paragraphs will deal with environmental predisposition of the two main stress axes during early life and will show that small variations in early rearing experiences may have a marked impact on adulthood stress responsiveness.

It is of great importance to know how infants are primed, in other words predisposed to specific behavioural patterns and disease susceptibility during adult life. Within this context the primary caregiver and the early family environment are critical in modulating

the infant's physiological arousal state and serve as major source of vulnerability during adult life. It largely determines the development of the infant's long-term stress response – a factor that will eventually determine the degree of stress vulnerability or resistance (40). Various factors play a role in determining the eventual stress vulnerability of the individual, including the nature of the cortical networks formed during critical stages of brain development. It is known that normal brain development and maturation require external stimulation for the formation of the appropriate cortical networks (41). These cortical networks are initially formed by the overabundant production of synapses – which are then sculpted by a process of parcellation, i.e., activity-dependent fine-tuning of connections and loss of excess circuitry (42). It is here that early experiences are critical. Early experiences determine the circuit wiring of, amongst others, the orbitofrontal cortex, which in turn contributes to the regulation of the responsiveness of the stress response – including the responsiveness of the autonomic nervous system – and monitors and adjust emotional responses (43). Environmental stressors can lead to dysregulated stress hormone levels in the brain that may give rise to pathomorphogenesis (43). During these critical periods of maturation developing neurons will establish or maintain aberrant connections, or even die, if the infant is subjected to severely adverse rearing experiences. This may lead to impaired cortical control over behaviour. The process may very well also apply to *in utero* stress where maternal stress influences the foetus. In addition, abnormal seizure-like activity (kindling) may occur. This could have a hyperactivating effect (42,43). As discussed in Chapter 2 and 3, and previously mentioned in this paragraph, these external influences may, in addition to their influence on morphological properties further influence the secretion of central nervous system neurotransmitters which will have a further influence on neural development and plasticity (41).

As this thesis focuses on psychoneuroimmunology in terms of the two main stress axes, it is relevant to look at the influence of early life experiences on the structures and functions pertaining to these systems. It would indeed appear as if the neural structures of the CNA/SAM-axis and CRH/HPA-axis are of paramount importance in the predispositioning to stress vulnerability or stress resistance. This is not surprising if one

takes into account the key role they play as neuromodulators of cerebral cortex, limbic system and autonomic function. The importance of the CNA/SAM-axis in the behavioural functions and its interactions with other neuronal structures that play a role in emotions and cognition, i.e., the psychoneurology of the system were discussed in Chapter 3. The potential impact of early rearing experiences on adult life can, in fact, easily be understood from the details presented in Chapter 3. It was, amongst others, shown that the CNA/SAM-axis

- can be presensitised by adverse environmental conditions
- plays a role in fear conditioning and in the recall of adverse events
- is susceptible to modulation and modificaton by environmental and psychosocial influences, i.e., stress adaptation and presensitisation
- can, through stress-induced noradrenaline secretion, modulate gene expression
- is involved in behavioural adaptation to stressors and can through such experiences be instrumental in the development of functional, as well as dysfunctional coping skills
- can be linked to personality characteristics
- activity would appear to differ between children with different temperaments - with high autonomic threshold and quick return to baseline in the so-called easy child and the reverse situation with a high predisposition for reactivation in the so-called difficult child
- plays a role in the development of fear and anxiety disorders
- is associated with several behavioural characteristics and disorders marked by a variety of dysregulations in central noradrenergic activity
- has a pervasive interaction with other systems involved in cognition, emotions and stress sensitivity
- abnormalities occur with concomitant dysregulations in other neuroendocrine/behaviour modulator systems – reflecting a multidirectional interaction between the systems
- is vulnerable to modulation of its structure and functions by psychological processes such as thoughts and perceptions

- is a target for psychological experiences that can serve as biological response modifiers and in so-doing influence the central noradrenergic system by, amongst others, changing the variable gene expression of the system – a phenomenon of importance in perinatal learning. as well as adaptational development and modification
- demonstrates differences between the effects induced on its structure and functions by controllable *versus* the effects induced by uncontrollable stressors - effects that are very much dependent on the type of perception the individual has about a potential stressor.

Studies on the CNA/SAM-axis very often include the rest of the autonomic system, culminating in investigations that focus on the autonomic balance and its interactions with other brain structures. In general, there seems to be a link between the orbitofrontal cortex, hemispheric dominance, autonomic control – specifically the degree of sympathetic dominance - and early life experiences. This is markedly evident with regard to the attachment experiences of the young. It would appear as if proper integration between left hemispheric functions (verbal coping, etc) and right hemispheric function (emotionality), in which emotions originating from the right hemisphere are recognised and dealt with by the left hemisphere, must develop in order to remain physically and emotionally healthy. It seems that individuals who intellectualize, but ignore their emotions (left dominant) tend to develop physical illness, while those who feel (right dominant) but cannot work through their emotions, lean towards the development of mental problems (42,43,44,45). In addition, development of the right balance between sympathetic and parasympathetic responsiveness is important for emotional wellbeing and a mothering style that leads to a secure attachment between mother and infant is said to be a major determinant in the development of this autonomic balance. In this development the orbitofrontal cortex with its connections to just about all other regions is of major importance. The orbitofrontal cortex receives input from all sensory associations, has an output to motor areas, and projects extensively to limbic areas (42). Two limbic circuits exist. The first, i.e., the excitational ventral tegmental limbic system, (encompassing the anterior cingulate, insula, temporal pole, central nucleus of the

amygdala, olfactory areas, glutamate responsive NMDA receptors of mesocorticolimbic dopamine neurons in ventral tegmental areas of the anterior reticular formation and centres in the paraventricular nucleus of the hypothalamus), is associated with CNA/SAM-axis activation (42). The link between the sympathetic nervous system and the paraventricular nucleus (CRH/HPA-axis) has been discussed in previous chapters. The second, i.e., the inhibitory lateral tegmental limbic circuit (innervating noradrenergic neurons in the medulla, and the vagal complex in the brain stem caudal reticular formation) stimulates the parasympathetic areas of the hypothalamus (9). If the excitational limbic circuit is damaged by extensive parcellation during early life, the inhibitory limbic circuit, and thus the parasympathetic component of the autonomic nervous system, will be dominant (42,43). Parasympathetically mediated passive coping is said to be driven by the inhibitory limbic circuit and leads to withdrawal directed towards reduction of the emotional impact of stress (42,43). Such individuals will, in adult life, show reduced overt emotionality, but inefficiency in regulating high arousal states under stress conditions. They will be vulnerable to overregulation and internalising psychopathologies (42,43). Conversely, damage of the inhibitory circuit will lead to sympathetic dominance, leading to a susceptibility to underregulation and externalising psychopathologies. Under severe stress, both these circuits may be in a state of activation, leading to increased sympathetic and parasympathetic outflow (42,43). In ideal circumstances, both sympathetic and parasympathetic outflow would be low. Optimal health will thus ensue when left and right hemispheres are integrated, and all autonomic outflow is low. At this stage in time it would appear to be the most probable outcome of sensitive responsive mothering.

It is feasible to suspect that certain patterns may exist according to which individuals could be classified on the basis of their hemispheric and autonomic dominance and that early life experiences may play a role in the development of these patterns. In line with this, intellectualising persons (left hemisphere dominant) with sympathetic dominance will typically suppress their negative emotions like anger and unhappiness and be prepared to take responsibility (46,47). At some stage in their lives such people are bound to feel helpless (45,47) – a feeling which, in chronic context, is often associated with

depression. A possible contributing factor to left hemisphere/sympathetic dominance would appear to be a rearing style of conditional love, i.e., affection shown only when the child is ill or 'good' (49,50).

Intellectualising persons with parasympathetic dominance would appear to have learnt to suppress most emotions successfully. They are externally driven, with the workaholic as prototype. In addition, they often are compulsively self-reliant, accordingly do not feel helpless, and thus do not secrete excessive amounts of cortisol (51). The humoral immune system of these individuals is usually overactive, and allergies and autoimmune diseases commonly occur in this group (46). Because these persons are usually relatively unaware of their emotions, they may interpret their physical manifestations of anxiety on a purely physical basis, e.g., palpitations, light-headedness and an inability to swallow. They therefore may be diagnosed with somatisation (44,49). Maternal neglect would appear to play a role in the genesis of the above disorders.

If children are exposed to severe physical or sexual abuse in the critical period of brain maturation, the stress overload may lead to limbic kindling, with resultant increased sympathetic as well as parasympathetic outflow, experienced subjectively as emotional chaos (42,52). One way of coping with these extreme experiences would be to shut off emotions completely, and dissociate. Post-traumatic stress disorder (PTSD) and several dissociative disorders would seem to fit into this category. Dissociation in this context has an adaptive function by allowing a person not to become overwhelmed in the face of trauma (53). Imaging studies have shown that combat-related PTSD leads to smaller right hippocampal volumes, and thus presumably dominance of the left hippocampal system (54). The latter assumption may, however, not necessarily be extrapolated to what is conventionally seen as dissociation disorders. Interesting work in this context show that in individuals with depersonalisation disorder (dissociation disorder with anxiety, where behaviour is sometimes referred to as *thinking without feeling)* aversive events appear to activate mainly the right ventral prefrontal cortex (an area associated with emotion regulation), with very little activation of the insula and occipito-ventral cortex (areas associated with perception or emotion-sensitivity) (55).

The picture appears somewhat different when we look at those individuals who are aware of what they feel, i.e., right hemispheric dominance. These "emotional" individuals are more likely to develop psychiatric than physical disorders. Emotional persons with sympathetic dominance typically feel anxious, the rearing style to which they were subjected often characterised by unpredictability (50), and their early experiences marked by a feeling of diminished control - a known risk factor for later anxiety (53,56). Anxiety disorders, panic disorders, obsessive-compulsive disorders, and histrionic and schizotypal personality disorders seem to fit into this category. For example, studies have shown that persons with panic disorder had more often experienced early loss of a caregiver or extremely inadequate caregiving, and persons with agoraphobia reported more early separation from their mothers as well as parental divorce (53).

Persons who are aware of their emotions but with parasympathetic dominance are said to be characterised by feelings of anger or emptiness. Eating disorders, substance abuse, conduct disorder, depression and narcissistic, borderline and antisocial personality disorders would seem to fit into this category. Maternal rejection and/or sexual abuse may be common features of this group. It is for instance well known that sexual abuse is extremely common in the histories of patients with borderline personality disorder (53). Imaging studies have shown that severely sexually abused women have smaller left hippocampal volumes, and thus presumably dominance of the right hippocampal system (54). Antisocial personality is associated with harsh discipline, inadequate supervision, prolonged separation from caregivers, unaffectionate mothers and deviant fathers (53). Patients with eating disorders have a decreased ability to examine their own psychological states (which is a function of the left hemisphere), and divert distress by focussing on their bodies instead. Their parents typically indicated support, while actually undermining their daughters' confidence (53). Anti-serotonin and anti-dopamine antibodies may play a role in the eating disorders (57). There appears to be a significant genotype-environment interaction in the brain metabolism of serotonin, wherein the ultimate effect of a gene polymorphism is highly dependent on the specific early attachment experience of the individual (58).

Children with right-dominance who are exposed to severe emotional abuse (e.g. extreme humiliation) may not be able to cope, and simultaneous sympathetic and parasympathetic activation could occur (42). As these children become increasingly shut off from their reasoning capabilities (in the left hemisphere), they may tend towards psychosis (11). Chronic schizophrenics are said to have significantly reduced grey matter in the left anterior hippocampal-amygdalar region (45). Furthermore, children at high risk for schizophrenia, have been reported to show left-sided movement abnormalities when challenged, reflecting overactivity of ascending dopaminergic systems in the right hemisphere (42).

From the discussion above it is clear that the sympathetic nervous system can, in association with other systems be programmed by early life experiences, especially by the influence of mothering style on the infant and child. In short, it is probably correct to say that optimal health ensues with integration of reason and emotion, i.e., with the appropriate hemispheric dominance and with low basal autonomic outflow – sympathetic as well as parasympathetic. It has, however, in Chapter 5 been shown that the central nervous system CRH neurons can to a large extent control, amongst others, the sympathetic nervous system and central noradrenergic activity. In view of this, as well as the fact that the CRH/HPA-axis represents the other major stress axis, the next couple of paragraphs will briefly deal with the way in which early life experiences can program adult neuroendocrine and behavioural responses through early influences on the CRH/HPA-axis. It should, however, be remembered that a reciprocal positive feedback exists between the CRH and noradrenergic systems and that activation of the one will in general lead to activation of the other (Chapter 3). It has, for instance, previously been mentioned that the CRH neurons of the hypothalamus are important targets of noradrenaline and that CRH in turn activates adrenomedullary catecholamine release (discussed in Chapter 3 and Chapter 5).

Chapter 5 demonstrated the central role of CRH in psychoneuroimmunology in terms of the two main stress axes. It was shown that both cortisol and CRH are of major importance for most adaptational events and that stress-induced changes in the regulatory

feedback mechanisms could have serious implications for the individual. It is obvious from the details presented in previous chapters that long-term alterations of the system could have far-reaching effects on the ability of the individual to cope with future life stressors and that it may predispose to both physical and behavioural problems.

Recent research indicates that the CRH/HPA system may be the major target through which adverse events in early life can predispose the individual to physical diseases and psychological abnormalities in later life. The supporting evidence to this effect is overwhelming and very much a topic of the day. The most important psychosocial variables involved with early life stress-sensitisation of the CRH/HPA-axis would again appear to be the nature of maternal care and the influence of the direct family environment. A comprehensive discussion of how variations in maternal care can regulate the development of stress reactivity would be far beyond the scope of this work and only some of the more salient points of evidence are therefore referred to. As most of the facts mentioned have been confirmed by the work of several different research groups many of the original workers are not referred to in this text. The following facts have been firmly established through empirical research

- Mental as well as physical disorders generally result from high levels of environmental demands superimposed on an underlying susceptibility or vulnerability. Susceptibility is, in turn, a function of both the genetic make-up and earlier life experiences that caused long-term alterations in neuroendocrine systems such as the CRH/HPA-axis and the noradrenergic system – the very same systems necessary for adaptation and coping. It is at this stage necessary to stress that severe abuse is not necessarily needed for high stress sensitisation, but that factors such as emotional neglect, poor infant-parental bonding, a cold or distant/detached family environment, periods of maternal separation and other relatively common occurrences can all alter the basic neuroendocrine-behavioural responsiveness and as such predispose to the development of mental and physical abnormalities in adult life – especially to those disturbances associated with the two main stress axes (59). It is

again to be stressed that presensitisation of the two axes can, as a result of their reciprocal activation, barely be distinguished between.

- Sensitive mothering with optimal positive physical contact between mother and infant can lead to a moderate HPA-response to aversive stress exposure and increased hippocampal negative feedback (increased hippocampal glucocorticoid receptor mRNA expression and decreased hypothalamic CRH mRNA) during adult life (60).
- Natural variations in maternal care give rise to individual differences to stress-induced HPA-axis-related behavioural responsiveness in adult life by its early effects on CNS systems such as forebrain noradrenergic activity that activate the HPA system or inhibit the GABA mechanisms (60).
- The offspring of mothers who demonstrate less contact and less positive mothering (as opposed to those who demonstrate optimal positive contact and sensitive mothering) show increases in the startling responses, lower exploratory behaviour in novel environments - in general greater fear of novelty and more severe stress responsiveness to any condition that may pose a potential threat (60,61)
- The adult offspring of mothers who show less favourable contact and less sensitive mothering behaviour (as opposed to those who demonstrate intensive positive contact and sensitive mothering) show higher CRH-induced central nervous system noradrenaline secretion (increased CRH receptor expression in the locus coeruleus and increased CRH mRNA expression in the central nucleus of the amygdala as well as decreased central benzodiazepine receptor expression in the amygdala and locus coeruleus) (60)
- Adults, who experienced favourable rearing conditions during early life do not only show a decrease in fearfulness, decreased mRNA in the PVN, and central nucleus of the amygdala in adverse circumstances, but also decreased CRH-content in the locus coeruleus – a fact that would lead to lower activation of the brain stem noradrenergic systems (59).
- Favourable rearing experiences do not only lead to strong negative feedback of glucocorticoids on the CRH/HPA system but also dampen stress-induced noradrenergic responses in the PVN (62).

