# Immunological outcomes of exercise in older adults

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**Abstract:** Aging is associated with a dysregulation of the immune system known as immunosenescence. Immunosenescence involves cellular and molecular alterations that impact both innate and adaptive immunity, leading to increased incidences of infectious disease morbidity and mortality as well as heightened rates of other immune disorders such as autoimmunity, cancer, and inflammatory conditions. While current data suggests physical activity may be an effective and logistically easy strategy for counteracting immunosenescence, it is currently underutilized in clinical settings. Long-term, moderate physical activity interventions in geriatric populations appear to be associated with several benefits including reduction in infectious disease risk, increased rates of vaccine efficacy, and improvements in both physical and psychosocial aspects of daily living. Exercise may also represent a viable therapy in patients for whom pharmacological treatment is unavailable, ineffective, or inappropriate. The effects of exercise impact multiple aspects of immune response including T cell phenotype and proliferation, antibody response to vaccination, and cytokine production. However, an underlying mechanism by which exercise affects numerous cell types and responses remains to be identified. Given this evidence, an increase in the use of physical activity programs by the healthcare community may result in improved health of geriatric populations.

**Keywords:** exercise, immunosenescence

## Introduction

Aging is associated with numerous physiological changes. Immunosenescence is a term coined to represent changes to the immune system associated with aging. While most studies have focused on age-related declines in immune function, it is more accurate to think of immunosenescence as a state of dysregulation because lymphocytes respond heterogeneously to aging.

From a clinical standpoint, immunosenescence impacts directly on morbidity and mortality. Older adults constitute the fastest growing population in the US. Compared with young or middle-aged adults, older adults exhibit heightened incidences of infectious disease, particularly influenza, pneumonia, and urinary tract infections (Bender 2003; Falsey and Walsh 2005; High et al 2005; Nichol 2005). Infectious diseases are also a major cause of death in the elderly.

Perhaps the most intuitive strategy for reducing these infections in the elderly is vaccination if available. Vaccination of older adults against these pathogens and others is effective at reducing morbidity and mortality (Mangtani et al 2004; Meyer 2001); however, elderly individuals exhibit much lower response and recall rates to numerous bacterial (eg, pneumonia, tetanus) and viral (eg, influenza, polio) vaccines as compared with younger counterparts (Castle 2000; El Yousfi et al 2005; Grubeck-Loebenstein et al 1998; McElhaney 2003; Nichol 2005). While immensely beneficial,

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current immunization strategies are not sufficient in themselves to combat increased infectious disease rates in the elderly (McElhaney 2005).

In addition to higher rates of infectious disease, older adults experience increased incidences of other medical conditions as well. Rates of autoimmune disease and related inflammatory conditions are greater in geriatric populations as compared with other segments (Franceschi et al 2000b; Wick et al 2000; Hasler and Zouali 2005). Immunosenescence may also render older individuals more susceptible to cancer (Ben-Yehuda and Weksler 1992; Sarkar and Fisher 2006).

The increased rates of infectious disease, autoimmune disorders, inappropriate inflammatory conditions, and cancer among older adults all translate to increased rates of clinical visits, home care nursing, and hospitalization (Nichol 2005; O'Meara et al 2005). Thus, the need to identify and implement strategies to counteract immunosenescence is a pressing issue, with physicians and researchers actively investigating possible compensatory therapies. Physical exercise has been proposed as one such therapy. Existing data suggest that moderate exercise may counteract the effects of immunosenescence through several diverse mechanisms (Bruunsgaard and Pedersen 2000; Drela et al 2004; Kohut and Senchina 2004). Exercise is also an appealing therapy from a logistical vantage point, as it is relatively easy to implement, requires little cost or equipment, and can be performed in either clinical or home settings.

In this review, we will explore the current knowledge regarding exercise and immunosenescence, how the implementation of an appropriate physical activity program in older populations may lead to beneficial clinical outcomes, and how inappropriate exercise may detrimentally impact health. Compared with previous reviews, the present work focuses on application of current data to the clinical setting and also provides an updated review of the literature.

## Immunosenescence

Immunity is classically conceptualized as two distinct but interacting systems: innate and adaptive. Innate immunity may be thought of as the basal or first immune response. Upon infection, innate resistance mechanisms (including both cellular and chemical systems) are quickly and automatically activated to respond to the invader. Innate immunity may or may not be adequate for a given threat. If innate immunity is not adequate and a more specialized defense is required, adaptive immunity is launched. Adaptive immunity utilizes innate immunity in its attack, but also develops additional responses specific to the particular threat.

There are several important differences between innate and adaptive immunity. While innate immunity may act within seconds of detecting a threat, the construction of a specialized adaptive immune response generally requires 2–5 days. Repeated exposure to a given pathogen will enhance the adaptive immune response, but not the innate, because only adaptive immunity has immunological memory (discussed below).

