

The role of stress in neurodegenerative diseases and mental disorders

Tobias Esch^{1,2}, George B. Stefano^{1,3}, Gregory L. Fricchione⁴ & Herbert Benson¹

1. The Mind/Body Medical Institute, CareGroup and Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston MA 02215, U.S.A.
2. Kliniken Essen-Mitte, Department for Internal and Integrative Medicine, 45276 Essen, GERMANY.
3. Neuroscience Research Institute, State University of New York at Old Westbury, NY 11568, U.S.A.
4. The Carter Center Mental Health Program, Atlanta GA 30307, U.S.A.

Correspondence to: Tobias Esch, M.D.
Mind/Body Medical Institute
Beth Israel Deaconess Medical Center
Harvard Medical School
110 Francis Street, Suite 1A
Boston MA 02215, U.S.A.
PHONE: (U.S.A.) 617-632-9548 FAX: (U.S.A.) 617-632-7383
E-MAIL: tesch@caregroup.harvard.edu

Submitted: April 4, 2002
Accepted: April 6, 2002

Key words: **stress; Alzheimer's disease; multiple sclerosis; anxiety; depression; PTSD; schizophrenia;**

Neuroendocrinology Letters 2002; 23:199-208 piii: NEL230302R02 Copyright © Neuroendocrinology Letters 2002

Abstract

OBJECTIVE: Evidence for a connection between stress and selected neurodegenerative diseases as well as mental disorders is analyzed. Does stress cause or exacerbate related pathophysiological disease processes? **METHOD:** The stress phenomenon is illustrated and the impact of stress on the nervous system, neurodegenerative diseases, and mental disorders is examined. The connection between stress and the hippocampus – and its association with memory functions – is described. In particular, the pathophysiological significance of stress in Alzheimer's disease, multiple sclerosis, anxiety, depression, posttraumatic stress disorder, and schizophrenia is investigated. **RESULTS:** Stress plays a major role in various (patho)physiological processes associated with neurodegenerative diseases and mental disorders. In principle, stress has the potency to exert either ameliorating or detrimental effects. The specific outcome depends on multiple variables. However, the amount of stress experienced in relation to activated physiological processes that aim at successful coping and positive adjustments (i.e., stress response) most often is overwhelming – and may thus become detrimental in the long-term. Moreover, the hippocampus is sensitive to stress, and its involvement in neurodegeneration – in the course of stress-related disease processes – may account for severe clinical disabilities (e.g., memory loss). **DISCUSSION/CONCLUSION:** Stress has a major impact upon neurodegenerative diseases and mental disorders. It plays a significant role in susceptibility, progress, and actual outcome. Also, subjective or individual differences have to be taken into account. However, stress – especially 'adequate' acute stress (stress that is not overwhelming) – may even improve performance/biological functions and be beneficial in certain cases.

CONTENTS

1. Introduction
 2. Stress
 3. Stress-related neurodegenerative diseases and mental disorders
 - 3.1. Neurodegenerative diseases
 - 3.1.1. Alzheimer's disease
 - 3.1.2. Multiple sclerosis
 - 3.2. Mental disorders
 - 3.2.1. Anxiety, depression
 - 3.2.2. Posttraumatic stress disorder (PTSD)
 - 3.2.3. Schizophrenia
 4. Discussion
 5. Conclusions
- Acknowledgements
References

1. Introduction

The term 'stress' first appeared in the index of *Psychological Abstracts* in 1944 [1]. However, this term has become widely popular only in the last few decades, and in industrialized countries, a 'stress epidemic' has been apparently ignited: Today, almost everybody seems to be affected by the negative effects of stress [1].

The history of the stress concept reaches further back: Thorough research of stress physiology was conducted throughout the late 19th and the entire 20th century [1]. Moreover, stress may have ameliorating or detrimental capacities. In the latter case the connection between stress and various diseases, though more and more accepted, is still controversially discussed [1].

With this work, we want to describe the modern stress concept – in short – and then look at evidence for an association of stress with disease processes that are related to neurodegenerative and mental disorders.

2. Stress

The pioneering research of the late Hans Selye is often credited with popularizing the concept of stress and its relationship to pathophysiological processes and the onset of diseases [1,2,3,4,5,6]. Indeed, Selye was so successful in his career-long efforts to promote the importance of stress in physiology and medicine that many contemporary theories relating to the etiology of chronic diseases include stress as a precipitating variable [1,4,5,6,7]. Moreover, stress has recently been shown to play an important role in the onset of cardiovascular diseases, immunological disorders, and pathophysiological consequences of normal aging [8,9,10,11,12].

A continuing matter of investigation in the field of stress research concerns the underlying mechanisms and pathophysiological pathways by which stress possibly influences the onset of diseases. Further, the concrete participation of stress in underlying processes that eventually facilitate specific disease processes is still controversially discussed [1,7]: For many diseases,

the evidence that stress triggers certain mechanisms of pathophysiological importance is still weak/little – or substantially mistrusted [7]. This is particularly true for neurological or neuroendocrine disorders, such as neurodegenerative and mental disorders – even though aspects of their pathophysiology may already be associated with stress [7].

Stress describes the effects of psychosocial and environmental factors on physical or mental well-being [1,5,7]. Stressors and related stress reactions are distinguished [1,5]. When stressors challenge an organism's integrity, a set of physiological reactions is elicited to counteract a possible threat and adjust the organism (the physiological setting) to the new situation: The 'stress response' [1,4,8,9]. Thereby, one stress-responsive neuroendocrine effector system that has been studied extensively over the past decades is the sympathetic-adrenal-medullary (SAM) system, which is under the control of central neural pathways [6,9,13]. Another component of the stress response (i.e., the physiological system that regulates the biological reactions elicited in response to stressful/challenging stimuli or stressors) is the hypothalamic-pituitary-adrenal (HPA) axis [6,14]. Frequently, the SAM is equated with the sympathetic nervous system (SNS). These two systems – HPA axis and SNS – are normally operating within a delicate state of balance ('homeostasis'), established to maintain the organism's integrity even under highly challenging conditions (perturbations: 'stress') [4,5,8,9,11]. However, the stress response represents a complex and sensible instrument that is yet susceptible to pathophysiological factors or processes and further has an impact upon many biological functions [1,7,15,16]. Thus, it may likewise exert ameliorating or detrimental effects. In other words, mediators of stress physiology can have both protective and harmful effects in organs like the heart, the brain and the immune system [8,9].