- Longer periods of separation from the mother may change the neurohormonal profile of the infant or child in a way that may predispose to depression in adult life (increased CRH gene expression in the PVN and amygdala, altered noradrenergic and serotonergic pathways, decreased GABAergic/central diazepine systems activity - which regulate central CRH and noradrenergic activity) (63).
- Lactation blunts the neuroendocrine responsiveness to stress in later life. (Lactation reduces noradrenergic inputs to the PVN CRH neurons and may lead to phenotypic changes in neuropeptide expression, e.g., reduced expression of CRH mRNA and increased expression of ADH mRNA, reduced pituitary sensitivity to CRH and increased sensitivity to ADH). This may occur through lactation-induced alterations in the CRH neurons of the PVN, which then modulate the expression of neuropeptides and neurotransmitters in the BNST and the amygdala (64). Of interest is the fact that breast-feeding mothers have lower levels of ACTH, cortisol, ADH and adrenaline responses to stressful events than non-breast-feeding mothers (65). This could very well underlie the changes seen in the infant.
- Intergenerational transmission of maternal behaviour, i.e., non-genomic transmission of parental behaviour and stress responsiveness occurs from generation to generation and the stress responsiveness is transmitted by the nursing mother and not necessarily the biological mother. This intergenerational transmission is most probably mediated by the fact that mothers with low stress reactivity, reflecting their own favourable early life experiences, provide the type of maternal care that installs low stress responsiveness in their offspring (66).
- Maternal stress can have *in utero* influences on the offspring. Although it is unlikely that maternal CRH would pass through the placenta, adrenocortical hormones released in response to stress-induced CRH-release can cross the placenta and probably mediate the gestational stress which leads to short-term, as well as long-term morphological and behavioural changes in the young (67).
- There can be no doubt that stress-induced alterations in the CRH system can occur as a result of early life experiences and that this can persist throughout adult life. It is also known that alterations of the CRH system are present in depression and in anxiety disorders (elevated), in stress-related disorders such as posttraumatic disorder,

Tourette's syndrome and obsessive-compulsive disorders (elevated), during fearful behaviour with high frontal brain electrical activity (elevated), and in suicide victims (elevated), and that this may, partially at least, result from the influence of early childhood experiences (68). Valuable information to this effect has been obtained through molecular biology and genetic engineering techniques.

- Evidence exist that separation stress in the young may, by increasing CRH neurotransmission in the raphe nuclei, alter serotonin activity and receptor expression in adult life (69). Changes in hippocampal cortisol receptors as a result of adverse early experiences have, in turn, been reported to be dependent on serotonin activity (70)
- In general it would appear as if favourable rearing experiences will lead to decreased pituitary-adrenal responses to stress, enhanced glucocorticoid receptor binding in the hippocampus (both pointing towards a down-regulation of the stress response), increased synaptogenesis in the hippocampus with good development of memory consolidation ability, decreased CRH mRNA expression in the hypothalamus with moderate stressor responsiveness, as well as decreased CRH receptor expression, increased presynaptic alpha-2-adrenoceptors and increased benzodiazepine receptors in the amygdala and locus coeruleus of the adult – all factors that contribute to protection against excessive vulnerability to stress-associated disorders and reactions. (71).
- There is evidence to believe that during the early stages of brain development CRH neurons may be involved in target recognition and synaptic organisation – the implication for abnormal CRH activity with regard to cerebral organisation is frightening (72).
- Inflammatory conditions during early life may also change CRH/HPA-responsiveness in adult life. (73). This is in agreement with the fact that immunological events can produce a central nervous system stress response similar to that initiated by psychological stressors – as discussed in Chapter 6.

This section provided evidence to support the assumption that early life experience can lead to alterations in the structure and function of the two main stress axes and in so-

doing predispose to abnormal reactivity to potential stressors during adulthood. It was shown how, by altering the receptor expression, the degree of negative feedback and other functions, the vulnerability of the two main stress axis can be predisposed to either hyper- or hyporesponsiveness to stressors. This section thus provided the empirical evidence that adverse early childhood experiences can alter the basic neurological structure, function and sensitivity of the brain in a way that it can be expected to react to the onslaught by psychological, physical and immunological stressors in a way different from that of individuals with more favourable early life experiences. It should again be stressed that differences can be induced by subtle variations in early life experiences and not necessarily only by overtly abusive situations. The question remains whether one ideal developmental pattern really exists for the stress systems as various environments may require different degrees of responsiveness during adult life.

7.2.2 The effects of early life experiences on the immune system

In Chapter 2 it was demonstrated that links exist between the immune status and all categories of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and that inflammatory conditions would often appear to be present in mental disturbances. A link was also described between the psychoimmunological relationships and cerebral laterality – a phenomenon shown, in the previous section, to have some bearing on early life experiences. In a short introductory overview in Chapter 2 it was seen that early life experiences might influence the immune status of adult life. The underlying mechanisms were largely ignored at that point. In Chapters 4 and 5, the mechanisms through which the two main stress axes can influence the immune system were discussed, but early childhood experiences were not dealt with. Chapter 6 dealt with the pathways through which immunological events can influence neurobehavioural functions. The following couple of paragraphs will now show the type of early childhood experiences that may predispose to immunological vulnerability in adult life and the role of the stress axes in this phenomenon.

In humans, most such studies are of a correlation nature, as relevant experimentation can for ethical reasons not be performed. It is, however, known that a significant part of the

results from animal experimentation do not necessarily apply to humans. Due to similarities in social relationship characteristics, the best extrapolations to humans can probably be made from non-human primate experimentation (74). The experimental evidence provided below will mainly be that derived form non-human primates with some evidence coming from human studies. Extrapolations from primates show that

- There is a strong maternal influence on the development of circadian rhythms in the offspring. In some species, the maternal zeitgeber function can be fulfilled by a conspecific female, but this is not always the case (75,76). The influence of disturbed circadian rhythms on immune development is well known and has been referred to previously.
- Differences in the development of the stress and other behavioural responses, as a result of variations in the mother-infant bond, points towards long-term effects on the immune system. Inconsistencies in the degree of maternal protectiveness, as well as rejection and inattentiveness have been shown as major tension-producing factors in the mother-infant relationship – eventually leading to deranged affiliative behaviours and social subordination, as well as higher levels of separation distress at a later stage in life (77,78). Similar exaggerated separation distress resulting from maternal rejection, inconsistencies or unresponsiveness, with subsequent abnormal stress coping behaviour during adult life, can develop in humans.
- There is enough evidence to show that nursery rearing of non-human primates and humans may lead to different immunological profiles from that of maternally raised individuals. This is but one form of separation stress and the acute immunological effects in animals other than primates were discussed in chapter 4. The effects of separation stress do, however, depend on the age the infant is removed from the mother and on other factors such as the degree of peer interaction. The main factor would appear to be the degree of emotional isolation. In some studies only the neurohormonal profiles of these adults were investigated, but, in view of the immune influences of these substances, as shown in previous chapters, it can with a fair amount of certainty be presumed that immune function would be abnormal (79,80,81). Interesting results are derived from studies where non-human primate

infants were handreared by humans. Although very few negative behavioural effects could be detected, long-term immunological changes, especially in response to mitogen-stimulation were observed - with continuation of the effects determined by the age of the initial separation from the mother (82,83,84). Although very little work was done on humans it can with confidence be said that normal mother-infant, as well as peer interaction is necessary for normal immunocompetence in the adult life of non-human primates. However, this type of study can easily be performed in humans by retrospective investigations of child rearing in combination with prospective investigation of the immune status and reactivity.

- Transient disruption of the mother-infant bond by temporary separation, even at an age where the non-human infant can already survive without the mother, still has deleterious effects on the immune system. The behavioural effects of such transient periods of separation are well known. These usually include initial vocal protestations followed by withdrawal if the separation is prolonged (85,86). The physiological changes would in general appear to be mediated through concomitant activation of the two main stress axes, as evidenced from an increase in sympathetic activation and elevated cortisol levels, and seem to covary with the degree of behavioural distress (87,88,89). Immunological effects are very often present and the vulnerability to infections, as would be expected, very often increased in parallel with heightened sympathetic nervous system and HPA-axis activity, as well as with behavioural changes (90,91,92,93,94). Although one could speculate, it would be of great interest to have empirical information about the effects of early admissions to nursery schools and day care centres on the immune system of the human infant. In the non-human primate the separation reactions, psychological as well as immunological, would appear to depend on prior mother-infant bonding – a factor of great importance in the development of later social separation vulnerability. Other factors such as variations in the form of social support, maternal dominance status, infant gender, infant parity and genetics, may, however also influence the outcome. At this stage it would appear that the outcome is largely dependent on stress axis presensitisation, which has a major role in both the immunological and the behavioural predisposition. In view of this and other observations, it has been suggested that baseline values of HPA- and

SAM-axis activity may perhaps be used as prognostic indicators of high risk for the development of both infectious and behavioural problems in later life (95). A small number of studies exist that corroborate similar predispositions in humans. Children with exaggerated baseline neurobehavioural response patterns have been reported to be at higher risk for the development of immunological diseases such as allergies and those with a blunted responses at a higher risk for the development of autoimmune diseases (96,97). Behavioural response patterns have also been linked to antibody titres such as that against cytomegalovirus, but more work is necessary for it to be conclusive. Although maternal separation, even transient separation, can have harmful effects on the immune system these effects can be buffered by substitute caregivers (98,99). This is applicable even during recovery from the common cold (100).

- Disruption of peer bonding, especially following upon maternal separation, has long been known to have a behavioural impact. This is also the case for immunocompetence and the two types of disturbances may very well run in parallel. The most marked peer separation disrupting effects on the immune system are seen upon multiple peer separations (101,102).

More work is needed to come to a clear understanding of the effects of separation distress on the eventual immune status of adulthood. What is, however clear is that, as in the case of the behavioural effects, it can have long-term consequences. The long-term consequences are to a degree modulated by other factors, including mother-infant bonding should reunion occur after a period of separation (103). Separation with subsequent augmented maternal care upon reunion had been implied to have the potential to lead to a stronger immune system in adult life. The consequences of repeated transient separation and reunion as occur with parents with busy professional lives, as well as with family disruption due to unfortunate socio-economic circumstances, are not known. There is however, plenty of evidence to show that permanent separation without adequate surrogate bonding will predispose to immunological-related disorders such as immunodeficiency, leukopenia and other malignancies (104), as well as to behavioural disturbances. These behavioural effects and immunological predispositions covary and it

can, with almost certainty, be said that they are to a large extent secondary, at least at effector level, to alterations in the CRH/HPA-axis. As most of the immune changes would essentially be modulated through neuroendocrine influences, it is feasible to extrapolate predictions from known neurobehavioural changes.

Predisposition to abnormal immunocompetence, as is the case for the behavioural functions, can also occur as a result of socio-environmental influences during adolescent and adult life – even in later stages of adult life. Disruption of social bonds, as well as rehousing may lead to marked alterations in behavioural and immunological parameters – again accompanied by changes in HPA-axis activity. The HPA-activity is usually one of hyperactivity, depending on the degree of adverse emotionalility experienced (105,106,107,108). Housing relocation in association with infectious complications may even increase morbidity and mortality (109). Relocation with subsequent lowering of social dominance or ranking and a decrease in affiliative behaviour may similarly have very serious implications for future immunocompetence (110,111). Even reintroduction into the previous social group may have grave consequences as seen by increased HPA-axis activity and a decline in CD4+ and CD8+ counts. The magnitude of the effects would often appear to be dependent on the degree of competitiveness and the presence of aggression (112). Similar changes have been reported in conditions with social instability due to constant reorganisation or changing of the environment. Here again the immunological effects appear to depend on alterations in social ranking and behavioural patterns such as affiliation and aggression, as well as other variables in the social interactions. Experimental work clearly showed that constantly changing social conditions and venues of social interaction might impact on the progression of immunological-related immune disorders (113,114). As would be expected, an influence for competitiveness on immune responsiveness has been shown. The degree to which subsequent life stages are influenced is not clear, but with the nature of the neuroendocrine control on the immune system, discussed in previous chapters, it can be assumed that it would depend on the period of exposure, as well as the intensity, i.e., whether permanent neuroendocrine alterations have been induced. Although dominance would not appear to be directly related to the degree of immunological alteration, losing

out on opportunities has been shown to have significant negative effects on especially the B-cell immunological responsiveness (115). Disruption of the social environment by, for instance, the introduction of an aggressive male, has been shown to impact on the immunocompetence – especially of females who become the recipients of the aggression (116). It is very tempting to speculate about the effects this factor may have in the work place, but many factors will have to be considered in such a study, not least prior priming and attitudes of the resident human female population.

It is, in short, feasible to extrapolate from experimental results obtained on non-human primates that, as in the case of behaviour a) immunological competence is influenced by early life psychosocial experiences, b) these early influences may predispose to immune-related disorders in later life, c) the main stress axes and especially the CRH/HPA-axis are involved in the immune alterations, d) baseline activity of the two main stress axes may be prognostic indicators of vulnerability to immune dysfunctions, and e) positive affiliative interactions may ameliorate the adverse effects of negative early life experiences on the immune system and through this once again on behaviour.

7.2.3 Mechanisms underlying the predisposition to stress hyperresponsiveness, hyporesponsiveness and stress resistance.

It is not completely clear how predisposition to high stress vulnerability develops. Some of the changes that could lead to a low threshold value for the two major stress systems, i.e., changes that would increase the stress responsiveness, and potentially lead to excessive reactivity, as well as behavioural and physical disturbances, were described in the previous paragraphs. They include a) pathomorphogenesis as a result of stress-induced abnormalities in hormone levels b) impaired cortical control as a result of stress-induced formation of aberrant neuronal connections, c) hyperactivation as a result of kindling, d) autonomic imbalance due to damage to either the excitation ventral segmental limbic system or to the inhibitory lateral segmental limbic system, e) above normal basal tone in both the sympathetic and the parasympathetic system due to limbic kindling, f) inappropriate hemispheric integration, g) inappropriate HPA-axis activation secondary to forebrain noradrenergic activity, h) inappropriate inhibition of GABAergic

activity due to high forebrain noradrenergic activity, i) increases in the CRH receptor expression in the locus coeruleus, j) increased CRH mRNA expression in the central nucleus of the amygdala, k) decreased benzodiazepine receptors in the amygdala, l) decreased benzodiazepine receptors in the locus coeruleus, m) increased CRH gene expression in the paraventricular nucleus, n) increased CRH gene expression in the amygdala, o) changes in serotonin activity and receptor expression due to variations in the CRH neurotransmission in the raphe nuclei and m) decreased glucocorticoid receptor expression in the hippocampus. Other interesting mechanisms, through which early life experiences can predispose to altered stress vulnerability and subsequently to disturbances in mind-body health in adulthood, were presented at the 4th World Congress on Stress, 2002 (117). Some of the more important facts presented on the effects of the environment on mental and physical health are summarised below.

- Stimulation of the basolateral amygdala CRH1/CRH2 receptors by urocortin leads to long-term anxiety-like behaviours and autonomic hyperreactivity. This is seen as a form of amygdalar plasticity involving NMDA-type glutamate receptors and calcium-calmodulin dependent kinase-II mediated intracellular changes – similar to long-term potentiation (118).
- As seen in Chapter 6, CRH pathways innervate the dorsal raphe nucleus (DRN). Adverse early life experiences can lead to CRH-induced augmentation of serotonin-dependent behaviour. Neonatal stress can, in addition, cause desensitisation of the 5-HT_{1A} receptor-mediated auto-inhibition, decreased sensitivity to 5-HT_{1A} mediated inhibition of forebrain serotonin-release, a decreased response to alpha-1-adrenergic excitatory input and increased vulnerability to psychiatric illness in adulthood (119).
- *In utero* exposure to increased glucocorticosteroids (maternal stress or glucocorticoid therapy) leads to HPA presensitisation that is linked to premature psychopathologies in aging (120).
- Repeated neonatal maternal separation leads to persistent changes in central nervous system gene expression (121). Alterations include clusters of gene expression changes in elements of DNA-RNA synthesis and repair, neuronal growth and adhesion, intracellular signalling cascades and glial cells. Examples

include upregulation of the genes for DNA methyltransferase and ZIC (a zinc finger protein gene) in the prefrontal cortex and hippocampus as well as upregulation of neural cahedrin, NCAM, BDNF, expression of PKC-alpha, the subunit of the G protein and MAP kinase 4K3 genes in the prefrontal cortex and hippocampus. This type of work is still in the early stages but indicates that early rearing experiences can induce long-term stress sensitivity or resistance in the offspring by changes in plasticity and intracellular signalling cascades.

- Repetitive pain during neonatal intensive medical care, especially in premature infants, alters neurobiological developments such as basal autonomic responses and arousal state. (122). This does not augur well for future behavioural functions such as attention, self-regulation and executive functions.
- In adult women with a history of childhood abuse, multiple regression analysis showed childhood trauma, in addition to stressful periods in adulthood to be the best predictor of high neurohormonal reactivity to laboratory stress tests or to pharmacological challenges. These abused women also showed high CSF CRH levels, structural hippocampal changes and high levels of pro-inflammatory cytokines (123). Hippocampal damage with resultant low negative feedback on the stress response as a form of presensitisation has been discussed before.
- An interesting related phenomenon is the dysregulation of CRH in the central nucleus of the amygdala and bed nucleus of the stria terminalis due to stress during neonatal life. These systems, in contrast to the PVN, are known to increase their CRH expression in response to high levels of glucocorticoids and are able to stimulate the expression in other brain regions. Their dysregulation is strongly linked to low cortisol-HPA-axis negative feedback and to conditions such as excessive shyness and fear in children, the development of anticipatory anxiety, melancholic depression, post-traumatic stress disorder and self-administration of psychotropic drugs (124).