Immunosenescence affects both innate and adaptive immunity. In order to understand the clinical consequences of immunosenescence, it is beneficial to first briefly explore the biological changes it induces at both the cellular and molecular levels. A more detailed review of this topic has been presented elsewhere (Miller 1996; Pawelec et al 1999; Effros 2001; Kohut and Senchina 2004).

### Immunosenescence and adaptive immunity

The bulk of research on immunosenescence has focused on changes to the adaptive immune system. Adaptive immunity includes antigen-specific cells such as B cells and T cells, the cytokines they secrete, and cytolytic mediators, but also recruits components of innate immunity in its efforts.

Most research has focused on the T cell, which can be divided into two broad classes based on cell surface expression of either CD4 or CD8. T cells expressing CD4 are also known as "helper T cells." Once engaged by antigen, they are able to stimulate other cells towards effector states. In general, Th1 CD4 T cells prime CD8 T cells and B cells, whereas Th2 CD4 T cells prime B cells and macrophages. T cells expressing CD8 are termed "cytotoxic T cells." CD8 T cells destroy other infected cells by a directed release of cytotoxic molecules. Before encountering antigen, T cells are said to be naïve; upon antigen encounter, they become effector cells. Following antigen clearance, most effector cells undergo apoptosis (cell suicide), but a few remain as "memory" cells committed to that particular antigen and capable of responding more rapidly to the same threat in the future. The generation of memory cells is one of the underlying principles of vaccination. Thus, both CD4 and CD8 T cells are necessary for attacking and clearing infectious agents, and thwarting repeated infections.

Aging is associated with declines in overall T cell number and function, and shifts in subpopulation composition (Schwab

et al 1992; Utsuyama et al 1992; Miller 1996; Solana and Pawelec 1998; Franceschi et al 2000a; Linton and Thoman 2001). This is largely due to the accumulation of antigen-committed memory T cells and a decrease in naïve T cells capable of responding to new antigens (Hong et al 2004; Naylor et al 2005). Other factors leading to T-cell dysregulation include age-associated changes in surface molecule expression (Schwab et al 1992; Xu et al 1992), alterations in intracellular signaling (Miller et al 1987; Ohkusu et al 1997), increased rates of apoptosis (Gupta 2000; McLeod 2000), and decreased proliferative capacity (Froelich et al 1988; Castle et al 1999). One cell surface molecule of particular interest is CD28, present on all CD4 T cells and some CD8 cells. CD28 expression may change with aging. CD28 has numerous functions, but is particularly important for the activation of CD8 T cells, as it binds to the co-stimulatory molecules CD80 (B7-1) and CD86 (B7-2) on antigen-presenting cells.

The proportion of memory cells versus naïve cells increases with aging. As an organism ages and encounters pathogens over time, more memory cells are generated; the body has only a limited capacity of cells it can sustain, and immunity favors memory over naïve cells. These alterations have been linked to immunosenescence (Kudlacek et al 2000; Hong et al 2004). However, one particular pool of memory cells, $CD8^+$ $CD25^+$ T cells, are found in older adults that demonstrate a more potent response to vaccines, and may represent a pool of memory cells with greater diversity (Herndler-Brandstetter et al 2005).

The effects of aging on the Th1/Th2 balance in older adults have also received attention. A classic method for exploring changes in the Th1/Th2 balance has been to observe changes in cytokine profiles: cytokines representative of a Th1 response include interleukin (IL)-2 and interferon (IFN)-γ, whereas cytokines such as IL-4, IL-6, and IL-10 are more indicative of a Th2 response. Based on recent reports, some researchers suggest that IL-10 is not a Th2 cytokine but should be considered a marker for T-regulatory cell or "suppressor T cell" activity. Rodent studies generally suggest that there is an age-associated shift in cytokine production. Findings from humans are less consistent. Most studies document an age-associated shift towards Th2 cytokine production in humans, for example, upon lipopolysaccharide (LPS), phytohemagluttinin (PHA), or *Staphylococcus aureus* (bacterium), or virus stimulation (Castle et al 1997; Rink et al 1998). Other investigators report a trend towards increased Th1 with aging upon LPS, PHA, PHA + phorbol myristate acetate (PMA), or 1,25-dihydroxyvitamin D3 stimulation (Fagiolo et al 1993; Riancho et al 1994). These discrepancies may be dependent on experimental factors such as stimulus chosen (Gardner and Murasko 2002).

Immunosenescence also impacts B cells. Upon antigen encounter, these cells mature into plasma cells that secrete antigen-specific antibody. Immunosenescence is associated with decreased B cell numbers and function (eg, declines in both antibody titer and antibody efficiency) (Whisler and Newhouse 1985; Zheng et al 1997; Frasca et al 2005). As with T cells, a number of age-associated biological mechanisms have been proposed to explain these changes, including diminished differentiation capacity and alterations in intracellular signaling (Ennist et al 1986; Whisler and Grants 1993). However, current data suggest some of the age-associated changes in B cell function are due not to changes in B cells themselves, but changes in their environment such as incomplete stimulation from other cells or alterations in the cytokine milieu (Spencer and Daynes 1997). With aging, B cell proliferation may be maintained, as when cultured in vitro with Staph protein A (SpA) (Ennist et al 1986), or may decline, as when cultured in vitro with monocytes pulsed with SpA (Whisler and Newhouse 1985).