Recently, new terms have been introduced into the stress concept to facilitate a better understanding of the interrelationships between external/environmental and internal (e.g., behavioral, cognitive) stressors, the physiological responses to these challenges (stress responses), and disease/illness. For example, 'allostasis' refers to the maintenance of overall stability (homeostasis) through the constant adjustment and balancing of various components in the process of adapting to challenge [5,8]. The result of this constant adjustment is a *dynamic* balance [1,5].

The body invests metabolic energy in order to repeatedly adapt to physical challenges and psychosocial threats. 'Allostatic load' refers to this perturbing wear and tear on the organism forced to use allostatic (rebalancing) mechanisms over and over in response to stressors [8,9]. As a result, an overuse of allostasis phenomena on one hand or an inefficiency in allostatic response functioning on the other may occur – related to the need to turn response pathways on and off in a suc-

cession of stress responses [9]. Here exists a possible threat to an organism's integrity and health [1,8,9].

The broad spectrum of stimuli capable of activating an intentionally protective allostatic response is remarkable and reflects upon how well integrated our perceptions of the physical and psychological worlds are [17]. In this context, the challenging 'stress' can be defined as a state of disharmony, or 'threatened homeostasis' [8,9]. In this state, SNS and HPA axis are actively involved [8,9].

Over time, particularly in chronic stress, the prolonged stimulation of SNS and HPA axis may lead to an enduring threat (threatened homeostasis), thereby eventually facilitating deleterious disease processes [1,7,8,9]. Here, especially the sympathetic activation may represent a dangerous momentum, since chronic SNS stimulation – or the defense of an 'overwhelming' acute stressor – may produce a sympathetic overflow [9,18]. This SNS activity (involving SNS overstimulation and norepinephrine overproduction), even though primarily associated with physiological autoregulatory signaling pathways (stress response pathways), may adversely/unexpectedly become pathophysiologically relevant [9]: Susceptibility to cardiovascular diseases or preexisting manifest problems of the circulatory system may characterize risk factors for stress- and SNS-related fatal developments [9]. With regard to the latter, stress has already been shown to increase the overall and specific risk for cardiovascular events [9].

Starting with the fundamental work of Walter Cannon [15,16], the SAM system has been viewed as a critical neuroendocrine effector system that is called into play when an organism is exposed to various physical, biological, chemical, or psychosocial (mental, behavioral etc.) stressors [5,6,8,9]. Thereby, the critical effector molecules of the SAM/SNS are the catecholamines – such as norepinephrine (NE) [6,14,15,16]. On the other side, there is the HPA axis, which, for example, regulates the immune response through the immunosuppressive effects of the glucocorticoids – one of the end products of an activated HPA axis [8,19]. More recently, other molecules involved in the stress physiology have been detected, e.g., melatonin [20] and anandamide [21], and the connection of nitric oxide (NO) with the stress response has further been proposed [21,22,23,24,25]. Thus, various hormonal and neuronal mechanisms are involved in (patho)physiological processes that are potentially related to stress. Hormonal mechanisms include activation of HPA axis and SNS – both crucial components of the stress response that have the potential to either exert ameliorating or detrimental effects [8,9]. A disturbance of the (usually) delicate balance between HPA/SAM pathways, between central/ peripheral or neuronal/hormonal parts of the stress response, may be associated with the exacerbation or development of diseases.

Now, one of the questions that arise in relation to stress and its possible impact upon pathophysiological

disease processes is: Does stress cause or exacerbate neurological diseases as well? In particular, does stress have an impact upon neurodegenerative and mental disorders?

3. Stress-related neurodegenerative diseases and mental disorders

While stress plays an important role in immunological [8] and cardiovascular [9] diseases, the question of stress in connection with its significance in onset, development, and progression of neurological disorders is not a simple one. This is partly due to the complexity and polymorphism of neurological disorders. For example, a great number of movement disorders, many of them of neurological origin, are affected by stress and trauma [26], and cardiovascular or immunological diseases may also manifest themselves in the nervous system [8,9]. Thus, we exemplarily selected the field of neurodegenerative and mental disorders for a more thorough analysis.

3.1. Neurodegenerative diseases

Neurodegeneration and stress seem to be connected with each other. For example, recent evidence suggests a linkage between the intensity of the stress response, the rate of age-dependent neurodegeneration, and the individual's life expectancy [27]. It has been proposed that an inherent hyperactivity to stressors is linked to a shorter life-span and to accelerated age-dependent neurodegeneration [27]. This hyperactive or 'excessive' stress response may be genetically determined [27] or (behaviorally) acquired in early life [28].

The pathophysiological effects of stress on the nervous system apparently are closely connected with functions of the hippocampus [29]. This formation of the central nervous system (CNS) has a profound relation to memory performance and is important in the inhibition of fear conditioning in the amygdala. Thus, stress has an impact upon these areas of biological integrity: Stress can contribute to neuronal degeneration in the brain, especially in the hippocampus formation, and here, the release of corticotropin releasing hormone (CRH) and/or corticosterone (e.g., as part of the stress response) represents a critical precondition [29] (also: see below).

Hence, pathophysiological patterns and similarities exist among different neurodegenerative diseases [27,28,29]. These similarities (regarding underlying mechanisms) make it possible to focus on particular neurodegenerative diseases and their associations with stress. We focus on two with growing clinical significance: Alzheimer's disease and Multiple sclerosis.

3.1.1. Alzheimer's disease

Stress has been demonstrated to cause deficits in memory performance [29,30,31,32,33,34], and this effect may be important for pathophysiological processes connected with Alzheimer's disease (AD; see below).

Further, a hippocampal atrophy may be involved in stress (patho)physiology and the association of stress with neurodegenerative mechanisms [29,31,32,34]. This is a relevant fact, because the stress-sensitive hippocampus is a structure which normally plays a crucial role in the storage of various events in long-term memory [34].

It is well documented that prolonged and high levels of stress, fear, and arousal commonly induce learning deficits and memory loss [29,34]. Amnesia or partial memory loss (especially spatial memory loss) are not uncommon following severe stress and emotional trauma [31,33,34]. As stress and arousal levels dramatically increase, learning and memory deteriorate in accordance with the classic inverse U-shaped curve [34]. These memory deficits are due to disturbances in hippocampal activation/arousal and to a stress-related corticosteroid secretion which suppresses hippocampal neural activity – associated with learning and memory – and induce hippocampal atrophy [29,32,33,34].