The examples given above pointed predominantly to predisposition to hyperactivity of the CRH/HPA system. It is however known that hypoactivty may exist in conditions such as the chronic fatigue syndrome. Many of the behavioural changes, with hyper- as well as

hyposensitivity are similar to that of sickness behaviour and even depression. The mechanisms underlying predisposition to hypoactivity are still largely unknown but certain processes are slowly becoming clear, including the following.

- Long-term desensitation of the HPA-axis may occur as a result of a single exposure to an extremely severe (homotypic but not heterotypic) stressor. This appears to be mediated through PVN gene transcription and can be induced by emotional as well as by immunological events. (125). This may very well have a bearing on the low CRH/HPA-axis activity seen in chronic fatigue syndrome and other disorders associated with stress system hypoactivity.
- Evidence also exists that a blunted HPA-response may develop as a result of early painful experiences or as a result of chronic pain (126). The apparent similarities between the suppressed HPA activity in chronic fatigue syndrome and in fibromyalgia, and the similarities between their behavioural symptoms and reported cognitive decline are striking.
- Reduced arousal and suppressed behavioural responsiveness may be related to deficient brain noradrenergic activity due to depletion (127) of noradrenaline stores. Noradrenergic depletion and alteration of alpha-2 receptors as a result of earlier stress experiences have been discussed in Chapter 3.
- The effect of intra-uterine predisposition to abnormal HPA-reactivity in later life seems to be dependent on a number of factors including birth weight and the gestational age at which the subject is born and it is suggested that, depending on such factors, foetal programming of the HPA axis may result in either hyper- or hypoactivation of the stress axis (128).

The previous paragraphs dealt with predisposition to either hyperactive or hypoactive activity of the stress response systems. There must, however be factors intended to render the individual stress-resistant. It has already been shown that positive early life experiences will lead to a lower stress reactivity and increased HPA-axis feedback control in the adult. It is also known that nutrition and physical activity can play a role in the sensitivity of the stress response systems. There are, however, other factors, which

between these two systems can lead to stress-related disturbances (134). The just referred to CRH-2 system mediates the stress-coping responses during the recovery phase of stress. In this context the peptide stresscopin, as well as stresscopin-related peptides, which act as specific ligands for the CHR-2 receptor, have recently been identified in humans (135). These peptides may represent endogenous ligands for maintaining homeostasis after stress and could very well become another potential pathway for therapeutic manipulation of stress-related diseases. Pharmacological studies, based on CRH-1 and CRH-2 receptor interactions are underway in an attempt to develop drugs to counter dysregulations in the stress systems. There can be no doubt that psychotherapy and other positive interpersonal interactions, which augment self-perception, will also lead to improvements of such dysregulations. The effects of prenatal glucocorticoid programming of the brain corticosteroid receptors and the implications for coping and behaviour can be found in a paper by Welberg *et al*, 2001 (136). The foetal and neonatally induced hyperresponsiveness of the HPA, as discussed before, and the effects on adulthood coping responses (137) can naturally not be seen out of context with the receptor systems, but the complexity of such interactions are beyond the scope of this writing.

From work presented in this section and in previous chapters it is clear that early exposure to any environmental or immunological event that predisposes the individual to either hyper- or hyporesponsiveness of the main neuroendocrine systems could also predispose to future neurobehavioural and immunological abnormalities. Figure 7.1 can now be expanded to include these facts. This is seen in Figure 7.3 on the next page.

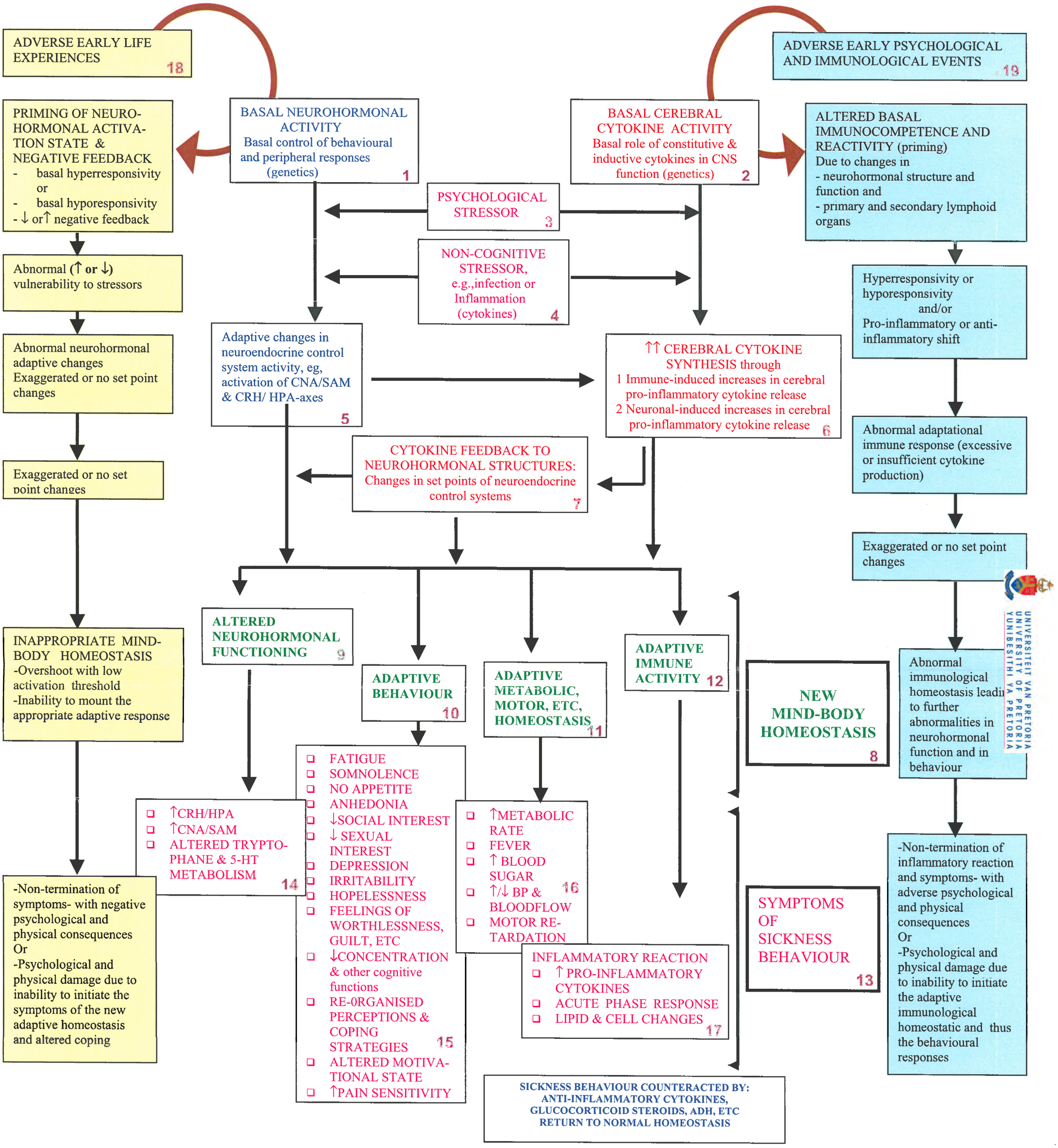

Figure 7.3: Sickness behaviour in psychoneuroimmunological context. Predisposition through early life experiences. [On the left of the diagram (18) it is shown that adverse life experiences can lead to hypo- or hyperreponsiveness of basal neurohormonal activity with subsequent abnormal stress vulnerability which may lead to an inappropriate adaptational homeostatic shifts and the potential for either non-termination of the symptoms of the adaptive homeostasis or an inability to mount the necessary new homeostasis. On the right of the diagram (19) it is shown that adverse psychological or immunological events can lead to altered basal immunocompetence and reactivity which upon subsequent challenges by stressors could give rise to abnormal adaptive immunological homeostasis with adverse effects on neurobehaviour funtion and the potential for non-termination or non-initiation of the symptoms of the adaptive stress response]

Legend to Figure 7.3

Figure 7.3: Sickness behaviour in psychoneuroimmunological context. Predisposition through early life experiences. [On the left of the diagram it is shown that adverse life experiences can lead to hypo- or hyperreponsiveness of basal neurohormonal activity with subsequent abnormal stress vulnerability, which may lead to an inappropriate adaptational homeostatic shift and the potential for either non-termination of the symptoms of the adaptive homeostasis or an inability to mount the necessary new homeostasis. On the right of the diagram it is shown that adverse psychological or immunological events can lead to altered basal immunocompetence and reactivity which, upon subsequent challenges by stressors, could give rise to abnormal adaptive immunological homeostasis with adverse effects on neurobehaviour function and the potential for non-termination or non-initiation of the symptoms of the adaptive stress response.]

Sickness behaviour was discussed in a previous section as a practical example of the psychoneuroimmunological interaction. Many of the symptoms of sickness behaviour correspond to that of certain mental disorders. It would therefore seem feasible to argue that continuation of the symptoms of sickness behaviour, after recovery from the physical disease, could give rise to mental abnormalities - especially in the person presensitised by genetic and early life experiences. This statement is presented later in this chapter as a hypothesis and its merits defended with appropriate examples. It almost speaks for itself that not only immune-related physical disease, but virtually any type of stressor that impacts on the neuroendocrine systems, could have the same effect. At this stage it becomes necessary to ask what mechanisms are involved in the termination of sickness behaviour and what could perhaps lead to failure to terminate the response with subsequent continuation of the symptoms.

7.3 Termination of the symptoms of sickness behaviour and failure to terminate the response.

Cortisol is probably the major feedback substance that not only suppresses the sickness behaviour-associated hyperactivity of the CRH/HPA axis, but also shifts the inflammatory response in an anti-inflammatory direction. The underlying mechanisms have been discussed in previous chapters and earlier in this chapter. The putative mechanisms through which the peripheral inflammatory response, as well as other potential psychological stressors can stimulate the CRH/HPA-axis have also been discussed. Through its negative feedback on the hippocampus, anterior pituitary and hypothalamus as well as its inhibition of the production of pro-inflammatory cytokines, cortisol can thus have a direct as well as an indirect suppressive effect on its own hypersecretion and on sickness behaviour in total. Factors that lead to cortisol resistance can thus by implication result in a continuation of the hyperactivity of the neuroendocrine systems, the pro-inflammatory activity, as well as the behavioural symptoms.

Several factors can contribute to cortisol resistance and therefore to continuation of sickness behaviour symptoms. One of these is a basal hyperactivity of the stress systems.

The predisposition to a hyperactive CRH/HPA-axis has been discussed in the previous section – with the major mechanisms being the down-regulation of hippocampal and upregulation of amygdalar glucocorticosteroid receptors and therefore a weaker negative feedback. It is obvious how such a predisposition can lead to the continuation of the sickness behaviour symptoms long after an immunological or psychological stressor has ceased to exist. It is also clear how the hyperactivity of the CRH/HPA, as well as the CNA/SAM-axis, can be further amplified by a negative emotional state which in itself can act as stressor and further propagate the symptoms characteristic of sickness behaviour, with the potential to develop stress-related disorders. It is perhaps at this stage necessary to recall that long-term depressive moods in themselves may lead to cortisol-induced atrophy of hippocampal neurons with subsequent lowering in the negative feedback system (138). The opposite is, however also true, i.e., that a positive psychological mood and a feeling of control may help to reduce the activation state of the neurological stress systems and thereby remove a strong stimulus for the production of intracerebral pro-inflammatory cytokines. These interactions were discussed in more detail in previous chapters.

Although glucocorticoid resistance is in the majority of cases a function of alterations in receptor expression, there are other reasons why it may be present, including some prereceptor (conversion of corticosterone to cortisol, plasma cortisol binding proteins) and some postreceptor mechanisms. Some of these have been referred to in previous sections and will not be discussed again. However, one mechanism very relevant to the contribution of cortisol resistance to the non-termination of the symptoms of sickness behaviour is the role of cytokines. Cortisol resistance due a suppressed negative feedback may be induced by the very same cytokines that form part of the sickness behaviour complex. Over 20 studies showed that cytokines, especially those involved in inflammatory conditions, could alter glucocorticoid receptor density and functioning. Some contradictions exist between the results of those studies using whole cell techniques and those using cytosolic radioligand binding (139). The overriding conclusion is, however, that pro-inflammatory cytokines can reduce the expression of glucocorticoid receptors as well as down-regulate their functioning (139). This would

naturally suppress the negative feedback on the HPA-axis and their effect on cytokine production, resulting in continued activation of the stress axes and augmentation of pro-inflammatory cytokine production. This can, via the cerebral cytokine relay system, further increase the activation state of the neuroendocrine stress axes - resulting in a type of positive feedback system that supports the continuation of the sickness behaviour with the potential to progress towards behavioural disturbances.

It should be mentioned that genetic abnormalities due to mutations in the glucocorticoid receptor gene is known to occur and that these receptor alterations generally appear to result in cortisol resistance (140). Genetic disturbances of the gene with glucocorticosteroid hypersensitivity and concurrent hypoactivity of the HPA-axis may exist. However, glucocorticoid receptor expression studies are not freely performed and such disturbances, if they exist, have not yet been reported.

Several substances, besides glucocorticosteroids, are involved in the control of pro-inflammatory activity, including the anti-inflammatory cytokines, ADH, α-melanocyte stimulating hormone, the SAM-axis and certain members of the interleukin-1 family (5,30,31). The molecular mechanisms involved in containment of the sickness response are sometimes referred to as the cryogens (32). The role of the glucocorticosteroids is generally that of normal negative feedback. The HPA-axis, as previously mentioned, is stimulated by pro-inflammatory cytokines. The glucocorticoids thus secreted can in turn control the cytokine-induced effects a) by down-regulation of pro-inflammatory cytokine synthesis and release through inhibition of transcriptional and post-transcriptional expression of the IL-1β gene and by decreasing the stability of the IL-1β mRNA, b) by decreasing the ratio of type I IL-1 to type II IL-1 receptors, and c) by suppressing the conversion of proIL-1β to its biological active form through inhibition of the IL-1β converting enzyme (30,34,35). ADH, a substance that acts in synergism with CRH, as shown in Chapter 5, is also involved. Fever-induced ADH has, for instance, been shown to limit the suppressive effect of IL-1β on the behavioural functions (33). Failure of any one of the factors involved in terminating the inflammatory process can contribute to the continuation of the sickness behaviour.

The interactions between the two main stress axes and cytokines, which are quite complicated, have been discussed in Chapters 4 and 5 and are for the sake of convenience summarised in Figure 7.4. As indicated in previous chapters, the two main stress neuroendocrine systems can be stimulated by pro-inflammatory cytokines and in turn can control these inflammatory mediators. Furthermore, both axes can influence as well as be influenced by the behavioural functions. It is, however, important to recall the effect of hyperactivation of the two main stress axes – as in the case of sickness behaviour – on the cytokine shift. In Figure 7.4 it is shown that both axes tend to shift the immune response away from cellular towards humoral immunity and the cytokine profile from a pro-inflammatory towards anti-inflammatory cytokine profile.

