Stress, ageing and their influence on functional, cellular and molecular aspects of the immune system

Ana Vitlic · Janet M. Lord · Anna C. Phillips

Abstract The immune response is essential for keeping an organism healthy and for defending it from different types of pathogens. It is a complex system that consists of a large number of components performing different functions. The adequate and controlled interaction between these components is necessary for a robust and strong immune response. There are, however, many factors that interfere with the way the immune response functions. Stress and ageing now consistently appear in the literature as factors that act upon the immune system in the way that is often damaging. This review focuses on the role of stress and ageing in altering the robustness of the immune response first separately, and then simultaneously, discussing the effects that emerge from their interplay. The special focus is on the psychological stress and the impact that it has at different levels, from the whole system to the individual molecules, resulting in consequences for physical health.

Keywords Stress · Ageing · Immune response · Caregiving

A. Vitlic · A. C. Phillips
School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT England, UK

A. Vitlic · J. M. Lord · A. C. Phillips (✉)
MRC-Arthritis Research UK Centre for Musculoskeletal Ageing Research, University of Birmingham, Birmingham, England, UK
e-mail: A.C.Phillips@bham.ac.uk

J. M. Lord
School of Immunity and Infection, University of Birmingham, Birmingham, England, UK

Ageing is a physiological process that emerged as a side product of normal development and the metabolic processes involved in the reproductive potential of the species (Cutler 1982). It has been developed most likely as a non-adaptive phenomenon with no biological function (Partridge and Gems 2002) and allowed to evolve through a trade-off mechanism (Williams 1957) (reviewed in Partridge and Barton 1993). According to Thomas Kirkwood's modification of Orgel's (1963) theory, ageing can also be linked to the attempt of the body to reduce energy expenditure when switching off from germ line to somatic cells, which is achieved by making protein production less accurate (Kirkwood 1977). Therefore, ageing is a dysdifferentiation (Cutler 1985), a phenomenon that emerged from the by-products of development (such as growth or sexual hormones), oxygen metabolism (active oxygen species) and also the by-products of stress (glucocorticoids, GC). Among these, development and oxygen metabolism are constant and necessary involuntary forces, and hence unchangeable, but the stress response in humans and other primates has changed over time, gaining another characteristic: the capacity to be chronic and detrimental (Sapolsky 2007).

This review will present the mechanisms by which stress can influence different aspects of immunity, as well as the interaction between ageing and stress and the consequences of this for immune health. It will first present stress as an adaptive phenomenon and explain its relationship with immune system generally. Second, we will focus on how psychological stress affects the immune system, with particular emphasis on the chronic stress of caregiving. In the latter part of the review, the

influence of ageing will be discussed, firstly describing the interplay between ageing and stress and then their additive effect on immunity. Finally, the review will discuss the pathophysiological consequences of the interaction between stress, ageing and immunity. Although the focus is mainly on humans, where applicable, studies using small animal models are included.

Stress

A challenging life demands tough reactions and has led to the development of a number of physiological changes that constitute the stress response in animals and humans. In a hostile environment, more complex organisms like vertebrates develop a response that Walter Cannon (1929) first introduced as 'fight or flight'. The main function of this response is maintaining body homeostasis. The key site involved in this process is the hypothalamus (Barrett 2005), a part of the brain that communicates by sending nerve impulses to other parts of the body. In this way, the hypothalamus acts within seconds and, via sympathetic nervous system, stimulates medulla of the adrenal gland to release catecholamines (adrenalin and noradrenalin). In addition, the hypothalamus also produces chemical messengers that act more slowly and in the next minutes travel through the hypothalamic-pituitary-adrenal (HPA) axis (Sapolsky et al. 2000). Chemical messengers in this pathway include corticotrophin releasing hormone (CRH) which stimulates anterior pituitary gland to release another hormone, adrenocorticotropic hormone or ACTH, into general circulation. The target organ of ACTH is again the adrenal gland, but this time, it is the cortical cells that synthesise and release species-specific GC into the blood. The tight control of these GC (mainly cortisol in humans) is sustained via negative feedback that controls and, in the end, terminates the release of CRH (Griffin and Ojeda 2004).

A clear distinction is made today between two types of stress, acute and chronic stress. From an evolutionary point of view, the acute component is beneficial in that it provides organisms with the mechanisms of the protection from the changeable and threatening environment. In that context, an interaction such as one between a lion and a zebra, even though there is no common interest for the outcome between these two animals, will trigger the same cascade of events in the body of both. Adrenalin and noradrenalin mainly, but with glucocorticoids

potentiating the effects, will increase arousal, alertness and vigilance; focus attention and elevate core temperature; and also increase the pain threshold (Kulkarni 1980), cardiovascular output, respiratory rate (Coles et al. 1956) and blood flow to the brain and skeletal muscle (Brown et al. 1979; Charmandari et al. 2005; Coles et al. 1956; Dowd et al. 2009; Kulkarni 1980). Skeletal muscle will gain the supply of the energy from the adipose and hepatic cells stores, whereas all other activities that are inessential in that moment, such as digestion, reproduction, feeding and growth, will be decreased through the action of GC (Cannon 1929; Selye 1956; Sorrells and Sapolsky 2007). Although acute stress and the events that follow have evolved as an adaptation, and are therefore beneficial, too great or too long of a response can be detrimental to the body. For example, synaptic plasticity in adult rats was negatively affected by prolonged stress exposure (Trentani et al. 2002). In humans, continuous or repeated psychological stress is strongly associated with detrimental effects on the cardiovascular system, and through it, with obesity and hypertension (McEwen 1998; Phillips et al. 2012; Sedova et al. 2004). However, despite the seemingly direct relationship between stress and different physiological functions, the general rule regarding the particular effects of GC alone on other organ systems is not sufficient to explain their action on the immune system, as described below. In other words, the negative effect of stress on the immune system is actually a non-adaptive phenomenon, as, using the analogy of Sapolsky, an injured animal would not survive and propagate the species if it escaped a predator only to then die of sepsis soon afterwards (Sorrells and Sapolsky 2007).

Stress and the immune system

GC and catecholamine effects of acute and chronic stress

It was previously thought that the stress response, through the action of GC, strictly suppresses immunity. There are several sources of evidence for this anti-inflammatory action of GC, such as involution of the thymus explained by Selye in the 1930s (Selye 1936; Viner 1999); the shift from a cellular Th1 to a humoral Th2 phenotype; limitation of the capacity of dendritic cells (DC) to interact with immature T cells by

preventing up-regulation of MHC class II and co-stimulatory molecules (Akdis et al. 1997; DeKruyff et al. 1998; Franchimont 2004; Ramirez et al. 1996); and inhibited production of the pro-inflammatory cytokines (interleukin (IL)-12, interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α)) (Franchimont et al. 2000; Hu et al. 2003; Steer et al. 2000), accompanied by the increased secretion of anti-inflammatory cytokines (IL-4 and IL-10) by Th2 cells (Elenkov and Chrousos 2002; Mozo et al. 2004; Wu et al. 1991). It is now known, however, that the way stress impacts immunity is not always straightforward and can be highly influenced by the duration of the stressor (Sorrells and Sapolsky 2007).

Initially in the acute stress response, the immune system is activated rather than suppressed (Sorrells and Sapolsky 2007), and only after this first reaction, in the following stages of the stress response, when levels of GC further rise, their anti-inflammatory effects come on the scene (Munck et al. 1984). Higher concentrations of GC will then help the organism to recover from the early phases of the stress response (Munck et al. 1984). However, it is certain that upon repeated stimulation by stress, or through prolonged, chronic stress, the immune system is suppressed, and this is, at least in part, mediated by the action of GC (Sorrells and Sapolsky 2007). The explanation for this dual behaviour of GC could be in the way they transmit their effects through steroid hormone signalling (Sorrells and Sapolsky 2007). The actual mechanism by which GC exert these different effects is yet to be elucidated. However, a potential explanation is that mineralocorticoid receptors, which paradoxically have much higher affinity for GC than GC receptors, completely bind GC when they are present in lower levels, so during the initial acute stress phase, and are thus responsible for much of the initial pro-inflammatory effects, as seen in the brain (De Kloet et al. 1998). In the following stages of the stress response, when mineralocorticoid receptors get saturated, GC receptors become increasingly occupied and can govern some of the anti-inflammatory action. On the other hand, it is uncertain if the same explanation could apply to the immune system in the periphery. For example, even though expressed in macrophages, mineralocorticoid receptors do not seem to be involved in modulating immune cells function by GC. Instead, that action is strictly confined to the concentration-dependent binding of the GC to the GC receptors (Lim et al. 2007). Nevertheless, it seems likely that a similar type of concentration-dependent effect of GC could be responsible for the difference in the effect of acute and chronic stress on the peripheral immune system, too (Sorrells and Sapolsky 2007). It is important to note here that GC are neither the only nor the primary inducers of immune alterations during the chronic stress response (Moynihan 2003). For example, the suppression of mitogen responses by rat lymphocytes was dependent only upon the production of β-endorphin and without any influence by corticosterone levels (Panerai et al. 1997). Similarly, Shi et al. (2003) showed that the apoptosis of lymphocytes during restraint stress was dependent on the state of opioid receptors only. The adrenergic receptor (β₂-AR) after binding catecholamines through two different signalling pathways triggers DNA damage as well as degradation of an important tumour suppressor in the brain of rats (Hara et al. 2011). Similar results were obtained after exposing rats to chronic restraint stress, whereas the administration of propanolol, a β-blocker, diminishes this effect (Hara et al. 2013). Finally, the mutual action of GC and catecholamines (CA) during chronic restraint stress will simultaneously affect migration of mononuclear cells in the peripheral blood of a specific mouse strain (Hermann et al. 1995), largely reduce cytokine expression from the lymph nodes and spleen (Dobbs et al. 1996), delay cytokine gene transcription in the lungs and lymph nodes (Sheridan et al. 1998), as well as diminish activation of cytotoxic T lymphocytes in the lymph nodes (Dobbs et al. 1993; Sheridan et al. 1998). However, it was also shown that chronic stress-induced changes in the concentrations of GC alone can have different effects on different pro-inflammatory cytokines, TNF-α, IL-1β and IL-6 (DeRijk et al. 1997). For example, daily fluctuations of these hormones were able to strongly affect TNF-α concentrations, whereas IL-1β responded only after exercise-induced increases in the levels of cortisol, and lowering IL-6 demanded pharmacological concentrations of GC (DeRijk et al. 1997). All three of these cytokines are predominantly produced by monocytes, but IL-6 can be produced by endothelial cells, fibroblasts and keratinocytes (Heinrich et al. 1990). Finally, while TNF-α and IL-1β are strictly pro-inflammatory, IL-6 can have both pro-inflammatory and anti-inflammatory effects (Scheller et al. 2011). Therefore, perhaps, the differential effects of stress hormones on TNF-α, IL-1β, and IL-6 are largely caused by the different roles of these cytokines.