Taken together (with regard to stress and memory loss), the stress-related activation of the HPA axis may represent a pathophysiological ‘starting point’ of memory loss [32]. In particular, stress may block hippocampal activity, thereby deteriorating memory performance [29,33]. In order to ‘achieve’ this devastating result, glucocorticoid pathways have to be activated, and steroids seem to be essential effectors in the stress-dependent hippocampal destruction [29,33] (Figure 1).

In contrast to stress-induced catecholamine effects that are more likely associated with emotionally-laden memories (e.g., connected with the amygdala) [32], glucocorticoids obviously are capable of modulating hippocampal synaptic plasticity over time, and high/lasting steroid levels appear to change dendritic structures [32]. Thus, stress may lead to a loss of neurons, particularly in the hippocampal area [32]. Moreover, the aging hippocampus apparently is more susceptible to stress, and this vulnerability may yet be increased in AD [35]. Also, strenuous exercise, taken to

the extreme, initiates an immune and vascular proinflammatory response (i.e., ‘excessive stress response’), whereas mild exercise seems to produce more health benefits [36]. Hence, the mentioned proinflammatory response may exert detrimental effects on neuronal integrity. Differences in (patho)physiology between mild and strenuous exercise may indicate distinct forms of nitric oxide (NO) production (constitutive versus inducible NO release) [36] (also: see below).

AD, the cause of one of the most common types of memory loss or dementia, is a brain disorder mostly affecting the elderly and is characterized by the formation of two main protein aggregates: Senile plaques and neurofibrillary tangles, which are involved in the process leading to progressive neuronal degeneration (and death) [38]. Thereby, neurodegeneration in AD represents a pathological condition – not just an accelerated way of physiological aging [38]. The senile plaques are generated by a deposition of fibrils of the beta-amyloid peptide (Abeta), a fragment derived from the proteolytic processing of amyloid precursor protein (APP) [38]. In contrast, the neurofibrillary tangles predominantly consist of tau protein – and of coupled helical filaments (consisting of tau protein) [38].

Experiments with hippocampal cells in culture have indicated a relationship between fibrillary amyloid deposits and the molecular cascade that triggers tau protein hyperphosphorylation by specific protein kinases: The tau hyperphosphorylation is induced by extracellular amyloid loading, and this reaction triggers a sequence of molecular events that eventually lead to neuronal degeneration [38]. Yet, there exists evidence that oxidative stress (as seen in inflammation, eventually modified by psychosocial stress [8]) may also represent an important factor in the alteration of normal signaling pathways in neuronal cells, leading to biochemical and structural abnormalities and neurodegeneration [38]. Thus, oxidative stress and chronic inflammation (→ stress) may be associated with AD (with both forms: sporadic and familial AD) as well.

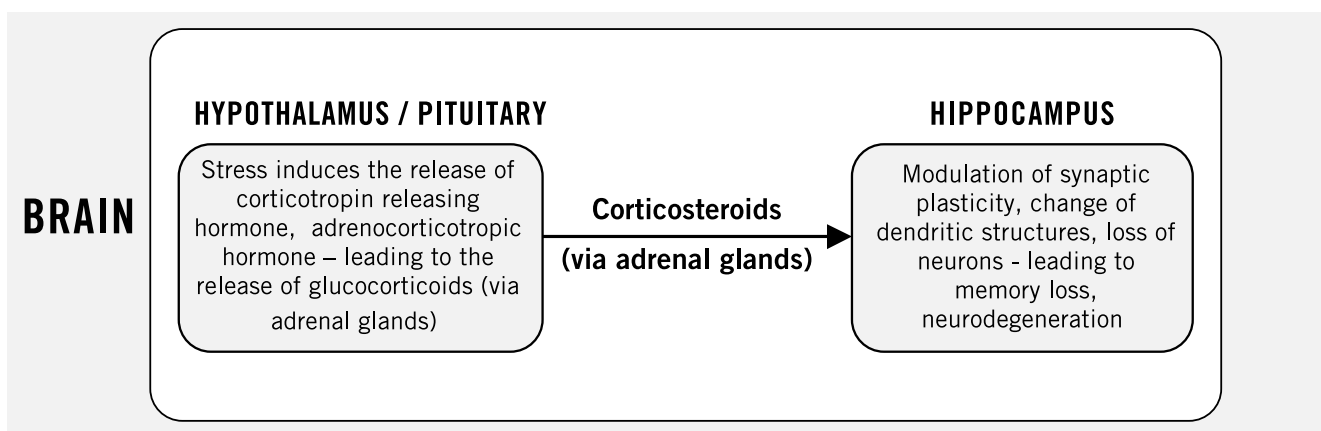


Figure 1. Stress and its impact upon hippocampal integrity: Association of stress with memory loss and hippocampal neurodegeneration. The hippocampus is necessary for memory consolidation and learning

(see text). Hippocampal atrophy induced by corticosteroids may play an important role not only in the pathogenesis of memory loss, but also in a broader range of neuropsychiatric disorders: Signs of hippocam-

pal damage (hypothalamus-pituitary-adrenal axis dysregulation in combination with memory impairment) are found in affective disorders, Alzheimer’s disease, and in post-traumatic stress disorder [37].

A loss of synapses and neurons in the cortices of demented persons – ultimately leading to a substantial and observable brain atrophy – appears to be a morphological correlate of clinical AD [39]. Neuronal degeneration – as detectable in AD (see above) – may also be associated with inflammatory processes and these may further be connected with the stress (patho)physiology [8,39]. In this scenario microglial activation may play a central role in the initiation of a cellular immune response. Microgliosis is a major component of senile plaques [40]. In addition, interleukin 6 (IL-6) immunoreactivity has been verified in AD plaques and in addition, elevated IL-6 concentrations have been measured biochemically in the brains of AD patients [39]. Thus, IL-6 expression may precede neuronal changes in AD, and immunological/inflammatory mechanisms may be involved both in the (trans)formation of plaques and the development of dementia [39]. Yet, the reason for an increased IL-6 activity in AD is still speculative, since slightly elevated basal IL-6 levels have been found along normal aging processes as well [39]. However, several studies indicate that IL-6 expression is related to psychosocial stress, and therefore, chronic stress may significantly contribute to the pathophysiology underlying AD [8,39].