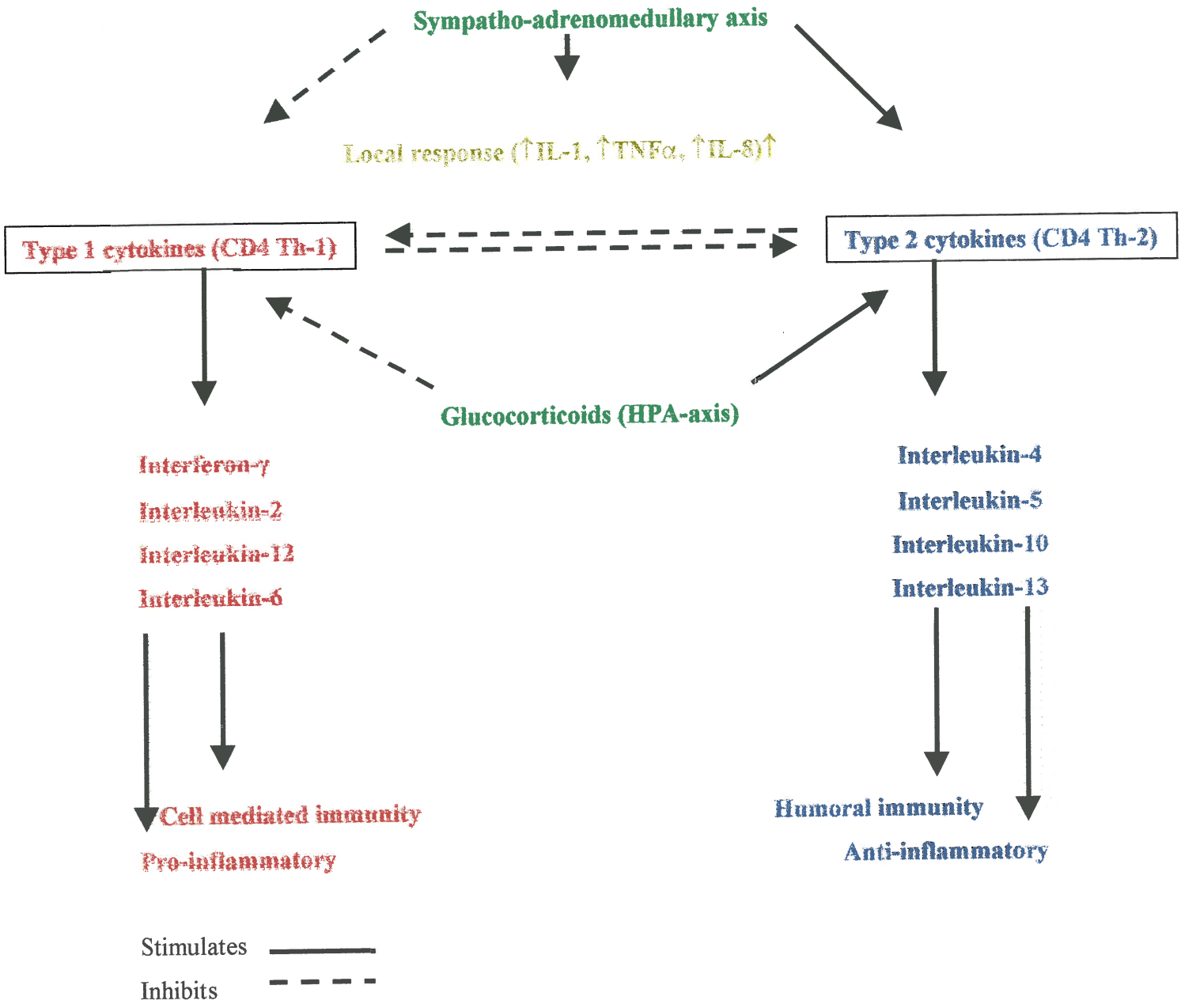

Figure 7.4: The interactions between the two main stress axes and cytokines. [Both the SAM-axis and the HPA-axis suppress the production of pro-inflammatory cytokines and stimulate the production of anti-inflammatory cytokines by switching CD4 cells from a Th-1 to a Th-2 pattern. They also inhibit production of IL-1 which acts as co-stimulator in T-cell activation]

It is highly possible that individuals who become resistant to the effects of the feedback mechanisms, either through psychological predisposition or through the combination of genetics and predisposition, and who subsequently, develop sickness behaviour may be at risk for non-termination of the sickness behavioural response and thus at risk for the development of physical or psychological disorders. Various factors, psychological, as well as physiological, could influence the eventual outcome. The following paragraphs are dedicated to providing the necessary information in order to support such a hypothesis.

7.4 The Hypothesis: Uncontrolled sickness behaviour may lead to any of a number of mental disturbances – partially dependent on predisposition by early life experiences.

Earlier in this chapter, the symptoms of sickness behaviour have been shown to represent a new adaptive homeostasis, which can be seen as a pattern of conscious and subconscious coping responses in the face of whatever the initiating stressor. We have further seen that many of the symptoms of sickness behaviour would appear to correspond to characteristics known to occur in certain mental disorders. These symptoms are largely the reflection of cytokine-induced neuroendocrine changes that include disturbances in the CRH/HPA-axis, the CNA/SAM–axis and the central serotonergic systems. Proof of the ability of cytokines to cause such neurobehavioural disturbances was demonstrated in Chapter 6 where it was shown that cytokines could induce disturbances ranging from mild constitutional symptoms (fatigue, chills, headaches, fever, etc) to serious psychiatric problems such as depression, delirium and psychosis. Examples of associations between classes of the DSM-IV and the inflammatory response were given in Chapter 2 and the links between disturbances of the neuroendocrine systems involved in sickness behaviour and a number of mental disturbances were touched upon in Chapters 3 and 5. Earlier in this chapter it was shown that the threshold for hyperactivation of these neuroendocrine systems could be lowered by early life experiences, and that resistance to the normal negative feedback mechanisms that terminate the hyperactivity of the neuroendocrine and immunological systems

involved in the symptoms of sickness behaviour can occur. It is therefore hypothesized that continuation of sickness behaviour after recovery from the initial stressor could form the basis of mental disturbances. This will be particularly relevant in individuals who are already vulnerable due to a genetic and psychological predisposition of the neuroendocrine and/or immune system. It is feasible to suspect that the type of disturbance likely to develop will be determined by the genetic disposition and the priming by early life experiences. It speaks for itself that psychological stress or a secondary inflammatory or infectious condition, even subclinical, would contribute to the psychiatric disturbance and even exacerbate the condition with dire consequences for mental health. The potential consequences for physical health are equally alarming and many physical disorders are presently known to be associated with stress-related disturbances of the HPA-axis. These physical disorders, although most of them now known to be associated with very specific behavioural characteristics, will largely be ignored. However, some of them will be referred to under mental disturbances due to general medical conditions.

7.4.1 Mental disorders as a continuation of sickness behaviour

In this section the similarities between sickness behaviour and a number of mental disorders are briefly discussed in support of the proposed hypothesis. The suggestion made in Chapter 2, i.e., that inflammatory processes of the brain may be a factor in a number of behavioural disturbances, will be elaborated upon and the role of antidepressants will be touched upon. Although a number of disturbances will be looked at, major depression will be the prime focus. It has to be stressed that the immunological involvement to be described is in no way suggested to replace other factors as the cause of whatever mental disturbance is discussed.

For quite a while, there have been indications that the immune system may play a role in the etiology of depressive moods, specifically in the etiology of major depression. In Chapter 2, reference was made to earlier publications showing the connection between abnormal immune functioning and mood disorders. The first major milestone in the development of the hypothesis that immune changes may underlie the etiology of major depression was the macrophage theory of depression by Smith in 1991 (141). Due

partially to the fact that immunology is still a developing field, immune suppression was initially thought to be a characteristic of major depression. We now know that it is merely a shift in immune function. The second major milestone was the interleukin hypothesis of major depression as described by Maes in 1995 (142). At present, it is fairly well accepted that depression is more often than not accompanied by a pro-inflammatory/Th-1 shift in immune functioning. There are, however, still many unexplained aspects and much more interdisciplinary research is needed. As the purpose of this last part of the thesis is to show that unbridled continuation of sickness behaviour can give rise to several behavioural and even psyciatric disturbances, the next couple of paragraphs will deal with the similarities between sickness behaviour and the mood disorders. It will also be shown why the major depressive disorder is sometimes described as a central nervous system inflammatory condition. Sickness behaviour and depression will be compared in terms of behavioural characteristics, neurohormonal shifts and immunological patterns.

Previously in this chapter, sickness behaviour was shown to represent a cerebral activation state where subsequent cytokine-induced neurohormonal changes can lead to a wide spectrum of behavioural changes. The similarities between the psychiatric symptoms of the mood disorders and the symptoms of sickness behaviour are striking. As previously seen, the differences in sickness behaviour symptoms vary with the severity and duration of the condition from flu-like constitutional symptoms to anhedonia to severe cognitive disturbances. It is tempting to speculate that this, except for the duration, may partially be reflected in the differences between the major depressive disorder and the dysthymic disorder. In comparing the list of symptoms (depressed mood most of the day; nearly every day; markedly diminished interest or pleasure in almost all activities; decreased appetite or weight loss, hypersomnia or insomnia nearly every day; psychomotor retardation or agitation nearly every day; fatigue or loss of energy nearly every day; feelings of worthlessness or excessive or inappropriate guilt; diminished ability to think or concentrate and recurrent thoughts of death, suicidal ideation or a suicide attempt) from which at least 5 have to be present to represent a major depressive episode (143), it is clear that they all fall within the scope of the behavioural symptoms (fatigue, somnolence, no appetite, anhedonia, loss of social and sexual interest,

depressive moods, irritability, feelings of hopelessness, worthlessness, guilt, a lack of concentration, and a decline in other cognitive functions, reorganised perceptions and coping strategies as well as altered motivational states) that may form part of sickness behaviour.

For as far as we are able to come to any dogmatic conclusions, there is a good correspondence between the basic neuroendocrine perturbations of sickness behaviour and major depressive disorders. Abnormalities of the CRH/HPA system with dysfunctions in the thyroid axis, as well as in noradrenaline and serotonin metabolism and receptor function are, as for sickness behaviour, known to be present in depression. Although most biological models of major depression describe CRH/HPA-axis hyperactivity as the norm, preliminary indications are that other patterns may also exist. There is some evidence for hypercortisolaemia to predominate in typical depression and hypocortisolaemia in atypical depression. Significant improvement has, in fact, been seen with prednisone augmentation of antidepressant therapy in treatment-resistant depressive patients with hypocortisolaemia and severe fatigue (144). Depression with severe fatigue and hypocortisolaemia obviously puts a very fine dividing line between depression and the so-called chronic fatigue syndrome.

The hypersecretory state of the HPA-axis of major depression is, as for sickness behaviour ascribed to hypersecretion of CRH due to, amongst other things, a suppression in the negative feedback mechanism – both exhibiting non-suppression of cortisol secretion upon dexamethasone administration. The degree of non-suppression would appear to correlate with the levels of IL-1β, both in depression and sickness behaviour. This is in agreement with findings that immune challenges could decrease the affinity of the corticosteroid receptors involved in the negative feedback of the HPA-axis (145). It is also known, as described in Chapter 6, that immune challenge-induced pro-inflammatory cytokine production could stimulate CRH activity and thus cause hyperactivity of the CRH/HPA system. Immunological activity, as seen in sickness behaviour can thus increase CRH activity both by stimulating the secretion directly and by inhibiting the negative feedback. Major depression is similarly associated by a central CRH drive as

represented by above normal CRH levels in the cerebrospinal fluid, increased CRH mRNA levels in the paraventricular nucleus and reduced CRH receptor density in the frontal cortex (146). This central CRH drive which is supposed to be of short duration during sickness behaviour and which is present in a more chronic form with major depression, is said to act as compensatory mechanism against the effects of the elevated cortisol levels on immune function. This may, however, be a potentially dangerous situation in conditions of glucocorticoid receptor downregulation where the glucocorticoid suppression of pro-inflammatory cytokines is reduced. Such a condition of pro-inflammatory stimulation by CRH (see Chapter 5 for details on the effects of CRH on the immune system) and downregulation of the cortisol anti-inflammatory activity may lead to unbridled continuation of sickness behaviour, or in the case of individuals with trauma or serious infections to the systemic inflammatory response syndrome, septic shock, or even multiple organ failure. In case of the first possibility, i.e., non-termination of sickness behaviour, it is highly feasible to expect that the symptoms would reflect that of major depression. In fact, that it could indeed be a case of sickness behaviour that developed into a chronic state of depression. Previously in this chapter, it was shown that priming of the CRH/HPA-axis by adverse early life experiences can predispose to above normal basal activity of the system. It is clear how such predisposition would lower the activation threshold and could render the individual vulnerable to non-termination and a switch from appropriate sickness behaviour to a dysfunctional major depressive state.

The main disturbance of the thyroid axis in major depression would appear to be suppression of TSH secretion (147). Such TSH suppression during HPA-axis hyperactivity is to be expected and does not require any explanation. In fact, if other endocrine systems controlled through hypothalamic liberins and statins are to be investigated the same pattern would most probably be found with regard to the tropic hormones. Sickness behaviour in the acute situation is, in contrast, accompanied by a hypermetabolic state. However, should sickness behaviour progress into a more chronic condition the hyperactive CRH/HPA-axis would lead to suppression of the thyroid axis – similar to that found in depression. The reason for this is that TSH is, in the case of hyperactivity of the CRH/HPA-axis, suppressed not only directly by above normal

cortisol levels but also indirectly through a CRH-stimulated increase in somatostatin that in turn inhibits TSH release (148). Not to be discussed here, but of interest with regard to the similarities between prolonged sickness behaviour and major depression, is the fact that hyperactivity of the CRH/HPA-axis can have similar suppressive effects on the reproductive axis and the growth axis (148).

The serotonin abnormalities associated with mood disorders (149) would appear to include

- central nervous system changes in presynaptic serotonergic neurons due to a deficiency in L-tryptophan availability
- compensatory increases in post-synaptic receptor density, affinity and responsiveness of 5-HT2 receptors
- down-regulated/desensitized post-synaptic 5-HT1A receptors.

A similar decrease in tryptophan availability has been described earlier in this chapter under the discussion of the neurological characteristics of sickness behaviour (14). This decrease in tryptophan deficiency of sickness behaviour, as previously discussed, results from a cytokine-induced shift to the kynurenine pathway. At this stage it would be risky to venture into an in depth comparison between the alterations in serotonin metabolism as it is becoming clear that the various cerebral areas undergo different changes in their serotonin metabolism and receptor activity – both during immunologically induced sickness behaviour and with major depression (146).

If sickness behaviour can evolve into mood disorders such as major depression or the dysthymic disorder it should in theory be possible that the factors responsible for the neurological disturbances of sickness behaviour should also be able to lead to the neurological disturbances of depression. In previous paragraphs and in Chapter 6 it was shown that cytokines can give rise to the total spectrum of behavioural and physiological changes seen in sickness behaviour, either directly or through cytokine-induced changes in neuroendocrine function. It has also been shown that the whole mechanistic cascade of sickness behaviour can be initiated by an initial non-cognitive stressor such as infection, inflammation or trauma, or by stress-induced neurological activity. We have furthermore

seen how the neurological stress systems can be activated by pro-inflammatory cytokines as the result of the impact of a non-cognitive stressor. Two questions thus apply, i.e., whether any correspondence exists between the immune response of sickness behaviour and that of the mood disorders and whether the pro-inflammatory immune pattern of sickness behaviour can be causally related to the neurological changes known to occur in mood disorders such as major depression. The first question will be dealt with in subsequent paragraphs. The second has, to a large extent been answered in previous sections and can be conceptualized by saying that

- Hyperactivity of the HPA-axis can be induced by IL-1 and IL-6 in cooperation with other cytokines, by inflammatory-related changes in noradrenaline and serotonin turnover, and by any factor that causes a downregulation of the negative feedback of the HPA-axis. With regard to the latter, we should recall that IL-1 can for instance downregulate glucocorticoid receptor expression or the translocation of the receptor from the cytoplasma to the nucleus. Not to be discussed here, but of importance for a more in depth understanding, are the roles and interactions of cytokines, eicosanoids and glucocorticoids in the activation of the HPA-axis by immune onslaughts. This can be found in a review by Buckingham *et al,* 1996 (150).
- Noradrenergic hyperactivity can be induced by cytokines, either directly, or as a result of the control of the CRH/HPA-axis over the system (Chapter 5), and the positive reverberating influence between the two stress axes (Chapter 3).
- Central serotonin is also known to be influenced by the pro-inflammatory reaction seen in sickness behaviour. Pro-inflammatory cytokines such as IL-1β, IFNγ and TNFα have, for instance, been shown a) to alter extracellular serotonin (5HT) levels in the hypothalamus, the hippocampus and the cortex, b) to modulate the activity of the serotonin transporter involved in central serotonergic neurotransmission by serotonin re-uptake, and c) to induce the activity of the first enzyme of the kynurenine pathway (indoleamine-2,3-dioxygenase) that converts tryptophan to kynurenic acid and quinolinic acid with a resultant tryptophan-depletion and/or reduction in the tryptophan:competing amino acid ratio with the potential for a reduced serotonin production [Reviewed by Maes, 1999 (151)].

- The downregulation of the thyroid axis can happen secondary to an upregulation of the HPA-axis and is therefore hardly necessary to discuss. Yet, there are indications that the depression-associated alterations of the thyroid axis can also be induced by inflammatory activity – whether this is indeed a direct effect or not is not always clear. What is known is that low basal TSH and abnormal T3 and T4 levels are present in the majority of physical diseases where activation of the inflammatory response happens to be a feature and that IL-1β and IL-6 are involved in inflammatory-related thyroid axis suppression (152,153).

To return to the first question. The immunological alterations described in, for instance, major depression follow virtually an identical pattern to that known to occur in sickness behaviour. These similarities were first pointed out by Maes in 1995 in his interleukin hypothesis of depression (142), and are well reviewed in a more recent paper (151). The reader is referred to his paper for references to the original authors. In the latter publication, Maes, 1999 (151), presented the evidence for the existence of an inflammatory response, similar to the response known to occur with physical diseases, in major depression by subdividing the supporting evidence into direct and indirect indicators of the inflammatory response. Direct evidence for the presence of a inflammatory response in mood disorders comprises findings such as increases in circulating monocytes and neutrophils, increased neopterin and prostaglandin levels, activation of the acute phase response (with increases in positive acute phase proteins and decreases in negative acute phase proteins), and increases in pro-inflammatory cytokines such as IL-1β, IL-6 and IFNγ. Indirect evidence, generally used in clinical diagnosis for the detection of the inflammatory response include a decreases in serum zinc and serum iron levels, alterations in lipid metabolism with a typical inflammatory response pattern of, amongst other, an increased C20:4ω6/C20:5ω3 ratio, and erythropoeitic changes typical for the systemic inflammatory response, including hypoferraemia in the presence of tissue iron overload. Evidence for the presence of such inflammatory response markers has repeatedly been shown in subsets of patients with major depression (151). In addition, the presence of membrane lipid abnormalities, typical for inflammatory conditions, are current major points of interest in psychiatry, including depression - with the focus on dietary supplementations for the correction of the C20:5ω3 component

(154). Of interest is the fact that most of the above discussed changes can be induced by the same pro-inflammatory cytokines responsible for the neurobehavioural symptoms of sickness behaviour. The fact that psychological stressors can induce a pattern of pro-inflammatory cytokine hypersecretion and a polyunsaturated fatty acid profile similar to the inflammatory response of sickness behaviour (155) once again demonstrates the similarities between the so-called psychological and the so-called medical disturbances.