Immuno-enhancing and immunosuppressive effects
of acute and chronic stress

There is a well-established difference in the effects that
acute and chronic stress exert on the immune response,
being immuno-enhancing and immunosuppressive, re-
spectively. The acute stress response and its associated
immunological changes closely resemble those related
to infection and involve both energy mobilisation and
activities of cytokines and neurotransmitters (Maier and
Watkins 1998). Acute brief restraint stress, applied be-
fore surgical sponge implementation into the rats, has
led to a more prominent increase in all blood leukocyte
count compared to the non-stressed group (Viswanathan
and Dhabhar 2005). Similarly, the same type of acute
stress administered before the immunisation increased
the number of memory and effector helper T (Th) cells
following immunisation (Dhabhar and Viswanathan
2005). This also seems to influence more robust im-
mune response upon repeated stimulation with the same
antigen months later (Dhabhar and Viswanathan 2005).
This can be beneficial in cases when increased
immunoprotection is needed, but detrimental in the
cases of immunopathology such as allergic conditions
and autoimmune disease (Atanackovic et al. 2013;
Dhabhar 2009; Dhabhar and Viswanathan 2005).

Chronic stress is generally accepted as being immu-
nosuppressive. However, if it was strictly immunosup-
pressive, it would not be able to negatively influence
disease outcomes in infectious and neoplastic disease
(associated with inadequate immunity) on the one hand,
and allergic and autoimmune disease (that emerge from
an excessive immune response) on the other, as ex-
plained by Segerstrom and Miller (2004). One possible
explanation for these seeming mutually exclusive con-
sequences of chronic stress was given by Marshall et al.
(1998), who suggested that chronic stress drives the
Th1-to-Th2 shift by altering patterns of cytokine expres-
sion. In that way, stress-induced suppression of Th1
cytokines (such as IFN-γ), involved in the defence
against many kinds of infection and some neoplastic
diseases, would lead to activation of Th2 cytokine pro-
duction, involved in allergies and different autoimmune
diseases, such as IL-10 (Marshall et al. 1998). In addi-
tion, it has been shown that chronic stress caused by
immobilisation affects the number of lymphocytes in
rats, but impacts on different subsets in different ways
(Dominguez-Gerpe and Rey-Mendez 2001). The over-
all decrease in the number of circulating lymphocytes

was accompanied by the increase in the number of
mainly immature T lymphocytes, suggesting one of
the potential mechanisms by which stress-associated
immunosuppression can affect and exacerbate autoim-
mune diseases (Moroda et al. 1997).

In summary, acute stressors usually, with the excep-
tions of natural killer (NK) cell function (Cunnick et al.
1988) and neutrophil superoxide production (Khanfer
et al. 2010, 2012), boost the immune system, particular-
ly its innate component which is the one able to act
quickly (Bosch et al. 2003; Dhabhar and McEwen 1997;
Sapolsky 1998). The majority of chronic stressors, on
the other hand, are associated with global immunosup-
pression and have an impact on both innate and adaptive
components of the immune system (Kiecolt-Glaser et al.
1991a; Phillips et al. 2006; Segerstrom and Miller 2004;
Thaker et al. 2006) to mention a few.

Beneficial and detrimental effects of acute and chronic
stress

Both the immune response and the fight-or-flight re-
sponse provide an adequate defence for survival and
further protection against infection after the injury oc-
curs. In that context, the relationship between acute
stress and immune up-regulation can be viewed as an
adaptive trait. On the other hand, chronic exposure to
stress appears to have detrimental effects on immunity
through continual activation of the same mechanisms.
This overlap between the stress response and the im-
mune response to infection could be the answer to some
of the seemingly contradictory processes that arise as the
consequence of different durations of the same stressor.
For example, in response to acute stressors, T cells in the
rat react by redistributing into the skin, which is the
organ that is the most likely to be affected in a life-
threatening situation when fighting the attackers. On the
other hand, prolonged action of the same type of stressor
will lead to the progressive decrease in this stress-
induced redeployment of T cells, as well as to the
suppression of delayed type hypersensitivity in the skin
(Dhabhar and McEwen 1997). Similarly, surgical oper-
ation in cancer patients after oesophagectomy has been
associated with an increase in peripheral blood lympho-
cyte apoptosis (Kono et al. 2001). The mechanism used
to explain this rise was increased Fas expression (Oka
et al. 1996) and changes in T lymphocyte signal trans-
duction through down-regulation of T cell receptor ζ
with a crucial influence of activated post-operative

monocytes on the process overall (Kono et al. 2001). Negative effects on lymphocytes associated with surgical stress were also observed in combination with psychological (daily life hassles) and physiological (cold pressor) stress upon stimulation of lymphocytes with phytohemagglutinin (PHA) and pokeweed mitogen, respectively (Linn et al. 1988). Through altering IFN-γ production and the ability to respond to both interferons and pro-inflammatory cytokines, e.g., IL-2, chronic restraint stress affects the activity of NK cells, components of the innate immunity important in resolving viral infections such as infection with herpes simplex virus (HSV) (Bonneau et al. 1991).

Psychological stress and immunity

A relationship between the central nervous system (CNS) and the immune system was first discovered in early animal experiments where it was revealed that immunosuppression could be induced through classical conditioning (Ader 2003; Ader and Cohen 1975; Garcia et al. 1955). A large number of studies have emphasised the behavioural changes that accompany chronic stress situations (such as alcohol consumption (Nguyen et al. 2012; Silva and Madeira 2012), smoking (Lee et al. 2007), nutrition (Thompson et al. 2013) and sleep disturbances) that are already known to have direct and serious health consequences and could mediate the negative effect of stress on health indirectly (Dallman et al. 2003; Hussain 2010). Other indirect effects might be via changes in social roles and social support associated with stress at the same time affecting health and quality of life (Baron et al. 1990; Pressman et al. 2005; Rutledge et al. 2004; Segerstrom and Miller 2004). However, many direct effects on immunity have also been demonstrated. Several studies reported changes in the cytokine profile in students during an academic examination period. The general pattern seems to be the emphasis of Th2 response through the decrease in pro-inflammatory cytokines (TNF-α, IL-6, IL-1, INF-γ) and higher levels of anti-inflammatory cytokines (IL-10 and IL-4) (Kang and Fox 2001; Marshall et al. 1998). Similar to these studies, delayed wound healing and a decrease in IL-1β, a key interleukin involved in this process, have been demonstrated in young healthy students during an examination period compared to a non-stressful holiday period (Marucha et al. 1998). The opposite is the case in students with

higher anxiety where levels of pro-inflammatory cytokines rise just before the important exam (Kamezaki et al. 2012; Maes et al. 1998). The explanation for this seemingly contradictory effect of examination stress is seen in its duration, as it can be divided into examination stress, its acute (i.e. immediately before the exam, as in Kamezaki et al. (2012) and Maes et al. (1998)) and its prolonged, chronic component (i.e. during the examination period, as in Kang and Fox (2001) and Marshall et al. (1998)); for a review, see Bosch et al. (2002)). In one of the first studies that examined the relationship between psychological stress and the immune system in humans, the strong psychological stressor of bereavement was associated with decreased function of T lymphocytes (Bartrop et al. 1977). In a similar way, neutrophils' killing ability was suppressed in the bereaved, the effect that was accompanied by the increase in cortisol/DHEAS (dehydroepiandrosterone sulphate) ratio (Khanfer et al. 2011), a parameter previously used as a measure of the effect stress hormones have upon immune system components (Butcher et al. 2005). Further, homeless people who reported higher stress levels had lower density of lymphocyte beta-adrenergic receptors (Dimsdale et al. 1994). This could indicate either a down-regulation of receptors due to higher stress hormone levels (CA or GC) or simply a change in the lymphocyte subsets, both of which could be a consequence of prolonged exposure to a stressful lifestyle. In addition, in children with a history of recurrent colds and flu who demonstrated higher levels of psychological stress, salivary IgA/albumin ratio was lower, indicating a potential link between stress and colds and flu (Drummond and HewsonBower 1997).

Loneliness affects NK cell activity not only in psychiatric patients (Kiecolt-Glaser et al. 1984b), but also in young and healthy medical students indicating general importance of social relationships for individuals' well-being (Kang et al. 1998; Kiecolt-Glaser et al. 1984a). Marital quality and recent separation among young women were associated with depressive symptoms and poorer immune function, seen through poorer proliferation of lymphocytes after stimulation with different mitogens (concavalin A and phytohemagglutinin) (Kiecolt-Glaser et al. 1987). More frequent marital concerns were associated with flatter cortisol profile (Barnett et al. 2005), an indicator of non-adaptive cortisol metabolism during chronic stress exposure.

One commonly studied model of the impact of stress on immunity is the role of caring for someone, be it a

spouse or child with a physical or mental illness or disability. Caregiving is now well established as having a serious effect on psychological well-being, physical health and self-efficacy among caregivers when compared to matched non-caregiving individuals (Pinquart and Sorensen 2003). For example, parents of cancer patients when compared to control parents had a decreased sensitivity to the anti-inflammatory effect of GC which could potentially contribute to the development of asthma, different cardiovascular and autoimmune diseases, as well as indicate dysregulation of the immune system that may become incapable of resolving infections (Miller et al. 2002). This is where we see the other side of stress effects on immune function where it exacerbates excessive immune response. Another study of adaptive immunity in mothers of children with developmental disabilities showed a lower T helper/ suppressor ratio, indicating again potentially less effective adaptive immunity for fighting the pathogens among the older age cohort of caregivers (mean age= 50.3 years) (Pariante et al. 1997).

A common approach for assessing the severity by which psychological stress affects the immune system is assessing antibody titres to latent viruses. Generally, latency is the ability of a virus to lie dormant in the host cell after the initial infection and emerge as an acute infection once the immune surveillance of the host weakens (Nowak 1991). Therefore, even though asymptomatic in the immunocompetent hosts, these infections could cause serious harmful and even fatal effects in the immunocompromised (Pawelec et al. 2005; Rasmussen 1991). In that context, separated women also had higher antibody titre against Epstein-Barr (EBV) virus, indicating poorer control of the virus, as well as lower number of both NK cells and helper T lymphocytes when compared to married women, with worse depression and immune outcomes seen in those with greater attachment to their ex-husband (Kiecolt-Glaser et al. 1987). In the case of married and separated men, those who went through divorce were more depressed, lonelier and had a higher antibody titre against both EBV and HSV (Kiecolt-Glaser et al. 1988). Finally, more negative behaviour in marriage has been shown to adversely affect endocrine responses in women and immunological activation, seen through antibody titres to EBV and the blastogenic response to T-cell mitogens, in both genders (Kiecolt-Glaser et al. 1997). Another study also demonstrated higher antibody titres against cytomegalovirus (CMV) in a group of caregiving individuals when

compared to the controls, indicating poorer latent virus control (Pariante et al. 1997).