T cells and B cells constitute the two major classes of cells ascribed to adaptive immunity, but several other smaller subpopulations exist that are also impacted by immunosenescence. One such class is the natural killer T cells (NKT), a special group of T cells characterized by cell surface expression of the NK receptor. Unlike typical T cells, numbers of NKT cells increase with age (Plackett et al 2004). The expansion of the CD28–, NK receptor-expressing T cell subset later in life may be a compensatory mechanism for the depleted and already differentiated T-cell pool (Abedin et al 2005). Another subgroup are the γδ T cells; however, the effects of immunosenescence on this population are less clear, as aging appears to influence these cells heterogeneously (Colonna-Romano et al 2000; Argentati et al 2002; Colonna-Romano et al 2004). Importantly, γδ T cells also stimulate T cells, and age-associated declines in the number of stimulatory γδ T cells may in turn contribute to loss of T cell function (Re et al 2005). NKT cells bearing the γδ receptor may be important facilitators of both innate and adaptive immunity in older adults (Mocchegiani and Malavolta 2004).

## Immunosenescence and innate immunity

Innate immunity consists of cells such as dendritic cells (DCs), macrophages, natural killer cells (NKs), and neutrophils, as

well as molecular systems such as complement and inflammation.

Dendritic cells reside in the lymphoid tissues and serve as storehouses and presenters of antigen, which they present to activate B cells and T cells; thus, DCs are important in initiating adaptive immune responses. The effects of aging on DC responses have not been studied extensively; however, some of the published data suggest that aging tends to be associated with diminished function. One study reported that peripheral blood plasmacytoid dendritic cell numbers declined with age, and that the in vitro IFN-α-producing ability of these cells also decreased with age (Shodell and Siegal 2002). Human monocyte-derived dendritic cells showed no reduction in antigen-presenting abilities with age (Lung et al 2000); however, research on mice has suggested that antigen processing efficiency may decline (Lung et al 2000; Aydar et al 2004). Other laboratories have reported no major effects of aging on human peripheral blood dendritic cells when cultured in vitro with granulocyte-macrophage colony stimulating factor (GM-CSF) and IL-4 (Steger et al 1996). In summary, aging may impact only certain types of DCs and/or their specific functions.

Macrophages are another class of lymphocytes belonging to the innate immune system that serve four important roles. They (1) present antigen to memory (but not naïve) cells, produce both (2) cytokines and (3) reactive nitrogen and oxygen species, and (4) clean up cellular debris. Similar to DCs, macrophages also link innate and adaptive immunity. Some of the earlier work using macrophages from rodents tended to suggest that certain functions (ability to produce oxygen radicals in response to bacterial challenge) did not decline with age (Esposito et al 1988). Obtaining pure macrophages from humans is logistically difficult, and researchers instead typically collect peripheral blood mononuclear cells (PBMCs) containing the immature progenitors of macrophages, the monocytes. Overall, immunosenescence is associated with a general decline in macrophage function (Sebastian et al 2005), possibly due to impaired ability of macrophages to respond to activation or due to a decline in activation signals from other cells. The antigen-presenting capacities of peripheral blood monocytes from older humans appears to be compromised due to alterations in MHC class II gene expression (Villanueva et al 1990), and the activities of infection-response proteins, such as heat shock proteins, may also be altered (Njemini et al 2005). In one human study that did obtain macrophages directly from the lungs, investigators found a decrease in accessory function of these cells (Zissel et al 1999).

Aging has been associated with alterations in the pro-inflammatory/antiinflammatory balance. Monocytes and macrophages, as well as other cell types, can produce proinflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor (TNF)-α. Though results from numerous studies suggest that serum levels of proinflammatory cytokines are increased with advancing age, it is less clear whether LPS-stimulated or pathogen-induced production of IL-1, IL-6, or TNF-α by monocytes/macrophages (or both) are altered with age. For example, one study using influenza virus stimulation demonstrated an age-related increase in production of a proinflammatory cytokine (TNF-α) and a concomitant age-related decrease in production of an anti-inflammatory cytokine (IL-10) (Saurwein-Teissl et al 2000). When LPS rather than influenza was used as the stimulus, an age-related reduction in monocyte TNF-α and IL-6 production was reported (Delpedro 1998). In contrast, when PHA and PMA were used as costimulants, an age-related increase in TNF-α, IL-1, and IL-6 was observed (Fagiolo et al 1993). Interestingly, in another study, researchers controlled for health status of both old and young subjects and concluded that aging did not induce any differences IL-6 production after PHA or concanavalin A (ConA) stimulation, nor on TNF-α production in unstimulated monocytes (Mysliwska et al 1999; Beharka et al 2001). However, during a period of illness (pneumonia infection), both serum levels of IL-1 and IL-6 as well as production of these cytokines by LPS-stimulated monocytes were impaired in older adults as compared to younger adults.