The discussion above confirmed the presence of an inflammatory response in mood disorders such as major depression. In fact, depression has recently been described as a state of cerebral inflammation. This is a vast oversimplification. The question that comes to mind is whether the idea of major depression as pro-inflammatory response presents a new independent hypothesis on the etiology of depression and whether some of the neuroendocrine-based or psychologically based theories are rendered obsolete by the inflammatory approach. The answer to both would be an emphatic no. It can rather be said that the inflammatory response represents a major component of mood disorders that had previously been overlooked. These interactions between the neuroendocrine changes and behaviour, between behaviour and cytokines and between the neuroendocrine functions and cytokines have all been discussed. The introduction of the cerebral inflammatory response, influenced by, as well as influencing the neuroendocrine-behavioural functions, explains the connection between peripheral infectious and inflammatory events and the behavioural functions, as well as between psychologically induced predisposition to, and exacerbation of physical diseases. It would appear to form the core of the psychoneuroimmunological interaction. This does indeed deprecate any dogma that approaches mind and body as two separate entities.

It is at this stage relevant to refer back to the biopsychosocial approach. The psychoneuroimunological approach as described above can now be applied to the multiple entry point concept as suggested by the biopsychosocial approach to disease – including mental disorders as it becomes virtually impossible to separate mental from physical disease. It is obvious that the stimulatory input can be at, and the effector output from, virtually any point in the behavioural, neuroendocrine or immunological spectra.

The time the effects are presented would further not necessarily have to correspond to that of the primary stimulus as presensitisation during early childhood, or even later, may find behavioural expression only in the event of a trigger situation. The psychoneuroimmunological alterations characteristic of sickness behaviour can serve both as presensitisation factors and as trigger situations. It is at this stage perhaps necessary to recall that the primary stimulus for presensitisation may occur as early as prenatal life. Examples of such influences were discussed in Chapters 3 and 4 and earlier in this chapter. Of specific relevance to this writing is the fact that cytokines are of significant importance during the development of the central nervous system where they are involved in processes such as neuronal development, synaptogenesis, regeneration and plasticity, and that over- or underproduction of cytokines may alter the development of the central nervous system (156).

To clearly demonstrate the totality of the mind-body interaction in terms of the CRH/HPA-axis it would be necessary to do a comparative review on all mental and physical disorders associated with alterations in each system and to note both the physical and mental changes in all of them. This would no doubt result in startling simplification and facilitation of a proper understanding of what at present involves a wide spectrum of psychological and physical conditions. Such a writing is, however beyond the scope of this thesis.

The brief for this section was to show the correspondence between sickness behaviour and mood disorders – particularly major depression. Having demonstrated the similarities in terms of symptomatology, neuroendocrine changes and immune status, and knowing that earlier life events may predispose to a lowered triggering threshold, as well as to termination-failure, it should perhaps be asked whether depression and sickness behaviour are not one and the same thing. This, in fact, has been suggested by the malaise theory of depression (157). The essence of the malaise theory of depression is that it proposes the state or emotion of malaise to be considered the core symptom of depression, rather than the sadness or mood. On this basis, the primary pathology of depressive disorder is suggested to be somatic with the variable mood changes secondary

responses to the physical disorder. This, on first glance would appear to make sense. However, to see depression as sickness behaviour is to equate the stress response, which represents a transient adaptive new homeostasis or coping mechanism, with stress pathology. The malaise theory further suggests that many antidepressants exert their antidepressant action primarily by alleviating the physical state of malaise – with improvement of the behavioural aspects as secondary gain. This concept would appear to contain some truth with strong empirical evidence for analgesic effects of tricyclic antidepressants and some support for the assumption that non-tricyclic antidepressants may also have analgesic properties (157,158,159,160). Perhaps more relevant to the similarities between the inappropriate continuation of sickness behaviour and major depressive disorder is the fact that certain antidepressants would appear to have anti-inflammatory effects mediated partially through suppression of the secretion of pro-inflammatory cytokines. Antidepressants have indeed been reported to successfully control the immune reactivity and cytokine responses in depressed patients (145). One example of the anti-inflammatory effects of cytokines is the selective phosphodiesterase inhibitor Rolipram that was shown to suppress the production of cytokines such as TNF-alpha and interferon-gamma (161). There are, however, indications that certain anti-inflammatory effects may be mediated primarily through the influence on neurotransmitters such as serotonin. Selective serotonin reuptake inhibitors have, for instance been shown to suppress the secretion of acute phase proteins, as well as IL-6 levels. (161). Results from different laboratories on the anti-inflammatory effects of the different antidepressants are, however, not always in agreement and could at present not summarily be used to rationalize such therapeutical applications of antidepressants (145,161). One aspect of antidepressants that is apparently never considered when examining the presumed anti-inflammatory effects is that such effects may indirectly be mediated via the influence on the CRH-producing neurons. There are for instance strong indications that antidepressants such as fluoxetine, phenelzine and idazoxan can reduce CRH synthesis in the paraventricular nucleus and that it can improve glucocorticoid receptor binding (162). The potential anti-inflammatory effect, i.e., suppression of the production of a potentially pro-inflammatory substance such as CRH (Chapter5), as well as an antidepressant effect through normalisation of the CRH/HPA-axis is obvious.

Having demonstrated how a functionally adaptive state such as sickness behaviour can give rise to a psychopathological condition such as major depression, and probably also to the dysthymic disorder, we will now briefly turn to depression due to a general medical condition.

The prevalence of depression due to a general medical condition is vastly underestimated as can be seen from statistics which show that at least 74 percent of men committing suicide during periods of major depression were, at that stage, treated for some or other medical condition (163). Although the incidence of depression was, a couple of years ago, said to be around 40 percent in the seriously physical ill, this can be assumed to be a significant underestimation as many ill individuals will not admit to, or may perhaps not even be aware of, the fact that they are depressed (164,165).

It has previously been shown that a variety of factors can lead to the typical neuroimmunological profile of sickness behaviour, which comprises activation of the inflammatory response accompanied by alterations in the CRH/HPA- and CNA/SAM-axis, as well as in central serotonergic activity. A host of medical conditions can cause such disturbances including almost all acute infectious and inflammatory afflictions, the majority of chronic infectious and chronic inflammatory conditions, as well as trauma and surgery – in fact virtually any form of tissue injury. Furthermore, as seen in Chapter 6, these symptoms can also be caused by certain medications. Under such circumstances one would then also find behavioural adaptations as occur in sickness behaviour or major depression, with symptoms such as depressive mood states, anhedonia, fatigue, suppressed appetite, disturbed sleeping patterns, psychomotor retardation, reduced interest in the environment and in ported social activities, altered pain perception and sometimes impaired cognitive abilities (145). Amongst the non-infectious medical conditions where hyperactivation and secretion of cytokines have been reported with the highest incidence are various autoimmune diseases, allergies, multiple sclerosis, rheumatoid arthritis, stroke, trauma, the premenstrual syndrome, post-partum depression and neurodegenerative disorders (145).

The question that should be answered is whether depression due to a general medical conditions is not merely a psychological reaction to the disability, pain and loss of functionality, and whether it does indeed form part of the new homeostasis of sickness behaviour. Empirical evidence suggests that the depression and several other cognitive symptoms found in such conditions are causally related to pro-inflammatory activity rather than mere expressions of psychological reactions to the medical condition (145). There can be no doubt that a reactive depressive mood could develop in many individuals in response to a disabling medical condition. However, sickness behaviour, which can result from a wide spectrum of stimuli, can without doubt exacerbate such a reactive depression, or even be the major cause of the depression associated with a general medical condition. Evidence that depression due to a general medical condition is more often than not related to the immune activation of sickness behaviour can be derived from the fact that the depressive mood associated with influenza can appear even in the absence of the clinical symptoms (166), that the depressive moods of recurrent herpes infections may precede the clinical manifestations (167), and that the development of depression in multiple sclerosis often precedes the neurological diagnosis or knowledge of the condition (168). Should, as just shown, sickness behaviour in the medically ill give rise to cytokine-induced depressive moods, it stands to reason that it could, just as previously described for the development of sickness behaviour into major depression or dysthymic disorder, give rise to major depression. In addition to the other factors, which could underlie the non-termination of sickness behaviour, reactive depressive moods resulting from the disability could contribute to the inappropriate continuation of the symptoms.

It has previously been argued that major depression may develop from the inappropriate continuation of sickness behaviour due to non-termination after recovery from the initiating physical disturbance. It was further suggested that such a depression could no more be seen as sickness behaviour but, should it fulfill the criteria for major depression or dysthymic disorder, be considered as such. In the case of depression due to a medical condition this argument falls away. As long as the causative medical condition is present the symptoms should indeed be seen as the adaptive sickness behavioural response,

intended to favour coping with, and recovery from, the primary physical disorder. It should, however, be remembered that both glucocorticoids and pro-inflammatory cytokines can, if the condition persists for too long, bring about a situation of non-termination – especially in those individuals predisposed to it through genetics and early life experiences. Non-termination as a result of glucocorticoid resistance, brought about by high glucocorticoid and anti-inflammatory cytokine levels, as well as by several other mechanisms, has previously been discussed. It is, however, also known that a decrease in other factors which contribute to the termination of sickness behaviour, such as the Clara cell 16kD protein (CC16), a natural anti-inflammatory secretory protein involved in modulating the cytokine network and its effectors (169), as well as other substances such as alpha-MSH and the anti-inflammatory cytokines mentioned before, may contribute to non-termination. A decrease in these anti-inflammatory mediators is known to occur in melancholic depression (145). The condition of resistance to termination can furthermore be exacerbated or prolonged by negative perceptions, feelings of no control or the inability to cope – in fact, by any factor that causes psychological stress (170). Should the individual experience such emotions in reaction to the disabling effect of the illness, or for whatever other reason, it could further exacerbate and prolong the sickness behaviour-induced behavioural disturbance. It is thus clear that, although the depression often found in association with medical conditions may be the expression of sickness behaviour, it does present with the possibility to develop into a chronic mood disorder – especially in individuals predisposed to it by their genetic make up and early life experiences.

In addition to be the stimulus for the expression of mood disorders, sickness behaviour may also – at least in theory - serve as the trigger for the development of other mental disorders to which the individual is predisposed. Instead of discussing the supporting details for the various mental disorders, the rationale on which the last statement is based will be presented, e.g., the fact that pro-inflammatory conditions are present in a variety of mental disorders, that pro-inflammatory cytokines could underlie the symptoms and that the pro-inflammatory cytokines can lead to the type of cerebral neurotransmitter alterations associated with a wide spectrum of psychiatric disturbances.

In Chapter 2 it was shown that immune alterations can be found in all categories of the DSM-IV. More important, it was shown that specific patterns of immunological alterations do not seem to be correlates of specific mental conditions. Not only are there strong similarities between the immune disturbances of various categories of mental disturbances, but also between that of mental disturbances and a host of physical syndromes. Examples of other mental disorders and syndromes where shifts in pro-inflammatory activity have been reported include delirium, dementia and other cognitive disorders (e.g., Alzheimer's disease, Creutzfeldt-Jacobs disease, Parkinson's disease, the neuropsychiatric symptoms of HIV/AIDS), mental disorders due to a general medical condition (e.g., autoimmune disorders, chronic inflammatory conditions, etc), schizophrenia and other psychotic disorders, certain anxiety disorders, dissociative experiences and disorders, eating disorders, sleep disturbances and disorders, as well as personality disorders and others (Chapter 2).

In referring back to Chapter 6, it is obvious that, at least in theory, all of the behavioural symptoms of the above disorders can potentially result from abnormal cerebral cytokine homeostasis. Examples of the possible effects of cytokines on behaviour include all the symptoms of sickness behaviour and major depression, as well as emotional instability, crying spells, agitation, irritability, overreaction to problems and frustrations, cognitive impairment, hallucinations, delirium, delusional ideation, amnesia, clouding of consciousness, disorientation, personality changes, seizures, coma, increased sensitivity to and inability to cope with pain, Parkinson's like symptoms and many others. The reader is referred to Chapter 6 for the roles of the various cytokines in these and other processes – as well as for the appropriate references.

The majority of mental disorders are associated with some form of alteration in central nervous system function or even structure. It can also with a fair amount of certainty be assumed that the behavioural effects of pro-inflammatory cytokines are largely mediated through their effects on the neurotransmitter systems of the CNS - and to a lesser extent, as in the case of certain types of pain, on the peripheral nervous system. Many of these cytokine effects on cerebral neurotransmission are indeed known, but we are still far from

understanding the influence of the synergistic interaction between the various cytokines on cerebral structure and function. The stimulatory effects of cytokines on the CRH/HPA-axis have been discussed in the last couple of paragraphs of Chapter 6. A more in depth account on the effects of cytokines on the CRH/HPA-axis can, however, be found in a review by Buckingham et al, 1996 (150). Amongst the other effects of individual cytokines which could have a bearing on psychopathology (161) are the facts that a) IL-1, with high receptor density in the hippocampus, hypothalamus and brain stem, stimulates the release of peripheral catecholamines as well as brain stem and hypothalamic noradrenaline, and increases the turnover of noradrenaline, serotonin, tryptophan and dopamine in the brain, b) IL-2, with high receptor density in the locus coeruleus and pyramidal cell layer of the hippocampus, stimulates dopaminergic neurotransmission - particularly dopaminergic metabolism in the prefrontal cortex and may exert an effect on motor function by regulating striatal dopaminergic functions. It also increases hippocampal noradrenergic metabolism and may have a sedative effect through its influence on the locus coeruleus and nucleus caudatus. It has further been shown to inhibit acetylcholine release in the hippocampus and frontal cortex and may lead to neuronal loss and degenerative changes in the hippocampus with loss of mnestic functions, c) IL-6, with its high receptor density in the hippocampus and prefrontal cortex, stimulates the secretion of dopamine and noradrenaline and increases dopamine and serotonin turnover in the hippocampus and prefrontal cortex, d) TNF-alpha would appear to have a biphasic influence with stimulatory effects on the catecholaminergic systems in the acute situation and suppressive effects upon chronic exposure. It has further been implicated in cytotoxicity and demyelinisation. Most of the above effects reflect that of single cytokines in the acute situation.

In the previous paragraphs the fact that the inflammatory response is present in a variety of mental disorders, that psychiatric symptoms associated with a variety of mental disorders could result from an increase in pro-inflammatory cytokines, and that the inflammatory cytokines could underlie alterations in neurotransmitter systems, were discussed. The potential implications are clear, i.e., that, depending on the genetic predisposition and priming by previous life experiences, the cerebral inflammatory

response that underlies sickness behaviour may be the trigger for expression of any of a number of mental disorders.

An interesting phenomenon that once again supports the assumption of a central role for the CRH/HPA-axis in integrated mind-body homeostasis, is that many of these disorders are associated with abnormal functioning of the axis. Hyperactivity of the CRH/HPA-axis would appear to be present in the majority of the stress-related disorders in which the status of the axis has been investigated. The ostensible contradiction between non-termination of the inflammatory response and hyperactivity of the HPA-axis has been explained earlier in this chapter based on evidence from a wide spectrum of empirical research results. In short, mental disturbances or pathophysiological conditions as a result of non-termination of the inflammatory response and the neurohormonal disturbances associated with sickness behaviour will develop only when the individual has become resistant to the actions of the natural anti-inflammatory mechanisms – including cortisol. It is at this point important to remember that additional psychological stress during the appropriate period of sickness behaviour, can contribute to the inappropriate continuation of the condition.

The previous paragraphs dealt with the possibility of sickness behaviour developing into mental disorders known to be characterized by a hyperactivity of the CRH/HPA-axis and a pro-inflammatory shift in the cytokine balance. It was shown that early life adverse experiences may predispose the individual to such a transition through, amongst others, suppression of normal negative feedback and by increasing the baseline activity of the CRH/HPA-axis. However, it is also known that early life experiences may predispose to hypoactivity of the CRH/HPA-axis. A fact that, at first glance, would appear to directly predispose to inappropriate continuation of the inflammatory response. In contrast to the predisposition to hyperactivity of the CRH/HPA-axis with its relative resistance to negative feedback and subsequent continuation of the cerebral inflammatory response, our knowledge on the physiological aspects of those mental disorders where hypoactivity of the axis has been reported is rather scant and results often contradictory. The next couple of paragraphs will briefly look at conditions in which hypoactivity of the

CRH/HPA-axis has been reported, as well as the level of the CRH/HPA-axis where the insufficiency of the axis occurs and consider the possibility of sickness behaviour being the trigger for their induction.

Hypocortisolaemia, often accompanied by baseline sympathetic hypofunction and low serum serotonin and L-tryptophan levels, is reported for subsets of patients with the post-traumatic stress syndrome, fibromyalgia (FM), chronic fatigue syndrome (CFS), chemical intolerance and other stress related somatic disorders (171,172,173).