Vaccination produces immune memory against specific pathogens, ready to respond to a real infection. An inadequate response and failure to provide required protection after vaccination, measured in terms of antibody titre, is indicative of a poorer immune response in the recipient. Unmarried older adults and those who had poor marital quality had a weaker antibody response to the influenza vaccination than happily married older adults (Phillips et al. 2006). Life events stress and perceived stress were also related to a lower antibody response after vaccination against flu and meningitis in students (Burns et al. 2002, 2003; Phillips et al. 2005), while greater social support enhanced antibody titres for some vaccine strains (Phillips et al. 2005). However, studies that have examined the antibody response to medical vaccination in younger caregivers have reported inconsistent results. The first study of this type compared hormonal and immune status between 41 partner of multiple sclerosis patients and 62 controls (Vedhara et al. 2002). Multiple sclerosis was chosen as a serious chronic and degenerative illness that usually causes physical and cognitive complications (Barcellos et al. 2002), and as such thought to cause equivalent level of burden for caregivers as seen in spouses and partners of dementia patients. Despite reporting higher levels of stress, but not anxiety and depression, caregivers showed no difference in either antibody response to an influenza vaccination, nor their IFN-γ and IL-4 levels. Similarly, cortisol and DHEAS ratio was not different between the groups, supporting previously shown preserved immune response in stressed, caregivers group. In contrast, a study conducted by Gallagher et al. (2009a) showed a poorer antibody response to pneumococcal vaccination in caregiving parents of children with developmental disabilities when compared to age- and sex-matched control parents at both 1 and 6 months follow-up. These findings were further supported by Gallagher et al. (2009b) which showed inability of caregiving parents to mount equally good antibody response as control parents after vaccination against the influenza virus. It was argued that the difference in immune response in these studies could be due to characteristics of the care-recipient such as challenging behaviours, rather than the caregiving role per se, and that perhaps the caregiving experience, reported as more challenging in case of parents of children with developmental disabilities, is what drives

these changes in immune function (Gallagher et al. 2009b). Indeed within the caregiving group, those parents who reported higher child problem behaviours had a poorer antibody response to the pneumococcal vaccine (Gallagher et al. 2009b).

Stressed individuals also show significant changes in the DNA repair process. Changes in DNA repair processes have been associated with different types of cancer such as cutaneous malignant melanoma (Wei et al. 2003), lung cancer (Wu et al. 2003) and breast cancer (Sharan et al. 1997). One of the theories of ageing suggests that the accumulation of DNA damage is a potential cause of gradual disruption in living organisms (Freitas and de Magalhaes 2011), emphasising the involvement of the repair mechanism in this process (de Boer et al. 2002). Several studies have shown correlations between stress and the action of the DNA repair machinery (Yang and Glaser 2003). This is also a demonstration of the complicated relationship between stress and body mechanisms, as it shows that in addition to the duration of stressor, the consequences of its action depend also upon the capacity of the organism to adapt to change and maintain homeostasis. The effect of stress was different depending on the population tested, with a decrease seen in the DNA repair mechanism after X-irradiation in psychiatric compared to non-psychiatric patients (Kiecolt-Glaser et al. 1985), whereas in young and healthy medical students, stress during an examination period influenced the increase in the extent of DNA repair after UV radiation (Cohen et al. 2000). As examination stress increases DNA damage and hence the need for its repair, it could be that the increase in the repair process in young and healthy students indicates their ability to meet this criteria, an ability that is not present in psychiatric patients who exhibit a decrease (Yang and Glaser 2003). Forlenza et al. (2000) confirmed this in a study that showed an increased rate of nucleotide exchange repair in medical students during an examination period when compared to the low stress holiday period. Further evidence can be found in the rat studies where sister chromatide exchange, a process that is known to occur with higher incidence in the presence of agents with oncogenic potential (Banerjee and Benedict 1979), showed a doubling potential in the bone marrow cells of rats subjected to different types of behavioural stressors, such as swimming, white noise and foot shock (Fischman and Kelly 1987). On the other hand, a decreased DNA repair capability was reported after carcinogen administration

in rats exposed to the rotational stress compared to a non-stressed group (Glaser et al. 1985).

When considering factors, tightly regulated and controlled, related to both maintaining and disturbing homeostasis on an intracellular level, structures that emerge as one of the key controllers of the cell cycle are telomeres. Telomeres are complexes of repetitive DNA sequences located on the very end of each chromosome surrounded by a large number of proteins. They have several functions, but are mainly involved in maintaining chromosome stability (Dahse et al. 1997). Due to the nature of DNA replication process, telomeres protect the core of DNA from shortening with every cell cycle, but at the same time, due to their own shortening, they are limiting factors that determine the number of cell division in physiological conditions (Dahse et al. 1997). As such, they are an attractive target for the process of tumourigenesis, but at the same time essential for understanding processes that are part of normal cell cycle, like senescence and apoptosis. Indeed, a large number of studies proved telomeres as an important factor in the process of ageing, as well as diseases such as HIV, hepatitis, Alzheimer's, inflammatory bowel disease and cancer (Jiang et al. 2007). The importance of adequate telomere length is a key to the immune system, particularly adaptive immunity, as cell division in lymphocytes is necessary for their response to antigenic challenge (Kaszubowska 2008). Studies have indicated that chronic stress might in this case mimic immunosenescence. For example, telomere length was shorter in parents caregiving for a chronically ill child and experiencing higher stress levels compared to those in the low stress caregiver group, even though there was no difference in telomere length between caregiving parents generally and their age- and sex-matched controls (Epel et al. 2004).

Another very important mechanism inside the cell that needs to be carefully regulated and kept in balance in order for the cell to function normally is programmed cell death or apoptosis. Apoptosis is essential for proper embryonic development, functioning of the immune system, as well as maintaining of the homeostasis in response to different physiological and pathological stimuli (Elmore 2007). Therefore, it is not surprising that different conditions, such as cancer, autoimmune diseases, neurodegenerative diseases and ageing are all linked to imbalance in the regulation of apoptotic processes (Elmore 2007). Apoptosis is one of the main mechanisms in the regulation of neutrophil function.

Neutrophils are key effector white blood cells in defending the host from bacterial infection by producing various cytokines and reactive oxygen species (Lloyd and Oppenheim 1992). However, neutrophils are also important factors in regulating inflammatory processes, and the existence of an adequate regulatory mechanism is necessary to prevent these protective components becoming a dangerous enemy. This is the reason for a very tight relationship between these cells and apoptosis (Sendo et al. 1997). With a half-life of 5–6 h, these cells are given enough time to perform their protective role and fight bacterial infection, but prevented from any deleterious effect on surrounding tissue that no longer requires their activity (Sendo et al. 1997). Intense exercise stress prolongs the survival of neutrophils, whereas longer lasting examination stress inhibits the process (Sendo et al. 1997). This, considered in the light of both aspects of neutrophil function, fighting infection and inflammation, indicates the variety of ways in which stress can affect health and emphasises the complexity that lies behind that relationship.

Ageing, stress and the immune system

One of the important components that should to be taken into account when considering the effect of stress on immunity is age. Even in cases where the effect of stress on the immune system is strong, such as in the case of caregiving, this might be even more evident or might change once the immune system is challenged by both ageing and stress simultaneously (Segerstrom and Miller 2004). Ageing is considered to weaken the body's ability to respond to stress, and with stress affecting organisms in a similar way as ageing, it may lead to accelerated ageing (Sapolsky 1999). It has been suggested that one of the factors contributing to this exacerbated effect of stress in the aged organisms is their inability to terminate the production of GC in response to stress (Sapolsky et al. 1986). According to the GC cascade hypothesis, failure of the control mechanism that should stop the production of GC after the effect of the stressor has ended is caused by the age-induced degeneration of the region of the brain responsible for communication with the endocrine system cascade (Sapolsky et al. 1986). In that way, excessive amounts of GC further damage the target brain region, starting a positive feedback cascade (Sapolsky et al. 1986). Functional connections between the immune and neuroendocrine systems stem from the existence of the interplay between their components, cytokines and hormones, on various levels (Ottaviani and Franceschi 1997); thus, the GC response to stress and ageing has a significant impact on immune function.

The way ageing and stress simultaneously act to affect the immune response seems to be influenced not only by the way organisms age, but it could be highly influenced also by early life event experience (Graham et al. 2006). Long-term effects seem to emerge not only after negative maternal behaviours, such as poor prenatal nutrition, but also following external, psychological and environmental stress in mothers (reviewed in Graham et al. 2006). For example, early life stress through the excess of maternal stress hormones, mainly GC (Painter et al. 2012), has been shown to relate to emotional problems and learning deficits, and it could lead to conditions such as type 2 diabetes and general depression and anxiety symptoms in adulthood (Weinstock 2008).

A theory of ageing known as 'disposable soma' hypothesis emphasises the difference between the efficiency of the translational machinery in reproductive and somatic cells, where the latter have traded accuracy in order to save energy for other more important functions (Kirkwood 1977). In the same manner, this theory explains longevity through the presence of the 'more successful' alleles of the genes involved in the protective mechanisms of the cellular response to a variety of physical stressors such as oxidative stress, radiation and heat (Kapahi et al. 1999). Further, it has been suggested that the immune system has been developed as a response to pathogens which are a specific type of stressors (i.e. antigenic stressors) (Ottaviani and Franceschi 1997). In that way, immunosenescence in more complex organisms such as vertebrates will be the product of the continuous accumulation of damage due to lifelong exposure to antigenic stress (Franceschi et al. 1999).

A typical consequence of ageing on immunity is not only involution of the thymus where T cells mature, but also changes in bone marrow stem cells that shift the number of circulating T cells from naive to a relative increase in memory T cells (Castle 2000; Miller 1996). NK cells show decreased activity per cell (Castle 2000), and dendritic cells show decreased ability to reach T cells as their target and promote adequate production of cytokines such as IFN-γ and IL-10 by influenza-specific T cells (Castle 2000). Toll-like receptors, membrane

proteins that recognise conserved structure from microbes, are present in lower levels on macrophages from aged mice than young mice (Renshaw et al. 2002). Further, neutrophils from elderly donors have poorer phagocytic function and diminished ability to fight off infections caused by Gram-positive bacteria, such as pneumonia, which is one of the major causes of death in the older population (Butcher et al. 2001).