3.1.2. Multiple sclerosis

Multiple sclerosis (MS), alternating interpreted or classified as an autoimmune disorder or a neurodegenerative disease, may show a relation to stress [8,41] (also: see below). Patients with multiple sclerosis may show a hypoactive HPA axis in the beginning of the disease [41], but in contrast, once the disease is established, they demonstrate significantly higher plasma cortisol levels at baseline – compared to matched controls [41]. The complex pathophysiology of this hypercortisolism in multiple sclerosis has not yet been fully explained. In this regard, stress may play a significant role [8,41]. It seems to be different from other known biological states of hypercortisolism (e.g., in depression) [41]. Nonetheless, stress and its impact on the HPA axis may represent a crucial pathophysiological component in multiple sclerosis.

MS shows pathophysiological connections with experimental autoimmune/allergic encephalitis (encephalomyelitis, EAE) [8,41]. However, the definite etiological classification of MS still remains unclear. Yet, EAE and MS demonstrate a possible association with stress [8,14,41,42]. Moreover, MS, interpreted as a (pro)-inflammatory disease, apparently involves nitric oxide-driven inflammatory cytokine activation [43,44, 45,46]. Thus, stress-sensitive inflammatory pathophysiological processes may be relevant in MS [8].

Current research suggests that interactions between genetic/internal and environmental/external factors (→ ‘stress’) modulate the susceptibility to neurodegenerative disorders, including inflammatory

and autoimmune diseases of the CNS, such as MS [8,47]. However, the pathogenesis of MS, the major neurological disease of young adults in the ‘western world’, is still poorly understood [8,41,48]. The clinical symptoms of MS result from inflammatory damage to the insulating myelin sheath of axons in the CNS and, at later stages, to axons themselves [48]. A local autoimmune process involving activation of T helper cells against CNS protein components is likely to be crucial in this development [8,48]. Especially at the first stages of MS, therapies aimed at the selective down-regulation of autoimmune responses may contribute to controlling the disease [8,48]. Interestingly, stress-related heat shock proteins have been identified as immunodominant myelin antigens in MS-affected myelin [48]. Thus, an inappropriate stress response pathway within the CNS itself may be crucial as an initiating event in the development of MS [8,48,49]. Here, glucocorticoids – the end products of the stress response-associated HPA axis that are important for the coordination of immune system functions [8], may serve as effector molecules for the induction of stress-related pathophysiological mechanisms in MS [47].

The relationship between psychosocial stress and the course of MS has been investigated in several studies. Thereby, the impact of acute or short-term stressors seems to be comparatively small, whereas chronic psychosocial stressors, such as interpersonal conflicts, loss and complicated bereavement, low perceived social support, anxiety, and depressive episodes, are regarded as possible risk factors for the development of MS exacerbations [7,8,50]. Moreover, psychological, cognitive-behavioral, or stress management interventions may become increasingly important therapeutic tools in the future treatment of MS [8,50].

3.2. Mental disorders

Diagnosis in medicine proceeds according to a pyramid of criteria. At the top is etiology followed in order of importance by pathophysiology, syndromic nature and symptomatology. In our present stage of knowledge, we are most certain of syndromic characteristics when it comes to mental disorders. Thus, controversial discussions about mental disorders and their pathophysiological formation as well as their specific clinical course are still prevalent: Different approaches still dictate different opinions. However, without doubt, mental disorders have a great clinical significance and this is why we will focus upon important mental disorders and their possible association with the stress phenomenon in the following.

3.2.1. Anxiety, depression

The possible association of anxiety and depression with stress has been discussed recently. Thereby, stress, in general, has been demonstrated to be part of mechanisms related to anxiety [30], and chronic stress,

involving chronic sympathetic activation, has specifically been linked to the onset of anxiety and depression [51]. In particular, stress may actually mediate, promote, or even cause mental disorders like depression [14,31,52,53,54], including major depression [14,55]. Here, acquired abnormalities in the stress response may serve a role in major depressive disorders [14,56], since prenatal and early postnatal experiences seem to contribute to individual differences in postnatal stress reactivity, which may then interact with cognitive and psychosocial vulnerabilities to increase the susceptibility to later onset of depression [53,55]. Additionally, stress-induced structural changes in brain regions such as the hippocampus may have clinical ramifications for disorders like depression and posttraumatic stress disorder [52]. Thus, stress may represent an important factor in anxiety/depression.

Only a few underlying molecular mechanisms with pathophysiological significance have been detected in anxiety/depression thus far. A pathologic hyperactivity of the stress response system ('excessive stress response') has been discussed in association with anxiety disorders, and apparently, this type of stress response is often a product of an experienced trauma in childhood/youth [30]. In contrast, a 'secure environment' seems to protect against stress-related illnesses [30]. Further, CRH enhances the organism's sensitivity to noxious stimuli and may be capable of mobilizing almost the entire cascade of the stress response [30]: A hyperactivity of CRH (facilitating enhanced cortisol levels) may be, in part, at the bottom of depression and anxiety [30]. Hence, there appears to exist a significant correlation between mother's extent of depressive symptomatology and child's cortisol levels. Additionally, children with low socioeconomic status present a significantly higher salivary cortisol level than children with high socioeconomic status [53]. However, the concrete relationship between an excessive activation of the HPA axis, its triggers and variables (including cortisol levels), and clinical depression is still a matter of discussion. Nevertheless, stress response pathways ('excessive' or 'inadequate'), serotonin-deficiency, and hypercortisolism are among the most likely factors to promote the multi-component pathophysiology associated with depression and anxiety [6,30,41]. Here, even melatonin may play an important role, since decreased melatonin levels represent an accepted key feature of 'winter depression' (seasonal affective disorder) [57].

In respect of signaling molecules, nitric oxide may also be involved in the (patho)physiology of anxiety/depression, because it interferes with various components and underlying mechanisms of the stress response on different levels, thereby potentially exerting protective or, simultaneously, detrimental effects (described above). Also, norepinephrine (over)stimulation, as seen in stress, may be part of underlying mechanisms of importance in depression: Cortical noradrenergic degeneration or retraction, possibly a result of prolonged

stress (SNS hyperactivity), is involved in the pathogenesis of depression [58,59]. Here, the relevant participating molecular pathways haven't been described, however, a lack of 'sufficient' NE levels for the maintenance of a regular physiological molecular signaling may very well lead to physical, biochemical, and psychological hypoactivity [58]. Thus, after all, both components of the stress response, the HPA axis and the SNS, may be involved in onset, development, and progression of anxiety or depression.