At this point in time the inconsistency in results confounds absolute conclusions. Amongst the disorders where HPA-axis hypoactivity can occur, PTSD differs from the others, not only in its etiology, but also at the level where the suppression occurs. PSTD is a typical severe stress-related disturbance, classified according to the DSM-IV as an anxiety disorder (174). In contrast to many other stressor-induced disorders, the precipitating traumatic event can usually be precisely identified, and re-experiencing of the event constitutes a major contribution to non-extinction and exacerbation of the allostatic load. Early life experience, genetics and support systems are bound to play a role in the development and progression as distinct differences exist between the psychological symptoms and neurological profiles of patients. Low cortisol levels have for instance been reported for combat-related PTSD (175), in PTSD-diagnosed women with a history of childhood sexual abuse (176), adolescents after an earthquake (177), and in other subsets of PTSD patients. However, there have been reports of normal and occasionally even high levels of cortisol in PTSD patients. A possible explanation comes from the fact that the activity of the HPA-axis in PTSD may change over time, depending on the psychiatric symptoms (178). It is thus essential that future research takes in consideration the stage as well as the symptoms. The best current conclusion on the CRH/HPA-axis disturbance in PTSD would appear to be that of Ehlert and Heinrichs, 2001, (173), i.e., that PTSD is associated with alterations of the axis that can be interpreted as a latent hypocortisolism with an increase in the feedback inhibition to the pituitary and the adrenals, while neuronal CRH release appears to be above normal. Of interest, and as could be expected, the elevated CRH is often accompanied by elevated

basal CSF noradrenaline levels. (162) It has been proposed that in PTSD patients with low cortisol levels the stress response is maladaptive rather than adaptive and that the reasons may be found in a combination of genetics and perinatal as well as childhood and adolescent stress (179,180) – a situation that could naturally influence the coping mechanism and the degree of control experienced by the individual. PTSD patients with low cortisol correspond to patients with melancholic depression in the fact that both groups demonstrate central hypersecretion of CRH, and differ in the fact that melancholic depression is characterized by hypercortisolaemia, in contrast to PTSD where hypocortisolaemia can be present. It is tempting to speculate that the relative adrenal insufficiency in PTSD could represent adrenal burn-out due to uncontrolled stress-induced stimulation during the earlier stages, and that the hypersecretion of CRH could partially be the result of cortisol-induced hippocampal damage at the stage of trauma or during the initial stages of development of PTSD – which would naturally present as a CRH oversecretion. A degree of hippocampal atrophy has indeed been observed in combat veterans with PTSD (181). However, the influence of CRH neurons in the prefrontal cortex and central nucleus of the amygdala as possible contributors should not be ignored.

In addition to PTSD low cortisol levels have also been reported in somatoform disorders and related syndromes[1]. According to the DSM-IV definition (182), somatoform disorders can be defined as the presence of physical symptoms that suggest a general medical condition but are not fully explained by a medical condition, by the direct effects of a substance or by another medical disorder. Idiopathic pain and gastrointestinal disturbances form important aspects, not only of several of the somatoform disorders, but

[1] No distinction will be made between somatoform disorders and either fibromyalgia or CFS – despite differences in their respective definitions. The corresponding aspects between them are, however stronger than the differences, especially if one looks at the somatisation, the undifferentiated somatoform and the pain disorder, and recalls that their symptoms are all described as not fully explainable by a medical condition. In fact, it has been suggested that most of the multisymptom syndromes like somatoform disorders, fibromyalgia, CFS and exposure syndromes such as Gulf War illnesses, sick-building syndrome, illnesses found in women with silicon breast implants, multiple chemical sensitivity and others are related in terms of their stress-exposure histories, their psychological profiles, and some neurological alterations (Clauw D. Potential mechanisms in chemical intolerance and related conditions Ann NY Acad Sci 2001;933:235-253.). Controversy still exists as to whether syndromes consisting of subjective health complaints represent several or variations on one general condition (Ursin H. Eriksen HR. Sensitization, subjective health complaints and sustained arousal. NY Acad Sci 2001;933:119-129).

also of multisystem syndromes where the symptoms can't at present fully be ascribed to a specific medical condition. Low cortisol levels have been reported in various types of idiopathic pain and with gastrointestinal disorders for which no organic cause could be found. Typical examples of hypocortisolism in association with idiopathic pain include recurrent headaches, idiopathic chronic pelvic pain in women, recurrent abdominal pain in children and idiopathic pain in combination with functional gastrointestinal disorders. In most of these patients where low cortisol levels were found, there were also histories of poor coping abilities, multiple major stressful life events, and in women with chronic pelvic pain, high rates of physical and sexual abuse. Preliminary indications are that a degree of adrenal insufficiency and an above normal sensitivity to the negative feedback may underlie the hypofunction of the HPA-axis (173,179,180,183).

Chronic fatigue syndrome represents a multisystem condition for which no medical cause has been established beyond doubt, where idiopathic pain and fatigue form the core symptoms, where chronic stress or previous trauma or infection have been implicated in the onset, and where hypoactivity has been reported in subsets of patients. The CRH/HPA-axis disturbance would appear to entail enhanced negative feedback as well as suppression of central CRH-release (173). It would at present appear as if the hypocortisolism of somatisation-associated disorders differs from that of PTSD in that the somatoform disturbances may be characterised by a deficiency in central CRH drive, while in PTSD the central drive corresponds to that of other stress-related disorders, i.e., hyperactivity.

It is known that prolonged perceptions of uncontrollability of a stressful situation may give rise to hypoactivation of the CRH/HPA-axis – whether it be primarily central or peripheral in origin. Interesting research data indicate that such hypoactivity may, by rendering the individual hypoaroused and apathetic, also increase the vulnerable to drug abuse. Such individuals may then turn to cocaine, amphetamines or other drugs to stimulate their minds and to get them to a comfortable state of arousal (184).

The focus, throughout this chapter, was on the negative effects of the environment on the CRH/HPA-axis, i.e., the priming to hyperactivity or hypoactivity. It was shown how this can predispose to the development of mental disorders and disease. However, indications are that the environment and social interactions may also function as stress buffering mechanisms by correcting basal CRH/HPA activity and through blunting stress-induced activation of the axis (192). These results confirm what has already indirectly been implied by the success of psychotherapeutic interventions and social support systems, i.e., that social buffering can correct environmentally induced abnormalities in neurohormonal systems. This at least offers some hope for those in whom CRH/HPA-axis dysfunction occurs as a result of previous life experiences. It also leaves the field wide open for more relevant interdisciplinary research. In considering work in this area of research it is, however, important to remember that CRH/HPA activity plays a role in the determination of social preferences (192) and, by implication, could determine whether an event or even treatment would be perceived as a stressor, or as a stress buffering mechanism. From animal experimental work it would appear that some changes, such as the development of cortisol resistance, should perhaps be seen as adaptational rather than as pathological (192). Several aspects need further investigation in order to come to a clear understanding on the proposed transition from sickness behaviour to psychopathology. From the reverse point of view, i.e., the influence of emotions on the development of physical and to an extent mental disorders, there is an urgent need for studies to be performed in psychoneuroimmunological context. Some such studies have already been conducted (1,2) and it would appear that distress-related immune dysregulations may represent the core mechanisms underlying the health risks associated with negative emotions.

7.5 Summary

This chapter presented sickness behaviour as a model of the psychoneuroimmunological interaction. Sickness behaviour is often mistakenly seen as the negative side effect of physical illness – the result of debilitation and exhaustion. The depressive mood and other behavioural effects are generally considered emotional reactions to the illness and

To accept that sickness behaviour can develop into syndromes and disorders marked by multiple subjective health complaints one would expect to find indications of pro-inflammatory activity. There are reasons to suspect that an inflammatory process may be present in those subsets of individuals characterized by hypoactivity of the HPA-axis. The first and most obvious reason is that of a deficiency of cortisol – one of the most potent inhibitors of inflammation. In fact, as shown in Chapter 5, subnormal cortisol may even be immune-enhancing, rather than immune-stimulatory. In addition, it is known that IL-6 levels can be associated with chronic distress, feelings of uncontrollability and posttraumatic stress disorder (169). It is also known that cytokines can stimulate inflammatory pain and that IL-1 *per se* may lead to an increase in pain sensitivity in general (173,185), The picture with regard to the inflammatory cytokines in the disorders with HPA-axis hypoactivity are, however far from clear. Some authors reported increases in most of the pro-inflammatory cytokines (IL-1, IL-6, TNF-alpha) (172,186,187) in chronic fatigue syndrome, but there are still many discrepancies in results. It seems necessary that researchers should subgroup their patients according to their HPA-axis activity and that psychiatric symptoms should be considered before investigating the immune status. Only then would it be possible to come to a better understanding on the immune status. However, even without proper empirical information on the pro-inflammatory status there are reasons to believe that sickness behaviour may render the individual vulnerable to the development of the somatoform and somatoform-related disturbances. The first reason is the similarity in symptoms. The second, more compelling, justification for the argument is that virtually all patients with clusters of subjective health complaints suffered either infectious complications – especially viral infections - or severe physical or emotional trauma (171). It has previously been shown that such events can initiate the development of sickness behaviour. It is also obvious that a hypoactivity of the HPA-axis can predispose to the development of inflammatory conditions and therefore to the inappropriate non-termination of sickness behaviour. Very interesting preliminary results that still need further investigation are that sickness behaviour can become a conditioned response (188,189,190,191). The implications speak for themselves.

debilitation. In this chapter it was shown that sickness behaviour should rather be seen as an adaptation to stress, i.e., a new adaptational homeostasis intended to aid in physical and psychological coping with the illness. The underlying mechanisms, as well as the adaptive value of the symptoms of sickness behaviour, were discussed. In line with Chapter 5 and Chapter 6 the central roles of the pro-inflammatory cytokines and the CRH/HPA-axis were illustrated and it was shown that cross-sensitisation can occur between the immunological (cytokines) and non-immunological stressors such as central neuroendocrine functions and cognitive phenomena like perceptions. Such cross-sensitisations can obviously influence the magnitude of the sickness behavioural symptoms, as well as the duration of the condition. Of additional importance is the fact that sickness behaviour can be initiated and maintained, not only by inflammatory or infectious conditions, but also by any form of tissue injury or psychological stress that alters the neuroimmunology balance towards a pro-inflammatory profile. It would, in fact, also appear as if sickness behaviour could be induced by conditioning.

Sickness behaviour, a condition afforded very little attention by the medical practitioner and seen largely as a reactive emotional state by psychologists, poses a potential threat to those rendered vulnerable to non-termination by their genetic makeup and early life presensitisation. Presensitisation, in the majority of cases, leads to hyperactivation of the major stress axes with a concomitant resistance to negative feedback to both the neurological systems and the pro-inflammatory cytokine activity. These characteristics are also present during sickness behaviour and constitutes characteristics of a number of mental disorders – including major depression of the melancholic type. The majority of the behavioural symptoms of sickness behaviour, which may range from mild constitutional disturbances to severe cognitive changes, result from the interaction between the pro-inflammatory cytokines and neurohormonal modulating systems such as the CRH/HPA-axis, the CNA/SAM-axis and the serotonergic system. Similar psychoneuroimmunological alterations marked by hyperactivity of the CRH/HPA-axis and the inflammatory response are seen in mental disorders such as major depression, the dysthymic disorder and, as classified by the DSM-IV, in depression due a general medical condition, as well as in other mental disturbances. In view of the similarities

between the neurohormonal, immunological and behavioural alterations of sickness behaviour and certain mental disorders, as well as the fact that non-terminations of sickness behaviour can occur due to early life predisposition and cross-sensitisation between non-cognitive and cognitive stimuli, it is postulated that sickness behaviour may, in certain circumstances, be the trigger for the development of mental disturbances. This hypothesis is particularly well supported by empirical evidence for mental disorders characterised by hyperactivity of the CRH/HPA-axis and pro-inflammatory activity. Despite the strong correspondence between the behavioural symptoms and possibly the presence of a cerebral inflammatory response in subsets of disorders associated with underactivity of the HPA-axis, research has not yet reached the point where an opinion can, with a fair amount of certainty, be expressed.

There can be no doubt that sickness behaviour represents a functional, adapted homeostasis intended to be of benefit to the individual. It is, however important to remember that sickness behaviour is in part a motivation state in which the afflicted individual is able to reorganize perceptions and behaviour within the existing internal and external limitations. In the knowledge that motivation states compete with each other for behavioural output, it is assumed that the hierachical organization of motivation states can be altered according to circumstances (193). In terms of sickness behaviour, any event perceived as more threatening than the illness may therefore transiently take precedence and the behaviour adapted to counter the new threat at the cost of the behavioural and physical adaptation for the illness. The expression of the behavioural aspects of sickness behaviour therefore becomes, within limits, a function of the individual's perceptions and needs. This, in line with stressor cross-sensitisation and the influence of cognitive functions, such as the perception of control, on the CRH/HPA-axis and immune status, thus also allows for a degree of modification of the biological symptoms of sickness behaviour by the psychological disposition - a good example of behaviour as biological response modifier. It is conceivable that, in certain individuals, sickness behaviour symptoms may consciously or subconsciously remain a preferred motivational state after recovery from the physical disorder. Such a condition, which

could possibly result from conditioning or the need to escape stressful situations, would contribute to the transition from sickness behaviour to psychopathology.

This chapter used sickness behaviour to illustrate the psychoneuroimmunological interaction in terms of the main stress axes. The central role of the CRH/HPA-axis and pro-inflammatory cytokines were described as major determinants of the sickness behavioural response and it was shown how psychological phenomena such as early life experiences and perception can act as biological response modifiers by altering the activities of the CRH/HPA-axis and the pro-inflammatory cytokines. The final sections of the chapter illustrated how sickness behaviour, which is intended as an adaptive homeostasis to facilitate coping and recovery, can, as a result of priming by negative life experiences, become the trigger for the expression of psychopathology. The next chapter will present conclusions on the thesis as a whole.

References

1. Kiecolt-Glaser JK, Mcguire L, Robles TF, Glaser R. Emotions, morbidity and mortality. New perspectives from psychoneuroimmunology. Ann Rev Psychol 2002;58:83-107.

2. Kiecolt-Glaser JK, Glaser R. Methodological issues in behavioral immunology research with humans. Brain Behav Immunol 1988;2:67-78.

3. Kiecolt-Glaser JK, Mcguire L, Robles TF, Glaser R. Zegans LS. Psychoneuroimmunology and psychosomatic medicine: Back to the future. Psychosom Med 2002;64:15-28.

4. Nature and nurture in psychiatry. A predisposition-stress model of mental disorders. Joel Paris. American Psychiatric Press, Inc, Washington DC, 1999.

5. Dantzer R, Bluthe RM, Castanon N, Chauvet N, Capuron L, Goodall G, Lelly KW, Konsman JP, Laye S, Parnet P, Pousset F. Cytokine effects of behaviour. In R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology (3rd ed, vol 1). Academic Press, San Diego, 2001, pp703-725.

6. Rabin BS The nervous system-immune connection. In: BS Rabin. Stress immune function and health. Wiley-Liss, New York, 1999, pp145-148.

7. Charlton BG. The malaise theory of depression: major depressive disorder is sickness behavior and antidepressants are analgesics. Medical Hypotheses 2000;54(1):126-130.

8. Bolles RC. Species-specific defense reactions and avoidance learning. Psychol Rev 1970;77:32-48.

9. Aubert A, Kelly KW, Dantzer R. Differential effect of polysaccharide on food hoarding behaviour and food consumption in rats. Brain Behav Immun 1997;11:229-238.

10. Nicola NA. Guidebook to cytokines and their receptors. Oxford University Press, Oxford, 1994.

11. Dinarello CA. Biological basis for interleukin-1 in disease. Blood 1996;87:2095-2147.

12. Dantzer R, Bluthe RM, Castanon NC, Capuron L, Goodall G, Kelley KW, Konsman JP, Laye S, Parnet P, Pousset F. Cytokine effects on behavior. In R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology (3rd ed, vol 1). Academic Press, San Diego, 2001, pp719-722.

13. Dunn AJ, Wang J, Ando T. Effects of cytokines on cerebral neurotransmission. Comparison with the effects of stress. In: R Dantzer, EE Wolmann, R Yirmiya (eds). Cytokines, stress and depression.. Advances in Experimental Medicine and Biology (vol461). Kluwer Academic/Plenum Publishers, New York, 1999, pp117-127.

14. Konsman JP, Parnet P, Dantzer R. Cytokine-induced sickness behavior: mechanisms and implications. Trends in Neurosci 2002;25(3):154-160.

15. Breder CD, Saper CB. Expression of inducible cyclooxygenase mRNA in the mouse brain after systemic administration of bacterial lipopolysaccharide. Brain Res 1996;713:64-69.

16. Lacroix S, Rivest S. Effect of acute systemic inflammatory response and cytokines on the transcription of the genes encoding cyclooxygenase enzymes (COX-1 and COX-2) in the rat brain. J Neurochem 1998;70:452-466.