The existence of compromised immunity in both younger stressed individuals (Cohen et al. 1997; Gallagher et al. 2009a, b) and older adults (Arora Duggal et al. 2013; Butcher et al. 2000, 2001; Hazeldine et al. 2012; Hazeldine and Lord 2013; Pawelec et al. 2005) suggests a potential common mechanism that may be shared between stress and ageing in relation to the immune system. Some forms of immunosuppression seen in response to stressors are also present with age. One example would be the change in cytokine production in the elderly, with cytokines from the Th2 response, such as IL-10 and IL-4, taking over from those typical for Th1 response, such as IFN-γ and IL-12 (Rink et al. 1998). Others are stress-induced thymus changes in both animals (Kioukia-Fougia et al. 2002) and humans (Gruver and Sempowski 2008), which are characteristic of normal ageing (Singh and Singh 1979), but also molecular changes seen as telomere shortening in chronically stressed (Epel et al. 2004) that also progressively occur with age (Cherif et al. 2003; Mikhelson and Gamaley 2008).

There is also an interesting association between age-related changes and stress in the pattern of sex steroid production (Arlt and Hewison 2004). Even though its exact effect on immunosenescence is yet to be established, DHEAS, a sex steroid, is considered to have an immune-enhancing capacity (Phillips et al. 2007). Another characteristic of this hormone is that it reaches its peak in the third decade of human life and then gradually declines with age (Orentreich et al. 1984). On the other hand, cortisol, a GC with known immunosuppressive effects, does not change with age, although it might be that its availability in the intracellular compartment of certain cells, including immune cells, does. This idea comes from the fact that activity of the enzyme capable of converting cortisone to active cortisol, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), is increased with the higher pro-inflammatory status, which is considered typical in the ageing process (Tomlinson et al. 2004). The result of this is a higher cortisol/DHEAS ratio, with the immunosuppressive effect of cortisol overcoming the immuno-enhancing effect of DHEAS (Phillips et al. 2007).

Many of the complex processes of ageing and the stress response remain unclear; nevertheless, research continues to suggest common pathways between them on all organisational levels, from those as big as organ systems or even the whole body, to those as small as intracellular pathways and their gene candidates. One component also involved in and frequently related to processes of ageing and the stress response is a transcriptional factor, nuclear factor-kappa B (NF-κB). NF-κB is a whole family of transcription factors (Gilmore 2006), involved in the regulation of both innate and adaptive immunity. Its dysregulation leads to autoimmune diseases and cancer, but it is also studied as an ageing- and stress-related factor. The suggested mechanism through which psychological stress can be transferred onto the intracellular level to affect NF-κB functioning and increase its binding activity involves a signalling pathway that is activated through binding of increased concentrations of noradrenalin to α_1- and β-adrenergic receptors during stress (Bierhaus et al. 2003). Another possible link between NF-κB and stress response is its interaction with GC receptors in a way that is yet to be elucidated (De Bosscher et al. 2003). It is not a surprise that a transcriptional factor that is involved in the response to so many key processes, such as oxidative stress, growth, immune function and DNA damage, like NF-κB, is also considered one of the components affected by ageing. Other molecular factors with a role in ageing, immunity and resistance to stress are forkhead box class O (FOXO3a) (Adler et al. 2007) and sirtuin 1 (SIRT1) (Longo and Kennedy 2006). Interestingly, they both act by inhibiting activation of NF-κB, emphasising the significance of this factor in both ageing and stress (Adler et al. 2008).

Chronic stress, ageing and the immune system

The main danger to immunity, however, occurs with synergy of ageing and *chronic* stress. In that respect, it might be that chronic stress is one of the main threats in already immune-compromised older age. As mentioned above, severe stressors with a long-term effect such as a loss after death of a close family member or friend have been shown to relate to changes in the ability of aged neutrophils to produce reactive oxygen species through which they kill rapidly dividing pathogens (Khanfer

et al. 2011). This detriment in neutrophil immunity was also accompanied by a higher cortisol/DHEAS ratio in the bereaved older adults relative to age-matched non-bereaved controls (Khanfer et al. 2011). Bereavement in older adults has also previously been associated with a poorer antibody response to vaccination against the influenza virus (Phillips et al. 2006). Changes in cortisol/DHEAS ratio with diminished immune function again suggest a potential mechanism through which stress could influence the body's defence mechanism against infection. For example, older adults who had suffered the physical stress of a hip fracture and gone on to develop a bacterial infection post-surgery showed decreased neutrophil superoxide production accompanied by a higher serum cortisol/DHEAS compared to age-matched controls (Butcher et al. 2005).

Older caregivers have most commonly been studied in this context, using the model of family dementia caregiving (Gouin et al. 2008). The severity of the stress in these circumstances comes not only from the patient's progressive deterioration in performing daily activities that pose growing problem for caregivers (Potkin 2002), but also from the loss of cognitive function, such as the ability to recognise people around them, and changes in behaviour such as hoarding, anger and repetitive behaviour (Grossberg 2002). Both innate and adaptive immunity are affected by chronic stress experienced by older adults, and both of these components are necessary for the protection against different pathogens that can damage the body. It was shown, for example, that wound healing was slower in older dementia caregivers when compared to age-, sex- and income-matched controls (Kiecolt-Glaser et al. 1995). Wound healing is a complex process comprised of various phases (immediate response, inflammatory response, proliferation, migration and contraction and resolution) that activates many different cells and molecules (Shaw and Martin 2009). Cells such as neutrophils and macrophages and high concentrations of cytokines are main players in inflammatory phase with a role to protect from invading pathogens and set the conditions for the repair process such as angiogenesis regulation (Shaw and Martin 2009). Lower production of pro-inflammatory cytokines involved in the wound healing process such as IL-1α, IL-8 (Glaser et al. 1999) as well as IL-1β (Kiecolt-Glaser et al. 1995) seen in caregivers compared to the controls indicates the possibility of a direct effect of stress on cytokine production in wound healing. Natural killer cell activity between older dementia

caregivers and controls showed no difference in the ability of these cells to kill K562 target tumour cells (Irwin et al. 1991), but in the presence of cytokine stimulation (recombinant INF-γ and IL-2), this similarity between stressed individuals and controls was not preserved; NK cells from caregivers responded more weakly compared to those from the controls (Esterling et al. 1994). All this, together with the stress-induced reduction in IFN-γ production (Glaser et al. 1986), indicates cytokines as a common target during chronic stress exposure and a potential effector through which much of the immune suppression may occur.

A further association between the chronic stress of caregiving was found for adaptive cell-mediated immunity; elevated cortisol levels as well as poorer proliferation to PHA and lower IL-2 production were shown in the caregiving group (Bauer et al. 2000). As observed in younger stressed participants (Marshall et al. 1998), caregiving stress in older adults has also been shown to be associated with the Th1-to-Th2 shift in cytokine responses, with the difference that in the older stressed individuals, this was driven purely by an increase in IL-10 production, with no difference in IFN-γ production by Th1 cells (Glaser et al. 2001).

Vaccination responses are affecting older adults due to immunosenescence, which makes them particularly vulnerable to frequent infections such as pneumonia and influenza, among the top five causes of high morbidity and mortality in this age group (Thompson et al. 2003). It would be expected that this aspect of immune incompetence would be further exacerbated in older adults affected by the chronic stress of caregiving. This is indeed the case: a significantly lower percentage of older caregivers of dementia patients showed a fourfold increase in antibody titre in response to vaccination against the influenza virus, a response that is clinically considered to be protective against infection (Vedhara et al. 1999). This was accompanied by a higher salivary cortisol concentration in this group when compared to the controls, pointing again to the role of the HPA axis in immune regulation among stressed individuals. Most microbial antigens, however, trigger both humoral, i.e. antibody response which is generated by B lymphocytes, as well as cellular responses, mainly mediated by cytotoxic CD8^{+} T cells (Glaser et al. 2000; Kiecolt-Glaser et al. 1996; Siergist 2008). In addition, CD4^{+} helper T cells are necessary as mediators between those two. It has been shown that both the antibody response to medical vaccination against the influenza virus, as

well as IL-2 production in response to antigen stimulation, was lower in caregivers comparing to the controls (Kiecolt-Glaser et al. 1996). In the case of the pneumococcal pneumonia vaccine, even though caregivers managed to exert an adequate immune response initially, shown as a rise in IgG antibody titre, it declined over time more rapidly in this group than in the group of matched controls, likely either as a consequence of a decrease in the number of antibody-specific B cells, or their ability to produce IgG (Glaser et al. 2000; Vedhara et al. 1999).

A frequently used approach for assessing the severity by which caregiving stress affects the immune system of older caregivers is that of studies of latent virus antibody titres. It is known, for example, that reactivation of latent viral infections, such as those initiated by herpes group (HSV-1, EBV, and CMV) is typical for immunosuppressed patients such as HIV and transplant patients (Rasmussen 1991). Interestingly, older caregivers had higher IgG antibody titres against EBV virus capsid antigen (VCA) compared to the matched controls, indicating poorer control of the latent infection in this group (Kiecolt-Glaser et al. 1991b). Together with the higher antibody titre to total viral antigen of HSV-1, caregivers also had a decreased virus-specific T-cell response, another component of immune system necessary for controlling the infection (Glaser and Kiecolt-Glaser 1997). Older parental caregivers have also been characterised by higher antibody titres against CMV when compared to the controls (Pariante et al. 1997).

Another concept that often occurs in the literature when discussing ageing of the immune system is inflammageing. Inflammageing indicates an imbalance between inflammatory factors necessary to fight the infection, but is damaging in excessive amounts, and anti-inflammatory components act as a counter weight. It has been suggested that ageing and longevity could, therefore, potentially be dependent on this balance (Franceschi et al. 2007). This would mean that immunosenescence, together with inflammatory markers such as different cytokines (IL-6, IL-8 and IL-15), as well as dysregulation at the molecular level and the presence of a certain genetic environment could all be predictors of the longevity of organisms. One consequence of this might be that chronically stressed older adults, such as dementia caregivers, could have elevated inflammatory markers even when compared to non-caregiving older adults who have immunosenescence. Indeed, not only did older caregivers show higher levels

of IL-6 (von Kanel et al. 2006), but its rate of increase was four times higher than in non-caregiving controls, leaving them particularly vulnerable to IL-6-related diseases such as frailty, cardiovascular diseases, osteoporosis and others (Ershler and Keller 2000).

Finally, even the effect of molecular mechanisms in ageing appears to be exacerbated by chronic stress in older adults. Caregivers of dementia patients had shorter peripheral blood mononuclear cells (PBMC), T cell and monocyte telomere lengths, and this was not due to having a higher number of these cells with shorter telomeres (Damjanovic et al. 2007). On the other hand, they also showed an increase in basal telomerase activity, which could indicate an attempt of these cells to compensate for the loss of their telomere length (Damjanovic et al. 2007).

Conclusion

In this review, we have seen that both the chronicity of stress and the ageing process prove detrimental to an organism's well-being. The mechanisms of these effects are yet to be elucidated more fully. However, it is clear that many of the ways in which both ageing and stress affect the body are through shared mechanisms, with particular regard to the neuroendocrine and immune systems from the level of the tissues, cells and even intracellular components. Less is known about the additive impact of ageing and stress on the innate immune system with the exception of studies of NK cells. A better understanding of the processes by which stress and ageing affect health will lead to a greater capacity for intervention, be it behavioural or pharmacological.