3.2.2. Posttraumatic stress disorder (PTSD)

To be given the diagnosis 'PTSD', a person has to have been exposed to an extreme stressor or traumatic event to which he or she responded with fear, helplessness, or horror and to have three distinct types of symptoms consisting of

- a) reexperiencing of the event (i.e., in the mind),
- b) avoidance of reminders of the event, and
- c) hyperarousal for at least one month [60].

Reexperiencing of the event refers to unwanted recollections of the incident (e.g., nightmares, images, 'flashbacks'), symptoms of avoidance consist of attempts to avoid reminders of the event – including persons, places, or even thoughts associated with the incident –, and symptoms of hyperarousal refer to physiological manifestations of a (constantly) activated stress response, such as insomnia, irritability, impaired concentration, hypervigilance, and increased startle reactions [60,61].

Within the first month after a traumatic experience, traumatized persons may suffer from an 'acute stress disorder'. Although this acute stress syndrome – consisting of symptoms like irritability, insomnia, depression etc. – is not always followed by PTSD, it is associated with an increased risk of PTSD [60,62]. Additional risk factors for PTSD are gender (women have a higher risk), having other psychiatric diseases in the medical history (though, controversial results have been obtained here), younger age, and trauma exposure that was repeated and ongoing or that involved childhood victimization [63]. This complexity of factors that may lead to an increased vulnerability to PTSD highlight the importance of systematically ascertaining trauma histories in patients with psychotic disorders [63]. However, most measures of PTSD symptoms are limited in that they focus only on a single traumatic event and cannot be used to assess symptoms in persons who report no or multiple traumatic events in their history [64]. Moreover, despite the high prevalence of childhood trauma, there are no developmentally oriented cognitive theories of PTSD currently existing [65]. Further research is much-needed.

PTSD is not uncommon after many types of traumatic events, from motor vehicle accidents to industrial explosions, and it can develop even in people with no history of psychiatric disorders [62,64,66]. Nearly all people have the acute form of the disorder at some

times in their lives, but most often, they recover rapidly [60,62,66]. If it persists, PTSD can be debilitating and may require psychotherapeutic, pharmacologic, and/or cognitive-behavioral intervention [66]. In a survey of 560 adults in the United States, conducted the week after September 11, 44 percent of the adults reported one or more substantial symptoms of stress [67]. For such a severe trauma, PTSD (i.e., stress-related symptoms lasting for at least a month) may actually represent a probable outcome, even a 'useful coping strategy' in the short-term [66]. However, the stress physiology that is constantly activated in PTSD and in a 'state of alert' may impose a substantial danger on people who are affected.

Evidence suggests that stressful life events may precede major psychiatric illnesses, such as major depression and/or schizophrenia, and that the severity of a traumatic event outside the range of 'normal' human experience may provoke PTSD [68]. Thereby, the most significant life events of importance in this context apparently are: Loss of job or income, broken relationships, serious illnesses or injuries in the victims, and death or illness in close acquaintances [7,68]. The number and severity of such additional stressful life events may signal a higher risk to develop PTSD [68]. Thus, PTSD is a complex problem that is not easy to assess and predict. However, treatment strategies may focus upon the stress physiology underlying the majority of the symptoms.

3.2.3. Schizophrenia

The etiology of PTSD and schizophrenia is still a matter of discussion. Although the two diseases may not have much in common – with regard to their clinical manifestation and development, stress may have an impact upon the pathophysiology of both entities. Because chronic stress is associated with some neuropsychiatric disorders, including schizophrenia [69], it is possible that an imbalance in the normal turnover of hippocampal cells (see above) plays a role in the pathophysiology not only of schizophrenia but also of other neuropsychiatric disorders that involve high levels of stress [69]. There is much evidence of hippocampal abnormalities in schizophrenia [70].

Traumatic life events are common among persons with severe mental illnesses, such as schizophrenia [71]. In this population of patients (i.e., patients with schizophrenia), also higher levels of PTSD occur [71]. However, the interrelationships between stress, trauma, PTSD, and severe mental illnesses are not fully understood yet. Recently, PTSD has been proposed to mediate negative effects of trauma on the course of schizophrenia [71]. Here, the stress physiology may significantly be involved [69].

With regard to schizophrenia, a substantial literature on the behavioral effects of psychosocial stressors on schizophrenia exists [72]. Further, research has been conducted on neurohormonal indicators of stress

responsivity, particularly cortisol release resulting from activation of the HPA axis [72]. Behavioral and biological data indicate that stress worsens symptoms of schizophrenia and that the diathesis is associated with a heightened response to stressors ('excessive stress response') [72]. However, as mentioned above, a chronic (hyper)activation of the stress physiology bears the risk of leading to a breakdown or lasting imbalances of stress response pathways and to a decreased regulative reactivity (e.g., [8,9,41]).

Yet, with reference to a hyperactive stress response, as detectable in clinical manifestations of schizophrenia, a neural mechanism for this phenomenon has been suggested by the augmenting effect of the HPA axis on dopamine synthesis and receptors [72]. Assuming the diathesis for schizophrenia involves an abnormality in dopamine receptors, it has been proposed that the HPA axis acts as a potentiating system by means of its effects on dopamine [72]. At the same time, dopamine receptor abnormality and hippocampal damage render the patient hypersensitive to stress [72] (also: see above). Furthermore, it has been suggested that a disruption in the interaction between cortical and subcortical dopamine neurons is involved in the pathophysiology of schizophrenia [73]. Yet, present data raise the possibility that this disruption is thoroughly influenceable by stress [73].

Not everyone believes that stress effects are prominent in schizophrenia pathophysiology. Weinberger downplays its significance by pointing out that schizophrenia is not characterized by gliosis, the hippocampus is not dramatically atrophied, and cortisol abnormalities are not usually seen [74]. Nevertheless, one might point to the effects of the stress cascade on apoptosis and synaptic modeling, which do not result in gliosis, to explain a connection with schizophrenia [70]. Stress could be an environmental factor that increases the vulnerability to schizophrenia bestowed by an early neurodevelopmental insult.