17. Wong ML, Rettori V, Al-Sheklee A, Boniorno PB, Canteros G, McCann SM, Gold PW, Licinio J. Inducible nitric oxide synthase gene expression in the brain during systemic inflammation. Nat Med 1996;2:581-584.

18. Dantzer R, Aubert A, Bluthe RM, Gheusi G, Cremona S, Laye S, Konsman JP, Parnet P, Kelley KW. Mechanisms of the behavioral effect of cytokines. In: Dantzer R, Wollman EE, Yirmiya R (eds). Cytokines, stress and depression. Advances in experimental medicine and biology. (Vol 461). Kluwer Academic/ Plenum Publishers, New York, 1999, pp83-105.

19. Kluger MJ, Kozak W, Mayfield KP. Fever and immunity. In: R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology (3rd ed, vol 1). Academic Press, San Diego, 2001, pp687-702.

20. Wang WC, Goldman LM, Schleider DM, Appenheimer MM, Subjeck JR, Repsky EA, Evans SS. Fever-range hyperthermia enhances L-selectin-dependent adhesion of lymphocytes to vascular endothelium. J Immunol 1998;160:961-969.

21. Mackowiak PA. Fever: Basic mechanisms and management (2nd ed). Lippincott-Raven, Philadelphia, 1997.

22. Kozak W. Fever: A possible strategy for membrane homeostasis during infection. Pers Biol Med 1993;37:14-34.

23. Krueger JM, Fang J, Majde JA. Sleep in health and disease. . In: R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology (3rd ed, vol 1). Academic Press, San Diego, 2001, pp667-685.

24. Sluzewska A. Indicators of immune activation in depressed patients. In: NP Plotnikoff, RE Faith, AJ Murgo, RA Good (eds). Cytokines, stress and immunity. CRC Press, Boca Raton, Florida. 1999, pp59-73.

25. Leonard BE, Song C. Stress depression and the role of cytokines. In: NP Plotnikoff, RE Faith, AJ Murgo, RA Good (eds). Cytokines, stress and immunity. CRC Press, Boca Raton, Florida. 1999, pp251-266.

26. Hart B. Biological basis of the behavior of sick animals. Neurosci Biobehav Rev 1988;12:123-137.

27. Yirmiya R, Weidenfeld J, Pollak Y, Morag M, Morag A, Avitsur R, Barak O, Reichenberg A, Cohen E, Shavit Y, Ovadia H. Cytokines, 'depression due to a general medical condition', and antidepressant drugs. In: Dantzer R, Wollman EE, Yirmiya R. (eds). Cytokines, stress and depression. Advances in experimental medicine and biology. (Vol 461). Kluwer Academic/Plenum Publishers, New York, 1999, pp283- 316.

28. Anisman H, Merali Z. Anhedonic and anxiogenic effects of cytokines. In: Dantzer R, Wollman EE, Yirmiya R (eds). Cytokines, stress and depression. Advances in experimental medicine and biology. (Vol 461). Kluwer Academic/Plenum Publishers, New York, 1999, pp199-233.

29. Komaroff AL, Fagioli LR, Geiger AM, Doolittle DH, Lee J, Kornish J, Gleit MA, Guerriero RT. An examination of the working case definition of chronic fatigue syndrome. Am J Med 1996;100:56-64.

30. Koorts AM, Kruger MC, Viljoen M. Intracellular calcium and transmembrane calcium fluxes in chronic renal failure patients. Clin Physiol & Func Im 2002;22:285-294.

31. Jones THJ, Wadler S, Hupart KH. Endocrine-mediated mechanisms of fatigue during treatment with interferon-α. Sem Oncol 1998;25(suppl 1):54-63.

32. Kluger MJ. Fever: Role of pyrogens and cryogens. Phys Rev 1991;71:93-127.

33. Dantzer R, Bluthe RM, Kelley KW. Androgen-dependent vasopressinergic neurotransmission attenuates interleukin-1 induced sickness behavior. Brain Res 1991;557:115-120.

34. Zuckerman SH, Shellhaas J, Butler LD. Differential regulation of lipopolysaccharide-induced interleukin-1 and tumor necrosis factor synthesis: Effects of endogenous glucocorticoids and the role of the pituitary-adrenal axis. Eur J Immunol 1989;19:301-395.

35. Laye S, Goujon E, Combe C, VanHoy R, Kelley KW, Parnet P, Dantzer R. Effects of polysaccharides and glucocoticoids on the expression of interleukin-1β converting enzyme in the pituitary and brain of mice. J Neuroimmunol 1996;68:61-66.

36. Miller AH, Pariante CM, Pearce BD. Effects of cytokines on glucocorticoid receptor expression and function. Glucocoticoid resistance and relevance to depression. In: Dantzer R, Wollman EE, Yirmiya R (eds). Cytokines, stress and depression. Advances in experimental medicine and biology. (Vol 461). Kluwer Academic/ Plenum Publishers, New York, 1999, pp107-115.

37. Lakatos K, Toth I, Nemoda Z, Ney K, Sasvari-Szekely M, Gervai J. Dopamine D4 receptor (DRD4) gene polymorphism is associated with attachment disorganisation in infants. Mol Psych 2000;**5**:633-637.

38. Collins WA, Macoby EE, Steinberg I, Hetherington EM. Contemporary research on parenting: the case for nature and nurture. Am Psychol 2000;55(2):218-232.

39. Fonagy P. The human genome and the representational world: the role of early mother-infant interaction in creating an interpersonal interpretive mechanism. Bull Menninger Clin 2001;65(3):427-448.

40. Luecken LJ. Childhood attachment and loss experiences affect adult cardiovascular and cortisol function. Psychosom Med 1998;60:765-772.

41. Joseph R. Environmental influences on neural plasticity, the limbic system, emotional development and attachment: a review. Child Psych Hum Dev 1999;29(3):189-208.

42. Schore AN. Early organization of the nonlinear right brain and development of a predisposition to psychiatric disorders. Devel Psychopath;1997;9:595-631.

43. Schore AN. The experience-dependent maturation of a regulatory system in the orbital prefrontal cortex and the origin of developmental psychopathology. Devel Psychopathol 1996;8(1):59-87.

44. Taylor GJ, Parker JDA, Bagby RM. Emotional intelligence and the emotional brain: points of convergence and implications for psychoanalysis. J Am Acad Psychoanal 1999;27(3):339-354.

45. Henry JP. Psychological and physiological responses to stress: The right hemisphere and the hypothalamo-pituitary-adrenal axis, an inquiry into problems of human bonding. Acta Physiol Scand Suppl 1997;640:10-25.

46. Kotler T, Buzwell S, Romeo Y, Bowland J. Avoidant attachment as a risk factor for health. Br J Med Psychol 1994;67(3):237-45.

47. Joubert D, Reza Sadeghi M, Elliott M, Devins GM, Laperriere N, Rodin G. Physical sequelae and self-perceived attachment in adult survivors of childhood cancer. Psycho-Oncology 2001;10:284-292.

48. Gunnar MR. Quality of early care and buffering of neuroendocrine stress reactions: potential effects on the developing brain. Prev Med 1998;27:208-11.

49. Stuart S, Noyes R. Attachment and interpersonal communication in somatisation. Psychosomatics 1999;40:34-43.

50. Watson JS. Contingency perception and misperception in infancy: some potential implications for attachment. Bull Menninger Clin 2001;65(3):296-320.

51. Spangler G, Grossmann KE. Biobehavioral organization in securely and insecurely attached infants. Child Dev 1993;64(5):1439-50.

52. Bremner JD, Southwick SM, Johnson DR, Yehuda R, Charney DS. Childhood physical abuse in combat-related posttraumatic stress disorder. Am J Psychiatry 1993;150:235-9.

53. Dozier M, Chase Stovall KC, Albus KE. Attachment and Psychopathology in adulthood. In: Handbook of Attachment: Theory, Research and Clinical Applications. J. Cassidy, PR. Shaver (eds). The Guilford Press, New York. 1999. pp. 497-519.

54. Lynch M, Cichetti D. Trauma, mental representation, and the organization of memory or mother-referent material. Dev Psychopath 1998;10:739-759.

55. Phillips ML, Medford N, Senior C, Bullmore ET, Suckling J, Brammer MJ, Andrew C, Sierra M, Williams SCR, David AS. Depersonalisation disorder: thinking without feeling. Stress 2002;5(suppl):10.

56. Chorpita BF, Barlow DH. The development of anxiety: the role of control in the early environment. Psychol Bull 1998;124(1):3-21.

57. Corcos M, Atger F, Levy-Soussan P, et al. Bulimia nervosa and autoimmunity. Psychiatry Res 1999;87(1):77-82.

58. Suomi SJ. Attachment in Rhesus monkeys. In: Handbook of Attachment: Theory, Research and Clinical Applications. J. Cassidy, PR. Shaver (eds). The Guilford Press, New York. 1999. pp. 181-197.

59. Francis DD, Caldji FC, Champagne F, Plotsky PM, Meany MJ. The role of corticotropin-releasing factor-norepinephrine systems in mediating the effects of early experience on the development of behavioural and endocrine responses to stress. Soc Biol Psychiatry 1999;46:1153-1166.

60. Caldji C, Diorio J, Meaney J. Variations in maternal care regulate the development of stress reactivity. Biol Psychiatry 2000;48:1164-1174.

61. Levine S. Psychosocial factors in growth and development. In: Levi L (ed). Society, Stress and Disease. London, Oxford University Press, 1975, pp43-50.

62. Pacak K, Palkovits M, Kopin I, Goldstein DS. Stress-induced norepinephrine release in hypothalamic paraventricular nucleus and pituitary adrenocortical and sympathoadrenal activity: In vivo microdialysis studies. Front Neuroendocrinol 1995;16:89-150.

63. Francis DD, Meany MJ. Maternal care and the development of stress responses. Curr Op Neurobiol 1999;9(1):128-134.

64. Walker C-D, Toufexis DJ, Burlet A. Hypothalamic and limbic expression of CRH and vasopressin during lactation: implications for the control of ACTH secretion and stress hyporesponsiveness. Progress in Brain Res 2001;133:99-110.

65. Altemus M, Deuster PA, Galliven E, Carter CS, Gold PW. Suppression of hypothalamic-pituitary-adrenal axis responses to stress in lactating mothers. J Clin Endocrinol Metab 1995;80:2954-2959.

66. Champagne F, Meany MJ. Like mother, like daughter: evidence for non-genomic transmission of parental behavior and stress responsiveness. Prog Brain Res 2001;133:287-302.

67. Hennessy MB, Davis HN, McCrea AE, Harvey AT, Williams MT. Short- and long- term consequences of corticotropin-releasing factor in early development. Ann NY Acad Sci 1999;897:76-91.

68. Bakshi VP, Kalin NH. Corticotropin-releasing hormone and animal models of anxiety: gene-environmental interactions. Biol Psychiatry 2000;48:1175-1198.

69. Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB. CRF, depression and anxiety. J Endocrinol 1999;160:1-12.

70. Meany MJ, Diorio J, Francis D, Weaver S, Yau J, Chapman K. Postnatal handling increases the expression of cAMP-inducible transcription factors in the rat hippocampus: The effects of thyroid hormones and serotonin. J Neurosci 2000;20:3926-3395.

71. Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: Preclinical and clinical studies. Biol Psychiatry 2001;49:1023-1039.

72. Cummings SL, Young WS, King JS. Early development of cerebellar afferent systems that contain corticotropin-releasing factor. J Comp Neurol 1994;350(4):534-549.

73. Calza L, Giardino L, Pozza M, Micera A, Aloe L. Time-course changes in nerve growth factor, corticotropin-releasing hormone and nitric oxide synthase isoforms and their possible role in the development of inflammatory response in

experimental allergic encephalomyelitis. Prog Nat Acad Sci USA 1997;94(7):3368-3373.

74. Hinde RA (ed). Primate social relationships: an integrated approach. Sinauer Associates, Suderland, 1983.

75. Lubach GR, Kittrell EM, Coe CL. Maternal influences on body temperature in the infant primate. Physiol Behav 1992;51:987-994.

76. Reite M, Seiler C, Short R. Loss of your mother is more than loss of a mother. Am J Psychiatry1978;135:370-371.

77. Andrews MW, Rosenblum LA. The development of affiliative and agonistic social patterns in differentially reared monkeys. Child Dev 1994;65:1398-1404.

78. Andrews MW, Rosenblum LA. Influences of environmental demand on maternal behavior and infant development Acta Paed Suppl 1994;397:57-63.

79. Harlow HF, Harlow MK. Effects of various mother-infant relationships on rhesus monkey behaviors. In: BM Foss (ed), Determinants of infant behavior (vol 4), Methuen, London,1969, pp15-36.

80. Sackett GP, Bowman RE, Meyer JS, Tripp RL, Grady SS. Adrenocortical and behavioral reactions by differentially raised rhesus monkeys. Phys Psychology 1973;1:209-212.

81. Gluck JP, Ozer H, Hensley LL, Beauchamp A, Mailman RB, Lewis MH. Early isolation in rhesus monkeys: Long-term effects on survival and cell-mediated immunity. Society of Neuroscience Abstracts 1989;15:197.

82. Worlein JM, Sackett GP. Social development in nursery-reared pigtailed macaques. Am J Primatol 1997;41:23-35.

83. Lubach GR, Coe CL, Ershler WB. Effects of early rearing environment on immune responses of infant rhesus monkeys. Brain Behav Immun 1995;9:31-46.

84. Shannon C, Champoux M, Suomi. SJ. Rearing condition and plasma cortisol in rhesus monkey infants. Am J Primatol 1998;46:311-321.

85. Mineka S, Suomi SJ. Social separation in monkeys. Psychol Bull 1978;85:1376-1400.

86. Bowlby J. Attachment and loss II. Separation: anxiety and anger. Basic Books, New York, 1973.

87. Levine S, Weiner SG. Psychoendocrine aspects of mother-infant relationships in non-human primates. Psychoneuroendocrinology 1988;13:143-154.

88. Kraemer GW, Ebert MH, Schmidt DE, McKinney WT. Strangers in a strange land: A psychobiological study of infant monkeys before and after separation from real or inanimate mothers. Child Dev 1991;62:548-566.

89. Laudenschlager ML, Boccia ML, Berger CL, Gennaro-Ruggles MM, McFerran B, Reite ML. Total cortisol, free cortisol, and growth hormone associated with brief social separation in young macaques. Dev Psychobiol 1995;28:.199-212.

90. Laudenschlager ML, Reite M, Harbeck RJ. Suppressed immune response in infant monkeys associated with maternal separation. Behav Neural Biol 1982;36:40-48.

91. Coe Cl, Rosenberg LT, Levine S. Prolonged effect of psychological disturbance on macrophage chemiluminescence in the squirrel monkey. Brain Behav Immun 1988;2:151-160.

92. Coe CL, Rosenberg LT, Levine S. Effect of maternal separation on the complement system and antibody responses in infant primates Int J Neurosci 1988;40:289-302.

93. Coe CL, Erickson CM. Stress decreases lymphocyte cytolytic activity in the young monkey even after blockade of steroid and opiate hormone receptors. Dev Psychobiol 1997;30:1-10.

94. Laudenschlager ML, Rasmussen KLR, Berman CM, Suomi SJ, Berger CL. Specific antibody levels in free-ranging rhesus monkeys: Relationship to plasma hormones, cardiac parameters and early behavior. Dev Psychobiol 1993;26:407-420.

95. Boccia ML, Laudenschlager ML, Reite ML Intrinsic and extrinsic factors affect infant responses to maternal separation. Psychiatry 1994;57:43-49.

96. Kagan J Snidman N, Julia-Sellers J, Johnson MO. Temperament and allergic symptoms. Psychosom Med 1991;53:332-340.

97. Cacioppo JT. Social neuroscience: autonomic neuroendocrine and immune responses to stress. Psychophysiol 1994;31:113-128.

98. Caine N, Reite M. The effect of peer contact upon physiological response to maternal separation. Am J Primatol 1981;1:271-276.

99. Laudenschlager ML, Held PE, Boccia ML, Reite ML, Cohen JJ. Behavioral and immunological consequences of brief mother-infant separation: A species comparison. Dev Psychobiol 1990;23:247-264.

100. Cohen S, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM. Social ties and susceptibility to the common cold. J Am Med Assoc 1997;277:1940-1944.

101. Suomi SJ, Harlow HF, Domek CJ. Effect of repetitive infant-infant separation on young monkeys. J Abn Psychol 1970;76:161-172.

102. Scanlan JM, Coe CL, Latts A, Suomi SJ. Effects of age, rearing and separation stress on immunoglobulin levels in rhesus monkeys. Am J Primatol. 1987;13:11-22.

103. Laudenschlager ML, Berger CL, Boccia ML, Reite ML. Natural cytotoxicity towards K562 cells by macaque lymphocytes from infancy through puberty. Effects of early social challenge. Brain Behav Immun 1966;10:275-287.

104. Capitanio JP, Lerche NW. Psychosocial factors and disease progression in simian AIDS: A preliminary report. AIDS 1991;5:1103-1106.