References

Ader R (2003) Conditioned immunomodulation: research needs and directions. Brain Behav Immun 17:S51–S57

Ader R, Cohen N (1975) Behaviorally conditioned immunosuppression. Psychosom Med 37(1):83–83

Adler AS, Sinha S, Kawahara TLA, Zhang JY, Segal E, Chang HY (2007) Motif module map reveals enforcement of aging by continual NF-kappa B activity. Genes Dev 21(24):3244–3257. doi:10.1101/gad.1588507

Adler AS, Kawahara TLA, Segal E, Chang HY (2008) Reversal of aging by NF kappa B blockade. Cell Cycle 7(5):556–559

Akdis CA, Blesken T, Akdis M, Alkan SS, Heusser CH, Blaser K (1997) Glucocorticoids inhibit human antigen-specific and enhance total IgE and IgG4 production due to differential

effects on T and B cells in vitro. Eur J Immunol 27(9):2351–2357. doi:10.1002/eji.1830270933

Arlt W, Hewison M (2004) Hormones and immune function: implications of aging. Aging Cell 3(4):209–216. doi:10.1111/j.1474-9728.2004.00109.x

Arora Duggal N, Upton J, Phillips AC, Sapey E, Lord JM (2013) An age-related numerical and functional deficit in CD19(+) CD24(hi) CD38(hi) B cells is associated with an increase in systemic autoimmunity. Aging Cell 12(5): 873–881

Atanackovic D, Nowottne U, Freier E, Weber CS, Meyer S, Bartels K, Hildebrandt Y, Cao YR, Kroger N, Brunner-Weinzierl MC, Bokemeyer C, Deter HC (2013) Acute psychological stress increases peripheral blood CD3(+)CD56(+) natural killer T cells in healthy men: possible implications for the development and treatment of allergic and autoimmune disorders. Stress Int J Biol Stress 16(4):421–428. doi:10.3109/10253890.2013.777702

Banerjee A, Benedict WF (1979) Production of sister chromatid exchanges by various cancer chemotherapeutic agents. Cancer Res 39(3):797–799

Barcellos LF, Oksenberg JR, Green AJ, Bucher P, Rimmler JB, Schmidt S, Garcia ME, Lincoln RR, Pericak-Vance MA, Haines JL, Hauser SL, Multiple Sclerosis Genet G (2002) Genetic basis for clinical expression in multiple sclerosis. Brain 125:150–158

Barnett RC, Steptoe A, Gareis KC (2005) Marital-role quality and stress-related psychobiological indicators. Ann Behav Med 30(1):36–43. doi:10.1207/s15324796abm3001_5

Baron RS, Cutrona CE, Hicklin D, Russell DW, Lubaroff DM (1990) Social support and immune function among spouses of cancer patients. J Pers Soc Psychol 59(2):344–352. doi:10.1037/0022-3514.59.2.344

Barrett EJ (2005) The adrenal gland. In: Boron WF, Boulpaep EL (eds) Medical physiology: a cellular and molecular approach. Elsevier Inc, pp 1049–1065

Bartrop RW, Lazarus L, Luckhurst E, Kiloh LG, Penny R (1977) Depressed lymphocyte function after bereavement. Lancet 1(8016):834–839

Bauer ME, Vedhara K, Perks P, Wilcock GK, Lightman SL, Shanks N (2000) Chronic stress in caregivers of dementia patients is associated with reduced lymphocyte sensitivity to glucocorticoids. J Neuroimmunol 103(1):84–92. doi:10.1016/s0165-5728(99)00228-3

Bierhaus A, Wolf J, Andrassy M, Rohleder N, Humpert PM, Petrov D, Ferstl R, von Eynatten M, Wendt T, Rudofsky G, Joswig M, Morcos M, Schwaninger M, McEwen B, Kirschbaum C, Nawroth PP (2003) A mechanism converting psychosocial stress into mononuclear cell activation. Proc Natl Acad Sci U S A 100(4):1920–1925. doi:10.1073/pnas.0438019100

Bonneau RH, Sheridan JF, Feng N, Glaser R (1991) Stress-induced suppression of herpes simplex virus (HSV)-specific cytotoxic lymphocyte T and natural-killer cell activity and enhancement of acute pathogenesis following local HSV infection. Brain Behav Immun 5(2):170–192. doi:10.1016/0889-1591(91)90015-3

Bosch JA, Berntson GG, Cacioppo JT, Dhabhar FS, Marucha PT (2003) Acute stress evokes selective mobilization of T cells that differ in chemokine receptor expression: a potential pathway linking immunologic reactivity to cardiovascular disease. Brain Behav Immun 17(4):251–259. doi:10.1016/s0889-1591(03)00054-0

Bosch JA, Ring C, de Geus EJ, Veerman EC, Amerongen AV (2002) Stress and secretory immunity. Int Rev Neurobiol 52:213–253

Brown HF, Difrancesco D, Noble SJ (1979) How does adrenaline accelerate the heart. Nature 280(5719):235–236. doi:10.1038/280235a0

Burns VE, Drayson M, Ring C, Carroll D (2002) Perceived stress and psychological well-being are associated with antibody status after meningitis C conjugate vaccination. Psychosom Med 64(6):963–970. doi:10.1097/01.psy.0000039836.67401.28

Burns VE, Carroll D, Drayson M, Whitham M, Ring C (2003) Life events, perceived stress and antibody response to influenza vaccination in young, healthy adults. J Psychosom Res 55(6): 569–572. doi:10.1016/s0022-3999(03)00073-4

Butcher SK, Chahal H, Lord JM (2000) Ageing and the neutrophil: no appetite for killing? Immunology 100(4):411–416. doi:10.1046/j.1365-2567.2000.00079.x

Butcher SK, Chahal H, Nayak L, Sinclair A, Henriquez NV, Sapey E, O'Mahony D, Lord JM (2001) Senescence in innate immune responses: reduced neutrophil phagocytic capacity and CD16 expression in elderly humans. J Leukoc Biol 70(6):881–886

Butcher SK, Killampalli V, Lascelles D, Wang K, Alpar EK, Lord JM (2005) Raised cortisol : DHEAS ratios in the elderly after injury: potential impact upon neutrophil function and immunity. Aging Cell 4(6):319–324. doi:10.1111/j.1474-9726.2005.00178.x

Cannon WB (1929) Bodily changes in pain, hunger, fear, and rage. D. Appleton & Co., New York

Castle SC (2000) Clinical relevance of age-related immune dysfunction. Clin Infect Dis 31(2):578–585. doi:10.1086/313947

Charmandari E, Tsigos C, Chrousos G (2005) Endocrinology of the stress response. Annu Rev Physiol 67:259–284. doi:10.1146/annurev.physiol.67.040403.120816

Cherif H, Tarry JL, Ozanne SE, Hales CN (2003) Ageing and telomeres: a study into organ- and gender-specific telomere shortening. Nucleic Acids Res 31(5):1576–1583. doi:10.1093/nar/gkg208

Cohen S, Line S, Manuck SB, Rabin BS, Heise ER, Kaplan JR (1997) Chronic social stress, social status, and susceptibility to upper respiratory infections in nonhuman primates. Psychosom Med 59(3):213–221

Cohen L, Marshall GD, Cheng L, Agarwal SK, Wei QY (2000) DNA repair capacity in healthy medical students during and after exam stress. J Behav Med 23(6):531–544. doi:10.1023/a:1005503502992

Coles DR, Duff F, Shepherd WHT, Whelan RF (1956) Effect on respiration of infusions of adrenaline and noradrenaline into the carotid and vertebral arteries in man. Br J Pharmacol Chemother 11(3):346–350

Cunnick JE, Lysle DT, Armfield A, Rabin BS (1988) Shock-induced modulation of lymphocyte responsiveness and natural killer cell activity: differential mechanisms of induction. Brain Behav Immun 2:102–113

Cutler RG (1982) Longevity is determined by specific genes: testing the hypothesis. In: Adelman R, Roth G (eds) Testing the theories of aging. CRC Press, Boca Raton, pp 25–114

Cutler RG (1985) Dysdifferentiation and aging. In: Sohal RS, Birnbaum L, Cutler RG (eds) Molecular biology of aging:

gene stability and gene expression. Raven Press, New York, pp 307–340

Dahse R, Fiedler W, Ernst G (1997) Telomeres and telomerase: biological and clinical importance. Clin Chem 43(5):708–714

Dallman MF, Pecoraro N, Akana SF, la Fleur SE, Gomez F, Houshyar H, Bell ME, Bhatnagar S, Laugero KD, Manalo S (2003) Chronic stress and obesity: a new view of "comfort food". Proc Natl Acad Sci U S A 100(20):11696–11701. doi:10.1073/pnas.1934666100

Damjanovic AK, Yang YH, Glaser R, Kiecolt-Glaser JK, Nguyen H, Laskowski B, Zou YX, Beversdorf DQ, Weng NP (2007) Accelerated telomere erosion is associated with a declining immune function of caregivers of Alzheimer's disease patients. J Immunol 179(6):4249–4254

de Boer J, Andressoo JO, de Wit J, Huijmans J, Beems RB, van Steeg H, Weeda G, van der Horst GTJ, van Leeuwen W, Themmen APN, Meradji M, Hoeijmakers JHJ (2002) Premature aging in mice deficient in DNA repair and transcription. Science 296(5571):1276–1279. doi:10.1126/science.1070174

De Bosscher K, Vanden Berghe W, Haegeman G (2003) The interplay between the glucocorticoid receptor and nuclear factor-kappa B or activator protein-1: molecular mechanisms for gene repression. Endocr Rev 24(4):488–522. doi:10.1210/er.2002-0006

De Kloet ER, Vreugdenhil E, Oitzl MS, Joels M (1998) Brain corticosteroid receptor balance in health and disease. Endocr Rev 19(3):269–301. doi:10.1210/er.19.3.269

DeKruyff R, Fang Y, Umetsu DT (1998) Corticosteroids enhance the capacity of macrophages to induce Th2 cytokine synthesis in CD4(+) lymphocytes by inhibiting IL-12 production. J Immunol 160(5):2231–2237

DeRijk R, Michelson D, Karp B, Petrides J, Galliven E, Deuster P, Paciotti G, Gold PW, Sternberg EM (1997) Exercise and circadian rhythm-induced variations in plasma cortisol differentially regulate interleukin-1 beta (IL-1 beta), IL-6, and tumor necrosis factor-alpha (TNF alpha) production in humans: high sensitivity of TNF alpha and resistance of IL-6. J Clin Endocrinol Metab 82(7):2182–2191. doi:10.1210/jc.82.7.2182

Dhabhar FS (2009) Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection and immunopathology. Neuroimmunomodulation 16(5):300–317. doi:10.1159/000216188