Additional studies are needed to clarify the impact of aging on macrophage/monocyte cytokine release. This area of research is an important topic as reported by the data from a recent study of older adults, which suggested that both frailty and mortality were associated with an impaired production of pro-inflammatory (IL-1β, IL-6, TNF-α) and anti-inflammatory (IL-1Ra, IL-10) cytokines when LPS was used to simulate peripheral blood mononuclear cells (van den Biggelaar et al 2004). Beyond inflammation itself, these results also are important for adaptive immunity. Using aged T cells from mice, researchers were able to show that the age-associated impairment of T cell proliferation and IL-2 production was reversed when cells were supplemented in vivo with IL-1, IL-6, TNF-α, or adjuvant which evoked proinflammatory cytokine production (Haynes et al 2004).

It is likely that discrepancies in age-related responses of the monocyte or macrophage were related to either the type of stimulus or the cell source. Support for this possibility has

been found in several studies using rodents. In these studies, the effects of aging varied by source of the macrophage as well as the type of stimulus, and it has recently been suggested that the microenvironment in which the cell is located may be important in determining age-related changes (Kohut, Senchina, et al 2004; Stout and Suttles 2005). Thus, the effects of aging on macrophages are ultimately due to changes both intrinsic and extrinsic to the macrophage itself (Gomez et al 2005). The diminished capacity of macrophages to present antigen or produce anti-pathogenic cytokines and reactive species may translate to increased survival and reproduction of the pathogen as well as increased host damage or death (Gon et al 1996; Miller 1996; Pawelec et al 1998; Zissel et al 1999; Looney et al 2002).

Natural killer cells destroy infected cells through cytotoxic granule release, similar to the activity of T cells though in a nonspecific fashion. Circulating numbers of NK cells increase with age and total NK cell pool activity appears to be maintained with aging; however, the per se killing capacities and IFN-γ producing capacities of these cells appears to be impaired, perhaps due to an age-associated shift towards a "mature phenotype" (Solana et al 1999; Mocchegiani and Malavolta 2004; Plackett et al 2004). The response of aged NK cells to stimulation by IL-2 may be diminished (as is the case for proliferation, CD69 expression, Ca2+ mobilization, and some killing activities) or may be unaffected (as is the case for perforin induction or TNF-α production) (Borrego et al 1999; Solana and Mariani 2000). Age-associated defects in signal transduction may explain these observations (Borrego et al 1999). Production of IL-4 by NK cells appears to increase with age (Plackett et al 2004).

Neutrophils are the most prevalent white blood cell in the human blood on a per cell basis. As phagocytic granulocytes, they play an important role in consuming (through phagocytosis) and/or destroying (through granule release) extracellular pathogens. Regarding these two functions, immunosenescence appears to enhance phagocytic capacity (Tsukamoto et al 2002), but its effects on neutrophil cytokine and granule release are less clear, as researchers have reported conflicting findings based on the stimulus employed and lifestyle factors (Miyaji et al 2000; Plackett et al 2004).

Besides influencing cells of the innate immune system, immunosenescence is also believed to modulate several molecular systems associated with innate immunity, such as inflammation and complement (a component of inflammation), as described in the next section.

## Immunosenescence and inflammatory conditions

Links between aging, immunosenescence, and diseases associated with inflammatory conditions have recently received great attention. Aging is associated with an increase in inflammatory processes (Boren and Gershwin 2004; Franceschi et al 2000b) and as such may represent a predisposing factor for the development of several aging/inflammation-associated diseases including neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease (McGeer and McGeer 2004) and autoimmune diseases such as diabetes, rheumatoid arthritis, and systemic lupus erythematosus (Hasler and Zouali 2005; Licastro et al 2005). Chronic inflammation may also predispose individuals to cancer (Licastro et al 2005; Sarkar and Fisher 2006). Elevated serum proinflammatory cytokines have been associated with increased risk of heart disease, high blood pressure, type II diabetes, and atherosclerosis (Paulus 2000; Mangge et al 2004; Wisse 2004; Aukrust et al 2005). The precise role that elevated proinflammatory cytokines play in these chronic diseases remains to be established and may vary by disease. At this point, it may be useful to view elevated serum inflammatory cytokines as an early marker of potential chronic disease and make appropriate lifestyle modifications to reduce disease risk.