105. Gordon DP, Gust DA, Wilson ME, Ahmed-Ansari A, Brodie AR, McClure HM. Social separation and reunion affects immune system in juvenile rhesus monkeys. Phys Behav 1992;51:467-472.

106. Gust DA, Gordon DP, Wilson ME, Brodie AR, Ahmed-Ansari A, McClure HM. Removal from natal social group to peer housing effects cortisol levels and absolute number of T-cell subsets in juvenile rhesus monkeys. Brain Behav Immun 1992;6:189-199.

107. Boccia ML, Scanlan JL, Laudenschlager ML, Berger Cl, Hijazi AS, Reite ML Juvenile friends, behavior, and immune responses to separation in bonnet macaque infants. Physiol Behav 1997;61:191-198.

108. Gust DA, Gordon TP, Brodie AR, McClure HM. Effects of a preferred companion in modulating stress in adult female rhesus monkeys. Physiol and Behav 1994; 55:681-684.

109. Capitanio JP, Lerche NW. Social separation, housing relocation, and survival in simian AIDS: A retrospective analysis. Psychosom Med 1998;60:235-244.

110. Gust DA, Gordon TP, Wilson ME, Brodie AR, Ahmed-Ansari A, McClure HM. Formation of a new social group of unfamiliar female rhesus monkeys affects the immune and adrenocortical systems. 1991;5:296-307.

111. Boccia Ml, Reite ML, Laudenschlager ML. On the physiology of grooming in pigtail macaques. Physiol Behav 1989;45:667-670.

112. Gust DA, Gordon TP, Hambridge MK, Response to removal from and return to social group in adult male rhesus monkeys. Physiol and Behav 1993;53:599-602.

113. Cohen S, Kaplan JR, Cunnick JE, Manuck SB, Rabin BS. Chronic social stress, affiliation and cellular immune response in non-human primates. Psychol Sci 1992;3:301-304.

114. Cunnick JE, Cohen S, Rabin BS, Carpenter AB, Manuck SB, Kaplan JR. Alterations in specific antibody production due to rank and social instability. Brain Behav Immun 1991;5:357-369.

115. Boccia ML, Laudenschlager ML, Broussand CL, Hijazi AS. Immune responses following competitive water tests in two species of macaques.Brain Behav Immun 1992;6:201-213.

116. Alberts SC, Sapolsky RM, Altman J. Behavioral, endocrine and immunological correlates of immigration by an aggressive male into a natural primate group. Hormones and Behav 1992;26:167-178.

117. The Fourth World Congress on Stress, Edinburgh, UK, September 12-15, 2002.

118. Shekhar A, Sajdyk TJ, Rainnie DG, Gehlert. CRH-induced plasticity in the amygdala: a putative link between stress and human illness. Stress 2002;5(suppl):24.

119. Ingram CD, Fairchild G, Johnson DA, Troakes C, Lowry C, Lightman, SL, Gartside SE. CRH and glucocorticoid actions on raphe serotonergic neurons. Stress 2002;5(suppl):24.

120. Matthews SG, Owen D, Banjanin S, Andrews MH. Glucocorticoids, endocrine development and life after birth. Stress 2002;5(suppl):26.

121. Plotsky PM, Walker CD, Garlow SJ. Persistent changes in central nervous system gene expression in response to repeated neonatal separation. Stress 2002;5(suppl):27.

122. Grunau RE. Early repetitive stress in preterm infants: effects on behaviour and development. Stress 2002;5(suppl):27.

123. Heim C. Neurobiological correlates of early adverse experience in women. Stress 2002;5(suppl):28.

124. Schulkin J, Gold PW, McEwen BS. Induction of corticotropin-releasing hormone gene expression by glucocorticoids: implication for understanding the states of fear, anxiety and allostatic load. Psychoneuroendocrinology 1998;23(3):219-243.

125. Armario A. A single exposure to a severe stressor causes long-term desensitization of the physiological response to the homotypic stressor. Stress 2002;5(suppl):16.

126. Sanchez MM, Anand KJS. Long-term consequences of early painful experiences. Stress 2002;5(suppl):17.

127. Morilak DA. A modulatory role of norepinephrine in behavioural stress responsiveness and susceptibility to stress-related pathology. Stress 2002;5(suppl):25.

128. Phillips DIW. Fetal growth, the HPA axis and the metabolic syndrome. Stress 2002;5(suppl):28.

129. Walker CD, Proulx K, Richard D, Salzman CX, Gallo-Payet N. Leptin enhances glucocorticoid feedback sensitivity while limiting stimulated adrenal corticosterone release in rat pups. Stress 2002;5(suppl):29.

130. Brunton PJ, Russel JA. Endogenous opioids are involved in reduced neuroendocrine responses to immune challenges. Stress 2002;5(suppl):52.

131. Douglas AJ, Bosch O, Toschi N, Neumann ID. Stress hyporesponsiveness during parturition in the rat: antagonising brain oxytocin does not reveal an inhibitory influence. Stress 2002;5(suppl):54.

132. Levay PF, Viljoen M, Meij HS. Oksitosien: 'n Kort oorsig. Die Suid Afrikaanse Tydskrif vir Natuurwetenskap en Tegnologie 1993;12(3)61-66.

133. Ma S, Shipton MJ, Russel JA. Roles of neurosteroids in the attenuated hypothalamo-adrenal-pituitary (HPA) axis stress response in pregnant rats. Stress 2002;5(suppl):58.

134. De Kloet, Oitzl MS, Meijer OC, Karssen AM, Datson NA, Feldker DEM, Vreugdenhil E. Glucocorticoid signalling and responsive genes: implications for behavioural adaptations. Stress 2002;5(suppl):30.

135. Hsu SY, Hsueh AJ. Human stresscopin and stresscopin-related peptide are selective ligands for the type 2 corticotropin-releasing hormone receptor. Nature Medicine 2001;7(5):605-611.

136. Welberg LA, Seckl, JR, Holmes MC. Prenatal glucocorticoid programming of brain corticosteroid receptors and corticotropin-releasing hormone: possible implications for behaviour. Neuroscience 2001;104(1):71-79.

137. Weinstock M. Does prenatal stress impair coping and regulation of hypothalamic-pituitary-adrenal axis? Neurosci Biobehav Rev 1997;21(1):1-10.

138. Sheline YI, Wang PW, Gado MK, Csernansky JG, Vannier WW. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci 1996; 93:3908-3913.

139. Miller AH, Pariante CM. Effects of cytokines on glucocorticoid receptor expression and function. In: R Dantzer, EE Wollman, R Yirmiya (eds). Cytokines, stress and depression. Advances in Experimental Medicine and Biology, Vol 461. Kluwer Academic/Plenum Publishers, New York, 1999, pp107-127.

140. Ruiz M, Lind U, Gafvels M, Eggertsen G, Nilsson L. Characteristics of two novel mutations in the glucocorticoid receptor gene in patients with primary cortisol resistance. Clin Endocrinol 2001;55(3):363-371.

141. Smith RS. The macrophage theory of depression. Medical Hypothesis 1991; 35:298- 305.

142. Maes M. The interleukin hypothesis of major depression. Prog Neuropsychopharmacol Biol Psychiatry 1995;19:11-35.

143. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. American Psychiatric Association, Washington, DC, 1994, pp317-389.

144. Bouwer C, Claassen J, Dinan TG, Nemeroff CB. Prednisone augmentation in treatment-resistant depression with fatigue and hypocortisolaemia: a case series. Depression and Anxiety 2000;12(1):44-50.

145. Yirmiya R, Weidenfeld J, Pollack Y, Morag M, Morag Y, Avitsur R, Barak O, Reichenberg A, Cohen E, Shavit Y, Ovadia H. Cytokines, depression due to a general medical condition and antidepressant drugs. In: Robert Dantzer, Emmanuelle E Wollman, Yirmiya R. Cytokines stress and depression. Advances in Experimental Medicine and Biology (vol 461). Kluwer Academic/ Plenum Publishers, New York, 1999, pp283-307.

146. Lindhorst ACE, Reul JMHM. Inflammation and brain function under basal conditions and during long-term elevation of brain corticotropin-releasing hormone levels. In: Robert Dantzer, Emmanuelle E Wollman, Yirmiya R. Cytokines stress and depression. Advances in Experimental Medicine and Biology (vol 461). Kluwer Academic/ Plenum Publishers, New York, 1999, pp129-152.

147. Maes M, Bosmans E, Meltzer HY, Sharpe S, Suy E. Interleukin-1β: a putative mediator of HPA axis hyperactivity in major depression? Am J Psychiatry 1993;150:1189-1193.

148. Chrousos GP. Stressors, stress and neuroendocrine integration of the adaptive response. NY Acad Sci 1998;851:311-355.

149. Maes M, Meltzer HYM. The serotonin hypothesis of major depression. In: F Bloom, D Kupher (eds) Psychopharmacology: the fourth generation of progress. Raven Press. New York, 1995, pp933-944.

150. Buckingham JC, Loxley HD, Christian HC, Philip JG. Activation of the HPA axis by immune insults: roles and interactions of cytokines, eicosanoids, and glucocorticoids. Pharmacol Biochem Behav 1996;54:285-288.

151. Maes M. Major depression and activation of the inflammatory response system. In: R Dantzer, EE Wollman, R Yirmiya. Cytokines, Stress and Depression, Advances of Experimental Medicine and Biology, Vol 461, Kluwer Academic/Plenum Publishers, New York, 1999, pp25-46.

152. Nicoloff JT, LoPresti JS. Non-thyroidal illness. In: LE Braverman, RD Utiger (eds). The thyroid: A functional and clinical text. JB Lippencott Company, New York, 1991, pp357-367.

153. Spath-Schwalbe E, Hansen K, Schmidt F, Schrezenmeier H, Marshall L, Burger K, Fehm HL, Born J. Acute effects of human recombinant interleukin-6 on endocrine and central nervous sleep functions in healthy men. J Clin Endocrinol and Metab 1998;83:1573-1579.

154. Haag M. Poly-unsaturated fatty acids: cellular role and clinical applications. The Medical Journal 2001;43:13-17.

155. Maes M, Christophe A, Bosmans E, Lin A, Neels H. In humans, serum polyunsaturated fatty acid levels predict the response of proinflammatory cytokines to psychological stress. Biol Psychiatry 2000;47(10):910-920.

156. Merrill JE. Tumor necrosis factor alpha, interleukin 1 and related cytokines in related brain development: normal and pathological. Dev Neurosci 1992;14:1-10.

157. Charlton BG. The malaise theory of depression: major depressive disorder is sickness behavior and antidepressants are analgesics. Medical Hypothesis 2000;54(1):126-130.

158. Lee R, Spencer PSJ. Antidepressants and pain: a review of the pharmacological data supporting the use of certain tricyclics in chronic pain. J Internat Med Res 1997;5(suppl 1):146-156.

159. Portnoy RK, Kanner RM. Pain management: Theory and Practise. FA Davis, Philadelphia, 1996, pp226-229.

160. McDaniel JS, Musselman DL, Porter MR, Reed DA, Nemeroff CB. Depression inpatients with cancer: diagnosis, biology and treatment. Arch Gen Psychiatry 1995;52:89-99.

161. Muller M, Ackenheil M Psychoneuroimmunology and the cytokine action in the CNS: implication for psychiatric disorders. Prog Neuropsychopharmacol Biol 1998;22;1-33.

162. Kasckow JW, Baker D, Geratioti TD. Corticotropin-releasing hormone in depression and post-traumatic stress disorder. Peptides. 2001;22:845-851.

163. Chochinov HM, Wilson KG, Enns M, Lander S. Prevalence of depression in the terminally ill. Effects of diagnostic criteria and symptom threshold judgements. Am J Psychiatry 1994;4:537-540.

164. Katon W, Sullivan MD. Depression and chronic medical illness. J Clin Psychiatry 1990;51:3-11.

165. Isometsa ET, Aro HM, Henrikkson MM, Heikkinen ME, Lonnqvist JK. Suicide and major depression in different treatment settings. J Clin Psychiatry1994;55:523-537.

166. Smith AP, Tyrrell DAJ, Al-Nakib W, Coyle KB, Donovan CB, Higgins PG, Willman JS. The effects of experimentally induced respiratory virus infections and illness. Psychology and Health 1988;5:205-212.

167. Hickie I, Lloyd A. Are cytokines associated with neuropsychiatric syndromes in humans? Int J Immunopharmacol 1995;17:677-683.

168. Schiffer RB, Babigian HM. Behavioral disorders in multiple sclerosis, temporal lobe epilepsy, and amyotrophic lateral sclerosis. An epidemiological study. Arch Neurol 1984;41:1067-1069.

169. Reif W, Pilger F, Ihle D, Bosmans E, Maes M. Immunological differences between patients with major depression and somatization syndrome. Psychiatry Res 2001;105:165-174.

170. Maes M, Song C, Lin A, Jongh RD, Van Gastel A, Kenis G, Bosmans E, De Meester I, Benoy I, Neels H, Demedts P, Janca A, Scharpe S, Smith RS. The effects of psychological stress on humans: Increased production of proinflammatory cytokines and a Th-1 like response in stress-induced anxiety. Cytokine 1998;10:313-318.

171. Clauw DJ. Potential mechanisms in chemical intolerance and related conditions. Ann NY Acad Sci 2001;933:235-253.

172. Visser JTJ, De Kloet ER, Nagelkerken L. Altered glucocorticoid regulation of the immune response in chronic fatigue syndrome. Ann NY Acad Sci.2000;917:868-875.

173. Ehlert U, Heinrichs JGM. Psychoneuroendocrinological contributions to the etiology of depression, posttraumatic stress disorder, and stress-related bodily disorders: the role of the hypothalamus-pituitary-adrenal axis. Biol Psychol 2001;57:141-152.

174. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. American Psychiatric Association, Washington, DC, 1994, p424.

175. Baker DG, West SA, Nicholson WE, Ekhator NN, Kasckow JW, Hill KK, Bruce AB, Orth DN, Geratioti TD. Serial corticotropin-releasing hormone levels and adrenal cortical activity in combat veterans with posttraumatic stress disorder. Am J Psychiatry 1999;156:585-588.

176. Stein MB, Yehuda R, Koverola C, Hanna C. Enhanced dexamethasone suppression of plasma cortisol in adult women traumatizes by childhood abuse. Biol Psychiatry 97;42:680-686.

177. Goenjian AK, Yehuda R, Pynoos RS, Steinberg AM, Tashjian M, Yang RK, Najarian LM, Fairbanks LA. Basal cortisol, dexamethasone suppression of cortisol and MHPG in adolescents after the 1988 earthquake in Armenia. Am J Psychiatry 1996;153:929-934.

178. Wang S, Wilson JP, Mason JW. Stages of decompensation in combat-related posttraumatic stress disorder: a new conceptual model. Integr Physiol Behav 1996;31:237-253.

179. Heim C, Ehlert U, Hellhammer DH. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. Psychoneuroendocrinology 2000;25:1-35.

180. Heim C, Newport DJ, Wilcox M, Bonsall R, Miller AH, Nemeroff CB. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. J Am Med Assoc 2000;284:592-597.

181. Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW, Orr SP, Kikinis R, Jolesz FA, McCarley RW, Pitman RK. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. Biol Psychiatry 1996;40:1091-1099.

182. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. American Psychiatric Association, Washington, DC, 1994, pp445-469.

183. Heim C, Ehlert U, Hanker JP, Hellhamer DH. Abuse related posttraumatic stress disorder and alterations of the hypothalamic-pituitary-adrenal axis in women with chronic pelvic pain. Psychosom Med 1998;60:309-318.

184. Majewska MD HPA axis and stimulant dependence: and enigmatic relationship. Psychoneuroendocrinology 2002;27:5-12.).

185. Schaefer M, Stein C. Control of pain in peripheral tissue by cytokines and neuropeptides. In: NP Plotnikoff, Faith RE, Murgo AJ, Good RA. Cytokines, stress and immunity. CRC Press, Boca Raton, FL,1999, pp261-270.

186. Strauss SE, Chronic fatigue syndrome: point and counterpoint. J Infect Dis 1994;170:1-6.

187. Komaroff AL. Chronic fatigue syndrome: an update. Ann Rev Med 1998;49:1-13.

188. Bull DF, Brown R, King MG. Modulation of body temperature through taste aversion conditioning. Physiol Behav 1991;49:1229-1233

189. Exton MS, Bull DF, King MG. Behavioural conditioning of lipopolysaccharide-induced anorexia. Physiol Behav 1995;57:401-405.

190. Janz LL, Green-Johnson J, Murray L. Pavlovian conditioning of LPS-responses: effects on corticosterone, splenic NE, and IL-2 production. Physiol Behav 1996;59:1103-1109.

191. Bull DF, Exton MS, Husband AJ. Acute phase immune response: lipopolysaccharide-induced fever and sleep alteration are not simultaneously conditionable in the rat during the active phase (light) phase. Physiol Behav 1994;56:143-149.

192. DeVries AC. Interaction among social environment, the hypothalamic-pituitary-adrenal axis, and behaviour. Horm Behav 2002;41:405-413.

193. Dantzer R. Cytokine-induced sickness behavior: mechanisms and implications. Ann NY Acad Sci 2001;933:222-234.