Dhabhar FS, McEwen BS (1997) Acute stress enhances while chronic stress suppresses cell-mediated immunity in vivo: a potential role for leukocyte trafficking. Brain Behav Immun 11(4):286–306. doi:10.1006/brbi.1997.0508

Dhabhar FS, Viswanathan K (2005) Short-term stress experienced at time of immunization induces a long-lasting increase in immunologic memory. Am J Physiol Regul Integr Comp Physiol 289(3):R738–R744. doi:10.1152/ajpregu.00145.2005

Dimsdale JE, Mills P, Patterson T, Ziegler M, Dillon E (1994) Effects of chronic stress on beta adrenergic receptors in the homeless. Psychosom Med 56(4):290–295

Dobbs CM, Vasquez M, Glaser R, Sheridan JF (1993) Mechanisms of stress-induced modulation of viral pathogenesis and immunity. J Neuroimmunol 48(2):151–160. doi:10.1016/0165-5728(93)90187-4

Dobbs CM, Feng NG, Beck FM, Sheridan JF (1996) Neuroendocrine regulation of cytokine production during experimental influenza viral infection—effects of restraint stress-induced elevation in endogenous corticosterone. J Immunol 157(5):1870–1877

Dominguez-Gerpe, Rey-Mendez M (2001) Alterations induced by chronic stress in lymphocyte subsets of blood and primary and secondary immune organs of mice. BMC Immunol 2(7)

Dowd JB, Aiello AE, Alley DE (2009) Socioeconomic disparities in the seroprevalence of cytomegalovirus infection in the US population: NHANES III. Epidemiol Infect 137(1):58–65. doi:10.1017/s0950268808000551

Drummond PD, HewsonBower B (1997) Increased psychosocial stress and decreased mucosal immunity in children with recurrent upper respiratory tract infections. J Psychosom Res 43(3):271–278. doi:10.1016/s0022-3999(97)00002-0

Elenkov IJ, Chrousos GP (2002) Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. In: Cutolo M, Bijlsma JWJ, Lahita RG, Masi AT, Straub RH, Bradlow HL (eds) Neuroendocrine immune basis of the rheumatic diseases II, proceedings, vol 966. Ann N Y Acad Sci 290–303

Elmore S (2007) Apoptosis: a review of programmed cell death. Toxicol Pathol 35(4):495–516. doi:10.1080/01926230701320337

Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, Cawthon RM (2004) Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci U S A 101(49):17312–17315. doi:10.1073/pnas.0407162101

Ershler WB, Keller ET (2000) Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. Annu Rev Med 51:245–270. doi:10.1146/annurev.med.51.1.245

Esterling BA, Kiecolt-Glaser JK, Bodnar JC, Glaser R (1994) Chronic stress, social support, and persistent alterations in the natural killer cell response to cytokines in older adults. Health Psychol 13(4):291–298. doi:10.1037//0278-6133.13.4.291

Fischman HK, Kelly DD (1987) Sister chromatid exchanges induced by behavioral stress. Ann N Y Acad Sci 496:426–435. doi:10.1111/j.1749-6632.1987.tb35798.x

Forlenza MJ, Latimer JJ, Baum A (2000) The effects of stress on DNA repair capacity. Psychol Health 15(6):881–891. doi:10.1080/08870440008405589

Franceschi C, Valensin S, Fagnoni F, Barbi C, Bonafe M (1999) Biomarkers of immunosenescence within an evolutionary perspective: the challenge of heterogeneity and the role of antigenic load. Exp Gerontol 34(8):911–921. doi:10.1016/s0531-5565(99)00068-6

Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, Panouraia MP, Invidia L, Celani L, Scurti M, Cevenini E, Castellani GC, Salvioli S (2007) Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech Ageing Dev 128(1):92–105. doi:10.1016/j.mad.2006.11.016

Franchimont D (2004) Overview of the actions of glucocorticoids on the immune response—a good model to characterize new pathways of immunosuppression for new treatment strategies. In: Kino T, Charmandari E, Chrousos GP (eds) Glucocorticoid action: basic and clinical implications, vol 1024. Ann N Y Acad Sci pp 124–137. doi:10.1196/annals.1321.009

Franchimont D, Galon J, Gadina M, Visconti R, Zhou YJ, Aringer M, Frucht DM, Chrousos GP, O'Shea JJ (2000) Inhibition of Th1 immune response by glucocorticoids, dexamethasone selectively inhibits IL-12-induced Stat4 phosphorylation in T lymphocytes. J Immunol 164(4):1768–1774

Freitas AA, de Magalhaes JP (2011) A review and appraisal of the DNA damage theory of ageing. Mutat Res Rev Mutat Res 728(1–2):12–22. doi:10.1016/j.mrrev.2011.05.001

Gallagher S, Phillips AC, Drayson MT, Carroll D (2009a) Caregiving for children with developmental disabilities is associated with a poor antibody response to influenza vaccination. Psychosom Med 71(3):341–344. doi:10.1097/PSY.0b013e31819d1910

Gallagher S, Phillips AC, Drayson MT, Carroll D (2009b) Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. Brain Behav Immun 23(3):338–346. doi:10.1016/j.bbi.2008.05.006

Garcia J, Kimeldorf DJ, Koelling RA (1955) Conditioned aversion to saccharin resulting from exposure to gamma radiation. Science 122(3160):157–158

Gilmore TD (2006) Introduction to NF-kappa B: players, pathways, perspectives. Oncogene 25(51):6680–6684. doi:10.1038/sj.onc.1209954

Glaser R, Kiecolt-Glaser JK (1997) Chronic stress modulates the virus-specific immune response to latent herpes simplex virus type 1. Ann Behav Med 19(2):78–82. doi:10.1007/bf02883323

Glaser R, Thorn BE, Tarr KL, Kiecolt-Glaser JK, Dambrosio SM (1985) Effects of stress on methyltransferase synthesis—an important DNA repair enzyme. Health Psychol 4(5):403–412. doi:10.1037/0278-6133.4.5.403

Glaser R, Rice J, Stout JC, Speicher CE, Kiecolt-Glaser JK (1986) Stress depresses interferon production by leukocytes concomitant with a decrease in natural killer cell activity. Behav Neurosci 100(5):675–678. doi:10.1037/0735-7044.100.5.675

Glaser R, Kiecolt-Glaser PK, Marucha PT, MacCallum RC, Laskowski BF, Malarkey WB (1999) Stress-related changes in proinflammatory cytokine production in wounds. Arch Gen Psychiatry 56(5):450–456. doi:10.1001/archpsyc.56.5.450

Glaser R, Sheridan J, Malarkey WB, MacCallum RC, Kiecolt-Glaser JK (2000) Chronic stress modulates the immune response to a pneumococcal pneumonia vaccine. Psychosom Med 62(6):804–807

Glaser R, MacCallum RC, Laskowski BF, Malarkey WB, Sheridan JF, Kiecolt-Glaser JK (2001) Evidence for a shift in the Th-1 to Th-2 cytokine response associated with chronic stress and aging (vol 56, pg 477, 2001). J Gerontol Ser A Biol Sci Med Sci 56(11):M673–M673

Gouin JP, Hantsoo L, Kiecolt-Glaser JK (2008) Immune dysregulation and chronic stress among older adults: a review. Neuroimmunomodulation 15(4–6):251–259. doi:10.1159/000156468

Graham JE, Christian LM, Kiecolt-Glaser JK (2006) Stress, age, and immune function: toward a lifespan approach. J Behav Med 29(4):389–400. doi:10.1007/s10865-006-9057-4

Griffin JE, Ojeda SR (2004) Textbook of endocrine physiology. Oxford University Press, New York

Grossberg GT (2002) The ABC of Alzheimer's disease: behavioral symptoms and their treatment. Int Psychogeriatr 14:27–49. doi:10.1017/s1041610203008652

Gruver AL, Sempowski GD (2008) Cytokines, leptin, and stress-induced thymic atrophy. J Leukoc Biol 84(4):915–923. doi:10.1189/jlb.0108025

Hara MR, Kovacs JJ, Whalen EJ, Rajagopal S, Strachan RT, Grant W, Towers AJ, Williams B, Lam CM, Xiao KH, Shenoy SK, Gregory SG, Ahn S, Duckett DR, Lefkowitz RJ (2011) A stress response pathway regulates DNA damage through beta(2)-adrenoreceptors and beta-arrestin-1. Nature 477(7364):349–353. doi:10.1038/nature10368

Hara MR, Sachs BD, Caron MG, Lefkowitz RJ (2013) Pharmacological blockade of a beta(2)AR-beta-arrestin-1 signaling cascade prevents the accumulation of DNA damage in a behavioral stress model. Cell Cycle 12(2):219–224. doi:10.4161/cc.23368

Hazeldine J, Lord JM (2013) The impact of ageing on natural killer cell function and potential consequences for health in older adults. Ageing Res Rev 12(4):1069–1078. doi:10.1016/j.arr.2013.04.003

Hazeldine J, Hampson P, Lord JM (2012) Reduced release and binding of perforin at the immunological synapse underlies the age-related decline in natural killer cell cytotoxicity. Aging Cell 1–9

Heinrich PC, Castell JV, Andus T (1990) Interleukin 6 and the acute phase response. Biochem J 265(3):621–636

Hermann G, Beck FM, Sheridan JF (1995) Stress-induced glucocorticoid response modulates mononuclear cell trafficking during an experimental influenza viral infection. J Neuroimmunol 56(2):179–186. doi:10.1016/0165-5728(94)00145-e

Hu XY, Li WP, Meng C, Ivashkiv LB (2003) Inhibition of IFN-gamma signaling by glucocorticoids. J Immunol 170(9):4833–4839

Hussain D (2010) Stress, immunity, and health: research findings and implications. Int J Psychosoc Rehabil 15(1):94–100

Irwin M, Brown M, Patterson T, Hauger R, Mascovich A, Grant I (1991) Neuropeptide Y and natural killer cell activity—findings in depression and Alzheimer caregiver stress. FASEB J 5(15):3100–3107

Jiang H, Ju Z, Rudolph KL (2007) Telomere shortening and ageing. Z Gerontol Geriatr 40(5):314–324. doi:10.1007/s00391-007-0480-0

Kamezaki Y, Katsuura S, Kuwano Y, Tanahashi T, Rokutan K (2012) Circulating cytokine signatures in healthy medical students exposed to academic examination stress. Psychophysiology 49(7):991–997. doi:10.1111/j.1469-8986.2012.01371.x

Kang DH, Fox C (2001) Th1 and Th2 cytokine responses to academic stress. Res Nurs Health 24(4):245–257. doi:10.1002/nur.1027

Kang DH, Coe CL, Karaszewski J, McCarthy DO (1998) Relationship of social support to stress responses and immune function in healthy and asthmatic adolescents. Res Nurs Health 21(2):117–128. doi:10.1002/(sici)1098-240x(199804)21:2<117::aid-nur3>3.0.co;2-m