4. Discussion

Stress is a term that has become synonymous with modern life in the 'western world', and some have referred to a 'stress epidemic' in the last decades of the 20th century [1,75]. Stress seems to be everywhere, and the effects of stress upon the individual's health and integrity are apparently seen to be, nearly always, detrimental [1,76]. However, stress in fact has both capacities: it may exert ameliorating or deleterious effects, depending on a multitude of – even subjective/individual – factors and conditions [1]. Moreover, the common assumption that stress notably causes diseases is still under investigation in scientific stress research, and only recently, new concepts and knowledge about the relationship between stress and diseases has evolved [1,4,6,7,8,9].

Today, evidence exists that links stress and certain diseases, with particular reference to the major causes

of morbidity and mortality in the 'western world': cardiovascular diseases, cancer/immunological diseases, and depression [8,9,76]. They all show an association with the stress physiology. Thus, an argument can be made that stress is involved in the onset, development/course, and progress of many diseases, and stress-related disease processes represent a growing medical issue, especially in the area of primary care where most of the physical and psychological signs of stress are revealed [1,7,76]. Thereby, the term 'stress' more generally describes processes associated with challenging stimuli ('stressors'), situations that require behavioral adjustments, and the organism's ability to cope with coupled reactions [1,4,5]. Here, physiological pathways become activated, including the *fight-or-flight* or stress response, a set of physiological mechanisms that get started in challenging situations to facilitate behavioral adjustments, adaptation, and survival. [15,16]. These very same physiological pathways, although intentionally having protective properties, may also turn out to exert detrimental effects upon individual's integrity and health [1,7,8,9]. This may especially be true, when prolonged stress or an overwhelming acute stressor are involved [1,8,9]. Thereby, the enduring 'wear and tear' (allostatic load: see above) that an organism may experience, in the battle with stressful stimuli, may force the individual to seek a new state of dynamic balance, a state that is more appropriate in the new/changed ('rough') environment and that allows the individual to survive (c.p., allostasis: see above). An organism that encounters prolonged phases of such challenges may pay a price for the maintenance of its physiological and biological integrity: this is where pathophysiological disease processes in the face of stress may become activated. Thus, coming from a 'quiet' and healthy state of physiological balance (homeostasis: see above), an organism under stress – where the balance gets under severe pressure – may activate stress response pathways (with the intention to re-balance or adapt) that ultimately may trigger the onset or progression of certain diseases to which the individual is susceptible [8,9].

With regard to the stress response and its effects upon biological organisms, stressful stimuli may be involved in the basic pathophysiology that underlies specific diseases. Thus, we have found strong evidence for the existence of a connection between stress and neurodegenerative or mental diseases. As a result of this, stress management strategies, aimed at prolonging survival, improving adjustment, alleviating negative effects of stress, and enhancing the quality of life in stress-related neurological diseases, may represent an exciting area of future research and medical practice.

5. Conclusions

Stress describes the effects of internal/endogenous and external/exogenous factors on physical or mental well-being. Stressors and related stress-reactions are distinguished. Stress has a major impact upon the nervous system, its structures and functions, since stress is closely associated with its effectors, and profound connections between stress and neurodegenerative diseases as well as mental disorders exist. Thereby, the hippocampus and its obvious sensitivity to stress may represent a crucial component of stress-related pathophysiological disease processes in certain neurological diseases. Also, the primary molecular end products of activated stress responses, catecholamines and glucocorticoids, are integral parts of the pathology of neurodegenerative and mental disorders. However, the exact molecular mechanisms are yet to be determined.

Stress plays a significant role in susceptibility, progress, and outcome of neurodegenerative diseases/mental disorders. It may cause or exacerbate such diseases depending on the type of stressor involved (e.g., physical, chemical, biological, mental, psychosocial etc.) and/or duration of its influence on an organism. Hence, individual differences have to be taken into account. This fact can make it difficult to predict an expected result following the experience of challenging stimuli (stressors) that are able to evoke the (allostatic) stress response and lead to physiological, psychological, and behavioral adjustments. However, stress not only has detrimental but also ameliorating capacities. Here, particularly the maintenance of a dynamic balance (allostasis) in the midst of an enduring challenge (allostatic load: 'stress') seems to be of importance.

Stress management strategies, aimed at prolonging survival, slowing-down disease progression (or even deter the development/onset of certain neurological diseases), and enhancing quality of life in patients with neurodegenerative or mental disorders provide an exciting opportunity for future medical practice and research.

Acknowledgements

This work, in part, was supported by a research grant from the University of Essen, Germany and a grant from the Centers for Disease Control and Prevention (CDC) – number H75/CCH119124.