Complement is another molecular system associated with inflammation. Complement consists of plasma proteins that can automatically latch onto and destroy extracellular pathogens, either directly via formation of a membrane attack complex, or indirectly via opsonization, which induces other cells of the immune system to engulf the invader. Levels of complement proteins appear to increase with aging (Waitumbi et al 2004). The effects of aging on complement function are unclear, as different animal models have yielded different results. One study in rats demonstrated that efficiency of the complement system may diminish with aging (Lavery and Goyns 2002), but opposite findings were reported from German Shepherd dogs (Strasser et al 2000). Age-associated inflammatory conditions as described earlier may promote complement activation and consequently disease states such as Alzheimer's disease, Parkinson's disease, and age-related macular degeneration (McGeer et al 2005).

## Immunosenescence and chronic infection

Our discussion of immunosenescence has thus far focused on aging-induced changes to the immune system without

consideration of the external environment. However, as people age they are more likely to acquire chronic infections such as varicella (the cause of chickenpox and shingles), Epstein-Barr virus (EBV, the cause of mononucleosis), or cytomegalovirus (CMV).

Virological status is known to impact on immunity: chronic infection by these pathogens may alter the immune system and lead to consequences (immunosenescence) similar to those induced by aging directly (van Baarle et al 2005; Koch et al 2006). For example, most people are chronically infected with the herpes virus CMV (Bennekov et al 2004), acquired during infancy during breastfeeding (Schleiss 2006) or later in life via kissing, blood transfusion, or sexual intercourse (Frost 1996). Chronic CMV infection is associated with chronic activation of the T cell pool, leading to decreased naïve and early memory CD8 T cell pools and a polarization of the T cell response towards Th1 activity (Vescovini et al 2004; Akbar and Fletcher 2005; Almanzar et al 2005; Northfield et al 2005). Older adult CMV carriers also respond less vigorously to influenza vaccine (Trzonkowski et al 2003). In contrast, chronic EBV infection does not elicit such polarized responses by the immune system but does alter T cell pools (Vescovini et al 2004). The presence of multiple chronic infections may impact on the ability of the body to fight multiple viruses: in one study, it was found chronic CMV-infected impaired the ability of older adults to concomitantly manage chronic EBV infection (Khan et al 2004). IL-2 and IL-4 production by PBMC from CMV-infection older adults stimulated with PMA-ionomycin was lower compared with PBMC from noninfected age-matched controls, but this effect was not seen with IFN-γ (Almanzar et al 2005).

## Immunosenescence and nutrition

Nutrition also impacts on immunosenescence (Lesourd 2004). In fact, some of the commonly reported age-associated changes of immune response such as lymphocyte proliferation are not observed to the same extent in well nourished individuals (Molls et al 2005). The elderly often do not consume enough of both macro- (carbohydrates, protein) and micronutrients (minerals and vitamins) (Amati et al 2003; Ahluwahlia 2004). Numerous interventional studies have shown that macro- or micronutrient-supplementation may be able to restore immune function in elderly (High 2001). Independent, healthy adults supplemented with trace elements and vitamins demonstrated enhanced NK and T cell functions compared with placebo-treated peers (Chandra 1992). Daily multivitamin consumption in this population has been associated with increases in IL-2 (Chandra 1992; Kohut et al 2002). Institutionalized elderly given selenium sulfide, zinc sulfate, and vitamins exhibited increased antibody titer following influenza vaccination (Girodon et al 1999).

# Clinical consequences of immunosenescence

Immunosenescence has numerous and varied clinical consequences as have been hinted by the preceding discussion; in summary: (a) increased morbidity and mortality to bacterial and viral infection (Bender 2003; Falsey and Walsh 2005; High et al 2005; Nichol 2005); (b) decreased vaccine effectiveness (Grubeck-Loebenstein et al 1998; Castle 2000; El Yousfi et al 2005; McElhaney 2003; Nichol 2005); (c) increased incidence of autoimmune disease and related inflammatory conditions (Franceschi et al 2000b; Wick et al 2000; McGeer and McGeer 2004; Hasler and Zouali 2005; Licastro et al 2005); and (d) increased incidence of cancer (Ben-Yehuda and Weksler 1992; Licastro et al 2005; Sarkar and Fisher 2006). These phenomena are the direct or indirect results of many of the changes to both the innate and adaptive immune systems associated with immunosenescence.

Regarding innate immunity, impaired macrophage functions may protract the infection process, leading to increased pathogen longevity and greater potential for harm to the host. More data in humans is needed to assess the effects of immunosenescence on the functions of DCs, NK cells, and neutrophils as findings thus far are heterogeneous; however, it is likely immunosenescence impacts on the function of these cell types as well. Aging is associated with increased inflammatory (Franceschi et al 2000b; Boren and Gershwin 2004) and complement (Waitumbi et al 2004) activities. In addition to possibly predisposing elderly individuals to cancer or autoimmune/inflammatory conditions (discussed earlier), increased basal states of inflammation may also hamper the development or resolution of immune responses to pathogens.