Kapahi P, Boulton ME, Kirkwood TBL (1999) Positive correlation between mammalian life span and cellular resistance to stress. Free Radic Biol Med 26(5–6):495–500. doi:10.1016/s0891-5849(98)00323-2

Kaszubowska L (2008) Telomere shortening and ageing of the immune system. J Physiol Pharmacol 59:169–186

Khanfer RPAC, Carroll D, Lord JM (2010) Altered human neutrophil function in response to acute psychological stress. Psychosom Med 72(7):636–640

Khanfer R, Lord JM, Phillips AC (2011) Neutrophil function and cortisol:DHEAS ratio in bereaved older adults. Brain Behav Immun 25(6):1182–1186. doi:10.1016/j.bbi.2011.03.008

Khanfer R, Carroll D, Lord JM, Phillips AC (2012) Reduced neutrophil superoxide production among healthy older adults in response to acute psychological stress. Int J Psychophysiol 86(3):238–244. doi:10.1016/j.ijpsycho.2012.09.013

Kiecolt-Glaser JK, Garner W, Speicher C, Penn GM, Holliday J, Glaser R (1984a) Psychosocial modifiers of immunocompetence in medical students. Psychosom Med 46(1):7–14

Kiecolt-Glaser JK, Ricker D, George J, Messick G, Speicher CE, Garner W, Glaser R (1984b) Urinary cortisol levels, cellular immunocompetency, and loneliness in psychiatric inpatients. Psychosom Med 46(1):15–23

Kiecolt-Glaser JK, Stephens RE, Lipetz PD, Speicher CE, Glaser R (1985) Distress and DNA repair in human lymphocytes. J Behav Med 8(4):311–320. doi:10.1007/bf00848366

Kiecolt-Glaser JK, Fisher LD, Ogrocki P, Stout JC, Speicher CE, Glaser R (1987) Marital quality, marital disruption, and immune function. Psychosom Med 49(1):13–34

Kiecolt-Glaser JK, Kennedy S, Malkoff S, Fisher L, Speicher CE, Glaser R (1988) Marital discord and immunity in males. Psychosom Med 50(3):213–229

Kiecolt-Glaser JK, Dura JR, Speicher CE, Trask OJ, Glaser R (1991a) Spousal caregivers of dementia victims: longitudinal changes in immunity and health. Psychosom Med 53(4):345–362

Kiecolt-Glaser JK, Speicher CE, Glaser R, Dura JR, Trask OJ (1991b) Spousal caregivers of dementia victims—longitudinal changes in immunity and health. Psychosom Med 53(4):345–362

Kiecolt-Glaser JK, Marucha PT, Malarkey WB, Mercado AM, Glaser R (1995) Slowing of wound healing by psychological stress. Lancet 346(8984):1194–1196

Kiecolt-Glaser JK, Glaser R, Gravenstein S, Malarkey WB, Sheridan J (1996) Chronic stress alters the immune response to influenza virus vaccine in older adults. Proc Natl Acad Sci U S A 93(7):3043–3047. doi:10.1073/pnas.93.7.3043

Kiecolt-Glaser JK, Glaser R, Cacioppo JT, MacCallum RC, Snydersmith M, Kim C, Malarkey WB (1997) Marital conflict in older adults: endocrinological and immunological correlates. Psychosom Med 59(4):339–349

Kioukia-Fougia N, Antoniou K, Bekris S, Liapi C, Christofidis I, Papadopoulou-Daifoti Z (2002) The effects of stress exposure on the hypothalamic-pituitary-adrenal axis, thymus, thyroid hormones and glucose levels. Prog Neuro-Psychopharmacol Biol Psychiatry 26(5):823–830. doi:10.1016/s0278-5846(01)00297-4

Kirkwood TBL (1977) Evolution of ageing. Nature 270(5635):301–304

Kono K, Takahashi A, Iizuka H, Fujii H, Sekikawa T, Matsumoto Y (2001) Effect of oesophagectomy on monocyte-induced apoptosis of peripheral blood T lymphocytes. Br J Surg 88(8):1110–1116. doi:10.1046/j.0007-1323.2001.01833.x

Kulkarni SK (1980) Heat and other physiological stress-induced analgesia: catecholamine mediated and naloxone reversible response. Life Sci 27(3):185–188. doi:10.1016/0024-3205(80)90136-8

Lee WK, Rarnanathan M, Spannhake EW, Lane AP (2007) The cigarette smoke component acrolein inhibits expression of the innate immune components, IL-8 and human beta-defensin 2 by sinonasal epithelial cells. Am J Rhinol 21(6):658–663. doi:10.2500/ajr.2007.21.3094

Lim HY, Muller N, Herold MJ, van den Brandt J, Reichardt HM (2007) Glucocorticoids exert opposing effects on macrophage function dependent on their concentration. Immunology 122(1):47–53. doi:10.1111/j.1365-2567.2007.02611.x

Linn BS, Linn MW, Klimas NG (1988) Effects of psychophysical stress on surgical outcome. Psychosom Med 50(3):230–244

Lloyd AR, Oppenheim JJ (1992) Polys lament: the neglected role of the polymorphonuclear neutrophil in the afferent limb of the immune response. Immunol Today 13(5):169–172. doi:10.1016/0167-5699(92)90121-m

Longo VD, Kennedy BK (2006) Sirtuins in aging and age-related disease. Cell 126(2):257–268. doi:10.1016/j.cell.2006.07.002

Maes M, Song C, Lin AH, De Jongh R, Van Gastel A, Kenis G, Bosmans E, De Meester I, Benoy I, Neels H, Demedts P, Janca A, Scharpe S, Smith RS (1998) The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. Cytokine 10(4):313–318. doi:10.1006/cyto.1997.0290

Maier SF, Watkins LR (1998) Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. Psychol Rev 105(1):83–107. doi:10.1037/0033-295x.105.1.83

Marshall GD, Agarwal SK, Lloyd C, Cohen L, Henninger EM, Morris GJ (1998) Cytokine dysregulation associated with exam stress in healthy medical students. Brain Behav Immun 12(4):297–307. doi:10.1006/brbi.1998.0537

Marucha PT, Kiecolt-Glaser JK, Favagehi M (1998) Mucosal wound healing is impaired by examination stress. Psychosom Med 60(3):362–365

McEwen BS (1998) Protective and damaging effects of stress mediators. N Engl J Med 338(3):171–179

Mikhelson VM, Gamaley IA (2008) Telomere shortening is the sole mechanism of aging. Open Longev Sci 2:23–28

Miller RA (1996) The aging immune system: primer and prospectus. Science 273(5271):70–74. doi:10.1126/science.273.5271.70

Miller GE, Cohen S, Ritchey AK (2002) Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. Health Psychol 21(6):531–541. doi:10.1037//0278-6133.21.6.531

Moroda T, Kawachi Y, Iiai T, Tsukahara A, Suzuki S, Tada T, Watanabe H, Hatakeyama K, Abo T (1997) Self-reactive forbidden clones are confined to pathways of intermediate T-cell receptor cell differentiation even under immunosuppressive conditions. Immunology 91(1):88–94. doi:10.1046/j.1365-2567.1997.00222.x

Moynihan JA (2003) Mechanisms of stress-induced modulation of immunity. Brain Behav Immun 17:S11–S16

Mozo L, Suarez A, Gutierrez C (2004) Glucocorticoids up-regulate constitutive interleukin-10 production by human monocytes. Clin Exp Allergy 34(3):406–412. doi:10.1111/j.1365-2222.2004.01824.x

Munck A, Guyre PM, Holbrook NJ (1984) Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev 5(1):25–44

Nguyen KH, Lee JH, Nyomba BLG (2012) Ethanol causes endoplasmic reticulum stress and impairment of insulin secretion in pancreatic beta-cells. Alcohol 46(1):89–99. doi:10.1016/j.alcohol.2011.04.001

Nowak M (1991) The evolution of viruses—competition between horizontal and vertical transmission of mobile genes. J Theor Biol 150(3):339–347. doi:10.1016/s0022-5193(05)80433-3

Oka M, Hirazawa K, Yamamoto K, Iizuka N, Hazama S, Suzuki T, Kobayashi N (1996) Induction of Fas-mediated apoptosis on circulating lymphocytes by surgical stress. Ann Surg 223:434–440

Orentreich N, Brind JL, Rizer RL, Vogelman JH (1984) Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. J Clin Endocrinol Metab 59(3):551–555

Orgel LE (1963) The maintenance of the accuracy of protein synthesis and its relevance to ageing. Proc Natl Acad Sci U S A 49(4):517–521

Ottaviani E, Franceschi C (1997) The invertebrate phagocytic immunocyte: clues to a common evolution of immune and neuroendocrine systems (vol 18, pg 169, 1997). Immunol Today 18(5):215–215

Painter RC, Roseboom TJ, de Rooij SR (2012) Long-term effects of prenatal stress and glucocorticoid exposure. Birth Defects Res C Embryo Today Rev 96(4):315–324. doi:10.1002/bdrc.21021

Panerai AE, Sacerdote P, Bianchi M, Manfredi B (1997) Intermittent but not continuous inescapable footshock stress and intracerebroventricular interleukin-1 similarly affect immune responses and immunocyte b-endorphin concentrations in the rat. Int J Clin Pharmacol Res 17:115–116

Pariante CM, Carpiniello B, Orru MG, Sitzia R, Piras A, Farci AMG, DelGiacco GS, Piludu G, Miller AH (1997) Chronic caregiving stress alters peripheral blood immune parameters: the role of age and severity of stress. Psychother Psychosom 66(4):199–207

Partridge L, Barton NH (1993) Optimality, mutation and the evolution of aging. Nature 362(6418):305–311. doi:10.1038/362305a0

Partridge L, Gems D (2002) Mechanisms of ageing: public or private? Nat Rev Genet 3(3):165–175. doi:10.1038/nrg753

Pawelec G, Akbar A, Caruso C, Solana R, Grubeck-Loebenstein B, Wikby A (2005) Human immunosenescence: is it infectious? Immunol Rev 205:257–268. doi:10.1111/j.0105-2896.2005.00271.x

Phillips AC, Burns VE, Carroll D, Ring C, Drayson M (2005) The association between life events, social support, and antibody status following thymus-dependent and thymus-independent vaccinations in healthy young adults. Brain Behav Immun 19(4):325–333. doi:10.1016/j.bbi.2004.10.004

Phillips AC, Carroll D, Bums VE, Ring C, Macleod J, Drayson M (2006) Bereavement and marriage are associated with antibody response to influenza vaccination in the elderly. Brain Behav Immun 20(3):279–289. doi:10.1016/j.bbi.2005.08.003