REFERENCES

- 1 Esch T. [Health in Stress: Change in the Stress Concept and its Significance for Prevention, Health and Life Style]. *Gesundheitswesen* 2002; **64**:73–81.
- 2 Selye H. A syndrome produced by diverse noxious agents. *Nature* 1936; **138**:32.
- 3 Selye H. *The Physiology and Pathology of Exposure to Stress*. Montreal: Acta Inc. Medical Publishers; 1950.
- 4 Selye H. The Evolution of the Stress Concept. *Am Sci* 1973; **61**:692–699.
- 5 Esch T. Bestimmung von Vorgaengen zum aktiven Erhalt der zellularen Autonomie und Organisation mit Hilfe des Schwesterchromatid-Austausch-Verfahrens (Dissertation). Goettingen: Georg-August-Univ.; 1999.
- 6 McCarty R, Gold P. Catecholamines, Stress, and Disease: A Psychobiological Perspective. *Psychosom Med* 1996; **58**:590–597.
- 7 Jones F, Bright J, Clow A. *Stress: Myth, Theory and Research*. New York: Prentice Hall; 2001.
- 8 Esch T, Stefano GB, Fricchione GL, Benson H. An Overview of Stress and Its Impact in Immunological Diseases. *Mod Asp Immunobiol* 2002 (*in press*).
- 9 Esch T, Stefano GB, Fricchione GL, Benson H. Stress in cardiovascular diseases. *Med Sci Monit* 2002; **8**:93–101.
- 10 McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. *Arch Intern Med* 1993; **153**:2093–2101.
- 11 Weiner H. *Perturbing the Organism: The Biology of Stressful Experience*. Chicago: University of Chicago Press; 1992.
- 12 Goldstein DS. *Stress, Catecholamines, and Cardiovascular Disease*. New York: Oxford University Press; 1995.
- 13 McCall RB. Central neurotransmitters involved in cardiovascular regulation. In: Antonaccio, editor. *Cardiovascular Pharmacology*. New York: Raven Press; 1990.
- 14 Negrao AB, Deuster PA, Gold PW, Singh A, Chrousos GP. Individual reactivity and physiology of the stress response. *Biomed Pharmacother* 2000; **54**:122–128.
- 15 Cannon W. The emergency function of the adrenal medulla in pain and the major emotions. *Am J Physiol* 1914; **33**:356–372.
- 16 Cannon WB. *Bodily changes in pain, hunger, fear, and rage; an account of recent researches into the function of emotional excitement*. New York: Appleton and Company; 1915.
- 17 Watson SJ, Akil H. The brain's stress axis: An update. In: Tasman A, Goldfinger S, editors. *American psychiatric association press review of psychiatry*. Washington, D.C.: American Psychiatric Press; 1991. p. 498–512.
- 18 Morris MJ, Cox HS, Lambert GW, Kaye DM, Jennings GL, Meredith IT, et al. Region-specific neuropeptide Y overflows at rest and during sympathetic activation in humans. *Hypertension* 1997; **29**:137–143.
- 19 Sternberg EM. Neuroendocrine factors in susceptibility to inflammatory disease: focus on the hypothalamic-pituitary-adrenal axis. *Horm Res* 1995; **43**:159–161.
- 20 Brotto LA, Gorzalka BB, LaMarre AK. Melatonin protects against the effects of chronic stress on sexual behaviour in male rats. *Neuroreport* 2001; **12**:3465–3469.
- 21 Stefano GB. Endocannabinoid immune and vascular signaling. *Acta Pharmacol Sin* 2000, **21**:1071–1081.
- 22 Stefano GB, Fricchione GL, Slingsby BT, Benson H. The placebo effect and relaxation response: neural processes and their coupling to constitutive nitric oxide. *Brain Res Rev* 2001; **35**:1–19.
- 23 Stefano GB, Murga J, Benson H, Zhu W, Bilfinger TV, Magazine HI. Nitric oxide inhibits norepinephrine stimulated contraction of human internal thoracic artery and rat aorta. *Pharmacol Res* 2001; **43**:199–203.
- 24 Cordellini S, Vassilief VS. Decreased endothelium-dependent vasoconstriction to noradrenaline in acute-stressed rats is potentiated by previous chronic stress: nitric oxide involvement. *Gen Pharmacol* 1998; **30**:79–83.
- 25 Gumusel B, Orhan D, Tolunay O, Uma S. The role of nitric oxide in mediating nonadrenergic, noncholinergic relaxation in rat pulmonary artery. *Nitric Oxide* 2001; **5**:296–301.
- 26 Grimm RJ. A discussion of movement disorders. *Nurse Pract For* 1996; **7**:154–159.
- 27 Gilad GM, Gilad VH. Strain, stress, neurodegeneration and longevity. *Mechan Age Develop* 1995; **78**:75–83.
- 28 Habib KE, Gold PW, Chrousos GP. Neuroendocrinology of stress. *Endocrinol Metabol Clin North Am* 2001; **30**:695–728.
- 29 Mizoguchi K, Kunishita T, Chui DH, Tabira T. Stress induces neuronal death in the hippocampus of castrated rats. *Neurosci Lett* 1992; **138**:157–160.
- 30 Rachal Pugh C, Fleshner M, Watkins LR, Maier SF, Rudy JW. The immune system and memory consolidation: a role for the cytokine IL-1beta. *Neurosci Biobehav Rev* 2001; **25**:29–41.
- 31 McEwen BS. Stress and hippocampal plasticity. *Ann Rev Neurosci* 1999; **22**:105–122.
- 32 McEwen BS, Sapolsky RM. Stress and cognitive function. *Curr Opin Neurobiol* 1995; **5**:205–216.
- 33 Garcia R. Stress, hippocampal plasticity, and spatial learning. *Synapse* 2001; **40**:180–183.
- 34 Joseph R. The neurology of traumatic “dissociative” amnesia: commentary and literature review. *Child Abuse Negl* 1999; **23**:715–727.
- 35 McEwen BS, de Leon MJ, Lupien SJ, Meaney MJ. Corticosteroids, the Aging Brain and Cognition. *Trends Endocrinol Metabol* 1999; **10**:92–96.
- 36 Stefano GB, Prevot V, Cadet P, Dardik I. Vascular pulsations stimulating nitric oxide release during cyclic exercise may benefit health: A molecular approach. *Int J Mol Med* 2001; **7**:119–129.
- 37 Hoschl C, Hajek T. Hippocampal damage mediated by corticosteroids – a neuropsychiatric research challenge. *Eur Arch Psychiatry Clin Neurosci* 2001; **251** (Suppl. 2):II81–II88.
- 38 Maccioni RB, Munoz JP, Barbeito L. The molecular bases of Alzheimer's disease and other neurodegenerative disorders. *Arch Med Res* 2001; **32**:367–381.
- 39 Hull M, Strauss S, Berger M, Volk B, Bauer J. The participation of interleukin-6, a stress-inducible cytokine, in the pathogenesis of Alzheimer's disease. *Behav Brain Res* 1996; **78**:37–41.
- 40 Fricchione GL, Bilfinger TV, Stefano GB. The macrophage and neuropsychiatric disorders. *Neuropsychiatry Neuropsychol Behav Neurol* 1996; **9**:16–29.
- 41 Michelson D, Stone L, Galliven E, Magiakou MA, Chrousos GP, Sternberg EM, et al. Multiple sclerosis is associated with alterations in hypothalamic-pituitary-adrenal axis function. *J Clin Endocrinol Metab* 1994; **79**:848–853.
- 42 Sternberg EM, Wilder RL, Gold PW, Chrousos GP. A defect in the central component of the immune system-hypothalamic-pituitary-adrenal axis feedback loop is associated with susceptibility to experimental arthritis and other inflammatory diseases. *Ann N Y Acad Sci* 1990; **594**:289–292.
- 43 Kroencke KD, Fehsel K, Kolb-Bachofen V. Inducible nitric oxide synthase in human diseases. *Clin Exp Immunol* 1998; **113**:147–156.
- 44 Hooper DC, Bagasra O, Marini JC, Zborek A, Ohnishi ST, Kean R, et al. Prevention of experimental allergic encephalomyelitis by targeting nitric oxide and peroxynitrite: implications for the treatment of multiple sclerosis. *Proc Natl Acad Sci U S A* 1997; **94**:2528–2533.
- 45 Liu JS, Zhao ML, Brosnan CF, Lee SC. Expression of inducible nitric oxide synthase and nitrotyrosine in multiple sclerosis le-