Regarding adaptive immunity, the decreases in B cell/plasma cell number, function (antibody production), and proliferation could all translate to a blunted adaptive immune response to pathogen, leading to increased severity and time span of infection. A similar scenario has been evoked for T cells; in this instance, immunosenescence is associated with decreased co-stimulatory and killing activities. In addition, the depleted naïve T cell pool (Almanzar et al 2005) associated with aging may result in fewer naïve cells being capable of responding to antigen; indeed, the expanded memory pool

may actually prohibit respondent naïve cell populations from proliferating and expanding to adequate numbers.

## Exercise and immunosenescence

Considering all the impacts of immunosenescence on immunity in aged individuals, clinicians, physicians, and researchers alike are intensively investigating therapies to ameliorate these consequences. Exercise is one therapy that has received much scientific attention, both for its effectiveness and logistical advantages over other therapies (such as calorie restriction, dietary or herbal supplementation, endocrine modulation, immunomodulation, or additional vaccination). Compared with other modes, the advantages of exercise are manifold: low-cost, noninvasive, easy to implement, and amenable to being practiced in either home or clinical settings (Gueldner et al 1997; Kohut and Senchina 2004). Further, exercise prescribed for one ailment may beneficially impact other chronic diseases, including arthritis, heart disease, stroke, peripheral vascular disease, diabetes, osteoporosis, and pulmonary disease (Bean et al 2004).

### Risk of infection and exercise in the elderly

If exercise can delay or attenuate the process of immunosenescence, a clinical benefit that one may expect to observe is a reduction in the incidence or severity of infectious disease. Data in support of this possibility among older adults are limited, yet the data from both clinical exercise intervention trials and epidemiological studies lend some support. One large study that included older as well as younger adults demonstrated that the risk of community-acquired pneumonia decreased with increasing physical activity in women (Baik et al 2000). In a separate study, women aged 55 to 80 were followed for a period of 6 years, and physical inactivity was associated with an increased risk of hospitalization due to infection (Leveille et al 2000). Kostka and colleagues (2000) followed adults aged 66–84 for one year to assess both the number of upper respiratory tract infections (URTI) per year and the number of days with URTI. Physical activity was assessed with a questionnaire and aerobic fitness level ($VO_{2max}$) was measured. Sports activity negatively correlated with both number of URTI episodes per year and number of days with URTI, but $VO_{2max}$ did not correlate with URTI. The greatest protection from URTI appeared to be associated with higher levels of activity (equivalent to jogging 7 km/day or walking 90 minutes per day at a speed of ~ 19–20 minutes per mile) (Kostka et al 2000).

Several exercise intervention trials have also examined URTI. In one of the longest intervention trials (10 months), older adults assigned to a moderate-intensity exercise program 3 days per week had fewer days of self-reported URTI symptoms, but not episodes of URTI as compared with subjects not participating in regular moderate intensity exercise (Kohut and Senchina 2004). Two intervention studies of shorter durations reported conflicting results. Over a 12 week period, highly conditioned subjects and women participating in a 12 week walking program had a lower incidence of URTI as compared with a control group (Nieman et al 1993). In contrast, a 10-week moderate to vigorous exercise intervention was not associated with decreased URTI in older women (Fahlman et al 2000). Importantly, it may have been difficult to detect an effect of exercise in this study due to a relatively small number of subjects and a short exercise-training period (10 weeks).

The exercise intervention studies previously described included relatively healthy, independent older adults, and the findings generally suggest that exercise has some benefit with respect to reduced incidence or severity of infection. Only one study has evaluated the impact of exercise on infection in frail, nursing home residents. An 8-month exercise program did not alter the incidence of infection among frail adults (Schnelle et al 2002). The data are too limited to draw any conclusions at this point, but it is possible that once older adults have become frail, they may not be capable of exercise that is intense or prolonged enough to impact immunity. Frailty status has been associated with some specific immune alterations (Leng et al 2002; Schmaltz et al 2005; Semba et al 2005), and perhaps once a state of frailty has developed, it may not be possible to reverse these immunological changes through exercise. Additional studies with frail participants are needed to better evaluate the extent to which exercise might impact resistance to infection.

Finally, it is worthwhile to mention that younger adults who exercise strenuously appear to have an increased risk of infection (Nieman 1998). To our knowledge, this relationship between intense exercise and infection has not been demonstrated in older adults. It may be difficult to examine this possibility due the very limited number of older adults that exercise at extremely high volumes or "overtrain". In response to a single session of intense exercise (running a marathon), T cell responses decline, yet the degree of decline is similar in young as compared with older adults (Henson et al 2004). To summarize, it appears that moderate exercise may have benefits in terms of reduced incidence of infection

among older adults, yet further information is needed with respect to specific populations (frail elderly, nursing home residents, "overtrained" older adults).