Phillips AC, Burns VE, Lord JM (2007) Stress and exercise: getting the balance right for aging immunity. Exerc Sport Sci Rev 35(1):35–39. doi:10.1097/jes.0b013e31802d7008

Phillips AC, Roseboom TJ, Carroll D, de Rooij SR (2012) Cardiovascular and cortisol reactions to acute psychological stress and adiposity: cross-sectional and prospective associations in the Dutch famine birth cohort study. Psychosom Med 74(7):699–710. doi:10.1097/PSY.0b013e31825e3b91

Pinquart M, Sorensen S (2003) Differences between caregivers and noncaregivers in psychological health and physical health: a meta-analysis. Psychol Aging 18(2):250–267. doi:10.1037/0882-7974.18.2.250

Potkin SG (2002) The ABC of Alzheimer's disease: ADL and improving day-to-day functioning of patients. Int Psychogeriatr 14:7–26. doi:10.1017/s1041610203008640

Pressman SD, Cohen S, Miller GE, Barkin A, Rabin BS, Treanor JJ (2005) Loneliness, social network size, and immune response to influenza vaccination in college freshman (vol 24, pg 297, 2005). Health Psychol 24(4):348–348. doi:10.1037/0278-6133.24.4.348

Ramirez F, Fowell DJ, Puklavec M, Simmonds S, Mason D (1996) Glucocorticoids promote a Th2 cytokine response by CD4(+) T cells in vitro. J Immunol 156(7):2406–2412

Rasmussen LE (1991) Gene products of cytomegalovirus and their immunologic significance. In: Ho M (ed) Cytomegalovirus: biology and infection, 2nd edn. Plenum Medical Book Company, New York

Renshaw M, Rockwell J, Engleman C, Gewirtz A, Katz J, Sambhara S (2002) Cutting edge: impaired toll-like receptor expression and function in aging. J Immunol 169(9):4697–4701

Rink L, Cakman I, Kirchner H (1998) Altered cytokine production in the elderly. Mech Ageing Dev 102(2–3):199–209. doi:10.1016/s0047-6374(97)00153-x

Rutledge T, Reis SE, Olson M, Owens J, Kelsey SF, Pepine CJ, Mankad S, Rogers WJ, Merz CNB, Sopko G, Cornell CE, Sharaf B, Matthews KA (2004) Social networks are associated with lower mortality rates among women with suspected coronary disease: the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome evaluation study. Psychosom Med 66(6):882–888. doi:10.1097/01.psy.0000145819.94041.52

Sapolsky RM (1998) Why zebras don't get ulcers: an updated guide to stress, stress-related disease, and coping. Freeman, New York

Sapolsky RM (1999) Glucocorticoids, stress, and their adverse neurological effects: relevance to aging. Exp Gerontol 34(6):721–732. doi:10.1016/s0531-5565(99)00047-9

Sapolsky RM (2007) Robert Sapolsky discusses physiological effects of stress. Stanford News

Sapolsky RM, Krey LC, McEwen BS (1986) The neuroendocrinology of stress and aging—the glucocorticoid cascade hypothesis. Endocr Rev 7(3):284–301

Sapolsky RM, Romero LM, Munck AU (2000) How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev 21(1):55–89. doi:10.1210/er.21.1.55

Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S (2011) The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim Biophys Acta Mol Cell Res 1813(5):878–888. doi:10.1016/j.bbamcr.2011.01.034

Sedova L, Berube J, Gaudet D, Dumont M, Tremblay J, Hamet P, Pausova Z (2004) Diet-induced obesity delays cardiovascular recovery from stress in spontaneously hypertensive rats. Obes Res 12(12):1951–1958. doi:10.1038/oby.2004.245

Segerstrom SC, Miller GE (2004) Psychological stress and the human immune system: a meta-analytic study of 30 years of

inquiry. Psychol Bull 130(4):601–630. doi:10.1037/0033-2909.130.4.601

Selye H (1936) Thymus and adrenals in the response of the organism to injuries and intoxications. Br J Exp Pathol 17(3):234–248

Selye H (1956) The stress of life. McGraw-Hill, New York

Sendo F, Kato T, Yazawa H (1997) Modulation of neutrophil apoptosis by psychological stress and glucocorticoid. Int J Immunopharmacol 19(9–10):511–516. doi:10.1016/s0192-0561(97)00050-7

Sharan SK, Morimatsu M, Albrecht U, Lim DS, Regel E, Dinh C, Sands A, Eichele G, Hasty P, Bradley A (1997) Embryonic lethality and radiation hypersensitivity mediated by Rad51 in mice lacking Brca2. Nature 386(6627):804–810. doi:10.1038/386804a0

Shaw TJ, Martin P (2009) Wound repair at a glance. J Cell Sci 122(18):3209–3213. doi:10.1242/jcs.031187

Sheridan JF, Dobbs C, Jung JH, Chu XH, Konstantinos A, Padgett D, Glaser R (1998) Stress-induced neuroendocrine modulation of viral pathogenesis and immunity. In: McCann SM, Lipton JM, Sternberg EM, Chrousos GP, Gold PW, Smith CC (eds) Neuroimmunomodulation: molecular aspects, integrative systems, and clinical advances, vol 840. Ann N Y Acad Sci pp 803–808. doi:10.1111/j.1749-6632.1998.tb09618.x

Shi YF, Devadas S, Greeneltch KM, Yin DL, Mufson RA, Zhou JN (2003) Stressed to death: implication of lymphocyte apoptosis for psychoneuroimmunology. Brain Behav Immun 17: S18–S26

Siergist CA (2008) Vaccine immunology. In: Orenstein W, Offit P, Plotkin S (eds) Vaccines. Saunders, Elsevier, pp 17–36

Silva SM, Madeira MD (2012) Effects of chronic alcohol consumption and withdrawal on the response of the male and female hypothalamic-pituitary-adrenal axis to acute immune stress. Brain Res 1444:27–37. doi:10.1016/j.brainres.2012.01.013

Singh J, Singh AK (1979) Age-related changes in human thymus. Clin Exp Immunol 37(3):507–511

Sorrells SF, Sapolsky RM (2007) An inflammatory review of glucocorticoid actions in the CNS. Brain Behav Immun 21(3):259–272. doi:10.1016/j.bbi.2006.11.006

Steer JH, Kroeger KM, Abraham LJ, Joyce DA (2000) Glucocorticoids suppress tumor necrosis factor-alpha expression by human monocytic THP-1 cells by suppressing transactivation through adjacent NF-kappa B and c-Jun-activating transcription factor-2 binding sites in the promoter. J Biol Chem 275(24):18432–18440. doi:10.1074/jbc.M906304199

Thaker PH, Han LY, Kamat AA, Arevalo JM, Takahashi R, Lu CH, Jennings NB, Armaiz-Pena G, Bankson JA, Ravoori M, Merritt WM, Lin YG, Mangala LS, Kim TJ, Coleman RL, Landen CN, Li Y, Felix E, Sanguino AM, Newman RA, Lloyd M, Gershenson DM, Kundra V, Lopez-Berestein G, Lutgendorf SK, Cole SW, Sood AK (2006) Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. Nat Med 12(8):939–944. doi:10.1038/nm1447

Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, Fukuda K (2003) Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA J Am Med Assoc 289(2):179–186. doi:10.1001/jama.289.2.179

Thompson KJ, Swan RZ, Walling TL, Iannitti DA, McKillop IH, Sindram D (2013) Obesity, but not ethanol, promotes tumor incidence and progression in a mouse model of hepatocellular carcinoma in vivo. Surg Endosc Other Interv Tech 27(8): 2782–2791. doi:10.1007/s00464-013-2808-8

Tomlinson JW, Walker EA, Bujalska IJ, Draper N, Lavery GG, Cooper MS, Hewison M, Stewart PM (2004) 11 beta-hydroxysteroid dehydrogenase type 1: a tissue-specific regulator of glucocorticoid response. Endocr Rev 25(5):831–866. doi:10.1210/er.2003-0031

Trentani A, Kuipers SD, Ter Horst GJ, Den Boer JA (2002) Selective chronic stress-induced in vivo ERK1/2 hyperphosphorylation in medial prefrontocortical dendrites: implications for stress-related cortical pathology? Eur J Neurosci 15(10):1681–1691. doi:10.1046/j.1460-9568.2002.02000.x

Vedhara K, Cox NKM, Wilcock GK, Perks P, Hunt M, Anderson S, Lightman SL, Shanks NM (1999) Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. Lancet 353(9153):627–631. doi:10.1016/s0140-6736(98)06098-x

Vedhara K, McDermott MP, Evans TG, Treanor JJ, Plummer S, Tallon D, Cruttenden KA, Schifitto G (2002) Chronic stress in nonelderly caregivers—psychological, endocrine and immune implications. J Psychosom Res 53(6):1153–1161. doi:10.1016/s0022-3999(02)00343-4

Viner R (1999) Putting stress in life: Hans Selye and the making of stress theory. Soc Stud Sci 29(3):391–410. doi:10.1177/030631299029003003

Viswanathan K, Dhabhar FS (2005) Stress-induced enhancement of leukocyte trafficking into sites of surgery or immune activation. Proc Natl Acad Sci U S A 102(16):5808–5813. doi:10.1073/pnas.0501650102

von Kanel R, Dimsdale JE, Mills PJ, Ancoli-Israel S, Patterson TL, Mausbach BT, Grant I (2006) Effect of Alzheimer caregiving stress and age on frailty markers interleukin-6, C-reactive protein, and D-dimer. J Gerontol Ser A Biol Sci Med Sci 61(9):963–969

Wei QY, Lee JE, Gershenwald JE, Ross MI, Mansfield PF, Strom SS, Wang LE, Guo ZZ, Qiao YW, Amos CI, Spitz MR, Duvic M (2003) Repair of UV light-induced DNA damage and risk of cutaneous malignant melanoma. J Natl Cancer Inst 95(4):308–315

Weinstock M (2008) The long-term behavioural consequences of prenatal stress. Neurosci Biobehav Rev 32(6):1073–1086. doi:10.1016/j.neubiorev.2008.03.002

Williams GC (1957) Pleiotropy, natural selection, and the evolution of senescence. Evolution 11(4):398–411. doi:10.2307/2406060

Wu CY, Fargeas C, Nakajima T, Delespesse G (1991) Glucocorticoids suppress the production of interleukin 4 by human lymphocytes. Eur J Immunol 21(10):2645–2647. doi:10.1002/eji.1830211053

Wu XF, Zhao H, Wei QY, Amos CI, Zhang K, Guo ZZ, Qiao YQ, Hong WK, Spitz MR (2003) XPA polymorphism associated with reduced lung cancer risk and a modulating effect on nucleotide excision repair capacity. Carcinogenesis 24(3): 505–509. doi:10.1093/carcin/24.3.505

Yang EV, Glaser R (2003) Stress-induced immunomodulation: implications for tumorigenesis. Brain Behav Immun 17: S37–S40