- sions. *Am J Pathol* 2001; **158**:2057–2066.
- 46 de Groot CJ, Ruuls SR, Theeuwes JW, Dijkstra CD, van der Valk P. Immunocytochemical characterization of the expression of inducible and constitutive isoforms of nitric oxide synthase in demyelinating multiple sclerosis lesions. *J Neuropathol Exp Neurol* 1997; **56**:10–20.
- 47 Marchetti B, Morale MC, Testa N, Tirolo C, Caniglia S, Amor S, et al. Stress, the immune system and vulnerability to degenerative disorders of the central nervous system in transgenic mice expressing glucocorticoid receptor antisense RNA. *Brain Res Rev* 2001; **37**:259–272.
- 48 van Noort JM. Multiple sclerosis: an altered immune response or an altered stress response? *J Mol Med* 1996; **74**:285–296.
- 49 Morale C, Brouwer J, Testa N, Tirolo C, Barden N, Dijkstra CD, et al. Stress, glucocorticoids and the susceptibility to develop autoimmune disorders of the central nervous system. *Neurol Sci* 2001; **22**:159–162.
- 50 Strenge H. [The relationship between psychological stress and the clinical course of multiple sclerosis. An update]. *Psychother Psychosom Medizin Psychol* 2001; **51**:166–175.
- 51 Cunningham C, Brown S, Kaski JC. Effects of transcendental meditation on symptoms and electrocardiographic changes in patients with cardiac syndrome X. *Am J Cardiol* 2000; **85**:653–655.
- 52 McEwen BS. The neurobiology of stress: From serendipity to clinical relevance. *Brain Res* 2000; **886**:172–189.
- 53 Lupien SJ, King S, Meaney MJ, McEwen BS. Child's stress hormone levels correlate with mother's socioeconomic status and depressive state. *Biol Psychiatry* 2000; **48**:976–980.
- 54 Vaidya VA. Stress, depression and hippocampal damage. *J Biosci* 2000; **25**:123–124.
- 55 Meyer SE, Chrousos GP, Gold PW. Major depression and the stress system: a life span perspective. *Develop Psychopathol* 2001; **13**:565–580.
- 56 Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *J A M A* 1992; **267**:1244–1252.
- 57 Lewy AJ, Bauer VK, Cutler NL, Sack RL. Melatonin treatment of winter depression: a pilot study. *Psychiatry Res* 1998; **77**:57–61.
- 58 Kitayama I, Yaga T, Kayahara T, Nakano K, Murase S, Otani M, et al. Long-term stress degenerates, but imipramine regenerates, noradrenergic axons in the rat cerebral cortex. *Biol Psychiatry* 1997; **42**:687–696.
- 59 Kitayama I, Nakamura S, Yaga T, Murase S, Nomura J, Kayahara T, et al. Degeneration of locus coeruleus axons in stress-induced depression model. *Brain Res Bull* 1994; **35**:573–580.
- 60 Yehuda R. Post-traumatic stress disorder. *New Engl J Med* 2002; **346**:108–114.
- 61 North CS, Nixon SJ, Shariat S, Mallonee S, McMillen JC, Spitznagel EL, et al. Psychiatric disorders among survivors of the Oklahoma City bombing. *J A M A* 1999; **282**:755–762.
- 62 Harvey AG, Bryant RA. The relationship between acute stress disorder and posttraumatic stress disorder: a prospective evaluation of motor vehicle accident survivors. *J Consult Clin Psychol* 1998; **66**:507–512.
- 63 Neria Y, Bromet EJ, Sievers S, Lavelle J, Fochtmann LJ. Trauma exposure and posttraumatic stress disorder in psychosis: findings from a first-admission cohort. *J Consult Clin Psychol* 2002; **70**:246–251.
- 64 Carlson EB. Psychometric study of a brief screen for PTSD: assessing the impact of multiple traumatic events. *Assessment* 2001; **8**:431–441.
- 65 Salmon K, Bryant RA. Posttraumatic stress disorder in children. The influence of developmental factors. *Clin Psychol Rev* 2002; **22**:163–188.
- 66 Ursano R. Post-traumatic stress disorder. *New Engl J Med* 2002; **346**:130–132.
- 67 Schuster MA, Stein BD, Jaycox LH, Collins RL, Marshall GN, Elliott MN, et al. A national survey of stress reactions after the September 11, 2001, terrorist attacks. *New Engl J Med* 2001; **345**:1507–1512.
- 68 Maes M, Mylle J, Delmeire L, Janca A. Pre- and post-disaster negative life events in relation to the incidence and severity of post-traumatic stress disorder. *Psychiatry Res* 2001; **105**:1–12.
- 69 Arango C, Kirkpatrick B, Koenig J. At issue: stress, hippocampal neuronal turnover, and neuropsychiatric disorders. *Schizophr Bull* 2001; **27**:477–480.
- 70 Corcoran C, Mujica-Parodi L, Yale S, Leitman D, Malaspina D. Could stress cause psychosis in individuals vulnerable to schizophrenia? *CNS Spectrums* 2002; **7**:33–42.
- 71 Mueser KT, Rosenberg SD, Goodman LA, Trumbetta SL. Trauma, PTSD, and the course of severe mental illness: an interactive model. *Schizophr Res* 2002; **53**:123–143.
- 72 Walker EF, Diforio D. Schizophrenia: a neural diathesis-stress model. *Psychol Rev* 1997; **104**:667–685.
- 73 King D, Zigmond MJ, Finlay JM. Effects of dopamine depletion in the medial prefrontal cortex on the stress-induced increase in extracellular dopamine in the nucleus accumbens core and shell. *Neuroscience* 1997; **77**:141–153.
- 74 Weinberger DR. Cell biology of the hippocampal formation in schizophrenia. *Biol Psychiatry* 1999; **45**:395–402.
- 75 Stefano GB, Fricchione GL, Slingsby BT. Is stress stress? *Placebo* 2001; **3**:101–110.
- 76 Maddock C, Pariante CM. How does stress affect you? An overview of stress, immunity, depression and disease. *Epidemiol Psychiatr Soc* 2001; **10**:153–162.