## Exercise and immune alterations

Although there are numerous studies that have evaluated the effects of an acute bout of exercise on immune responses, this section will focus on the effects of exercise training and long-term physical activity in older adults. The response of a given immune parameter to an acute bout of exercise may not be predictive of how the same immune parameter responds to long-term training. Numerous studies have used questionnaires to assess the extent of physical activity, or measures of physical fitness in an effort to correlate physical fitness with immune responses. Other studies have employed an exercise intervention, with the assessment of immune function before or after the intervention. The results from both types of studies are discussed.

The age-related decline in lymphocyte proliferative response is a well-documented phenomenon. Four studies have compared lymphocyte proliferation in active elderly compared with sedentary elderly, and in three of these studies mitogen (PHA or pokeweed mitogen [PWM]) induced proliferation was greater in active older adults (Nieman et al 1993; Shinkai et al 1995, 1998). The active adults in these studies participated in vigorous activity (running). When influenza virus was used as the stimulus, the lymphocytes from active older adults proliferated to a greater extent than those from sedentary individuals (Kohut et al 2002). In the study with influenza virus, both vigorous activity as well as moderate activity (walking) appeared to be beneficial.

Natural killer cell activity has been assessed in several studies as well, although not all studies report an age-related decline in NK function. The concentration of CD16+CD56+ NK cells was greater in elderly exercisers as compared with sedentary subjects (Yan et al 2001). Elderly runners tended to have a greater NK cytotoxic function compared with sedentary subjects in two studies (Nieman et al 1993; Shinkai et al 1998), but no difference was found in a separate study (Shinkai et al 1995).

Lymphocyte expression of CD25 (IL-2 receptor) may indicate how well lymphocytes respond to activating signals. CD25 expression has been reported to decline with advancing age, although others have observed an increase specifically in the CD4+ population (Froelich et al 1988; Dennett et al 2002; Gregg et al 2005). In a comparison of active and inactive women aged 60–98, CD25 expression in response to mitogen activation was greater in the active women (Gueldner et al 1997). Another aging-related change that has been observed in some studies is a shift in the balance of Type 1 and Type 2 cytokines, although the extent to which this occurs in humans is less clear. A comparison of Type 1/Type 2 cytokines in active elderly, sedentary, and young showed that the number of CD8+ cells producing IL-2 was greater in the active elderly than in the sedentary elderly (Ogawa et al 2003). In the same study, IL-2 production by CD4+ cells tended to be higher in the trained elderly, but the difference was not statistically significant, likely due to larger variability in response.

Antibody titer and response to influenza vaccine has also been evaluated in several studies. Antibody (immunoglobulin M [IgM] and immunoglobulin G [IgG]) response to influenza vaccine measured 2 weeks post-immunization was greater in older adults who regularly participated in vigorous activity (intense enough to work up a sweat) than in moderately active or inactive adults (Kohut et al 2002). Similarly, a correlation between physical activity and greater antibody response to the H3N2 component of the influenza vaccine was found one-week post-immunization (Schuler et al 2003). Another study that included patients with congestive heart failure measured granzyme B levels after immunization and found that higher granzyme B was correlated with performance on the 6 minute walk test (McElhaney et al 2004). Granzyme B levels post-immunization correlate with resistance to influenza infection (McElhaney et al 2001).

Although the response to influenza vaccination has important clinical implications, influenza would generally not be considered a novel antigen as older adults are likely to have produced antibody to previous immunization or infections that may demonstrate cross-reactivity with antigens contained in the vaccine. It has been suggested that the immune response to novel antigens is compromised with advancing age. A recent study compared the response with a novel antigen (keyhole limpet hemocyanin [KLH]) in physically active and sedentary young and old subjects. As expected, IgM and IgG antibody titers were reduced in older adults compared with young. However at day 21 post-immunization, anti-KLH IgG and IgM was greater in older physically active than in older sedentary subjects. Anti-KLH IgG1 was also greater in the active older subjects, but there was no difference with respect to IgG2 (Smith et al 2004). In summary, cross-sectional comparisons generally show that greater activity in older adults is associated with greater immune responsiveness to immunization.

Multiple exercise intervention trials have been conducted in older adults ranging from several weeks up to two years. A variety of exercise types have been tested including calisthenics and strength training, although the majority of the studies used cardiovascular exercise at a moderate intensity. Generally, the longer-term interventions have observed improvements of immune function. For example, 12 months of exercise including both resistance (60 minutes/week) and endurance (60 minutes/week) components resulted in increased salivary IgA levels (Akimoto et al 2003). The authors suggested that the increased salivary IgA may protect against upper respiratory infection, although URTI incidence was not measured in the study. Another long-term (2 year) intervention demonstrated that elderly women who participated in the 2 year program had greater lymphocyte IL-2 production than a control group (Drela et al 2004). This is an important finding given that an age-related decline in IL-2 is well-documented in humans and animal models. Unfortunately the 2 year study did not assess cytokine production in the subjects before starting the intervention, and therefore the possibility remains that this group of subjects had greater IL-2 production at the beginning of the program. The impact of exercise on immune response to influenza vaccination was also evaluated in older adults. Vaccine efficacy has been shown to be reduced with advancing age and therefore, an exercise-induced improvement in response to the vaccine could have important clinical benefits. A 10-month program of exercise at a moderate intensity (65%–75% of maximal heart rate) resulted in a greater increase in antibody titer at 1 and 3 months post-immunization as compared to adults who were sedentary or participated in low-intensity exercise (Kohut, Thompson, et al 2004). In addition, the granzyme B activity was also greater in the subjects who participated in the exercise intervention. Granzyme B levels reflect cytolytic T cell function (CTL), and if an individual was to become infected with the influenza virus, CTL effector function is critical in clearing the infection.

Several shorter term interventions (10 weeks–6 months) involving either cardiovascular exercise at a moderate intensity (50%–70%) or resistance training (3 sets of 8 repetitions per set) did not significantly increase NK cell function, T cell proliferation, the number or percentage of CD3+, CD4+, CD8+ lymphocytes, IL-2 production, or delayed type hypersensitivity (DTH) response (Nieman et al 1993; Rall et al 1996; Flynn et al 1999; Woods et al 1999; Fahlman et al 2000; Bermon et al 2001). However, a trend toward increased lymphocyte proliferation and NK cytotoxicity was observed in the 6 month training study (Woods et al 1999). In general, it appears that the longer term interventions (~1 year) are more likely to demonstrate a significant impact on immune function, yet one shorter term study (16 weeks) observed improved NK cytotoxicity. Further research is clearly needed to determine the appropriate type of exercise, dose and intensity of exercise, the time period required before improvements are observed, and whether exercise-induced immune alterations result in clinical benefits (fewer or less severe infections).

To our knowledge, only two exercise intervention trials have involved the frail elderly. The results of these studies were not promising. An 8-month exercise program involving functional endurance and resistance training had no effect on lymphocyte proliferation to the mitogen PHA, lymphocyte activation markers (CD25, CD28, HLA-DR) or lymphocyte populations. The program was effective in improving performance of physical tasks such as distance walked (Kapasi et al 2003). A separate study that also involved a variety of exercises (flexibility, strength, endurance, coordination) for 17 weeks failed to increase the delayed-type-hyphersensitivity (DTH) response to 7 antigens, but tended to attenuate the decline in the response over time (although this did not reach statistical significance). In contrast to the longer-term studies in nonfrail elderly, exercise did not significantly improve immune response. The intensity and duration of endurance exercise was lower in the frail elderly, but may be at the limit at which they could perform. It is also possible that longer-term interventions are required in this population before significant changes are detected due to the limited functional capacity. Perhaps the immune alterations that occur in the frail state cannot be reversed. Certain immune alterations have been observed in the frail elderly (discussed in the next section). At this point, it is premature to draw any definitive conclusions regarding frail older adults based on only two studies, and further research with this population is needed.

## Immune and inflammatory markers of mortality/frailty

Aging has been associated with numerous changes in both the number and percentage of cell types, as well as changes in function. More recently, some of these alterations have been linked to the frailty phenotype. For example, frailty status is predicted by higher levels of CD8+ CD28– cells (Semba et al 2005). CD28 is an important co-stimulatory molecule for T cell activation, yet it is not known how CD28 expression is related to frailty. Poor lymphocyte proliferation is also

found to a greater extent in frail subjects (Leng et al 2004). Although preliminary data from our laboratory suggests that exercise training in healthy older adults may favorably alter the percentages of T cells expressing CD28 (Senchina et al 2006), the one study involving frail subjects failed to improve CD28 expression (Kapasi et al 2003). This limited data suggests that an intervention may be necessary before frailty has occurred.

Inflammatory mediators, particularly elevated serum levels of IL-6 have been associated with frailty and mortality in numerous studies. A growing body of literature has demonstrated that elevated proinflammatory cytokines are not only associated with numerous chronic diseases, but are also found to some extent with advancing age. Different proinflammatory mediators have been evaluated, but most of the published studies in older adults have focused on IL-6. Elevated levels of IL-6 have been shown to increase the risk of mortality, with the relative risk ranging from just over 1.0 to >4 fold depending on the study (Volpato et al 2001; Bruunsgaard et al 2003; Cohen et al 2003). In men, elevated TNF-α, another proinflammatory cytokine, was also associated with increased risk of mortality (Bruunsgaard et al 2003). Elevated levels of IL-6 as well as other inflammatory mediators also predicted functional disability (Cohen et al 1997; Reuben et al 2002). Multiple inflammatory markers (IL-6, TNF-α, C-reactive protein [CRP]) predicted mobility limitations, specifically the inability to climb 20 steps or walk one-quarter mile (Penninx et al 2004), and women with elevated IL-6 demonstrated declines in walking speed over time and disability in activities of daily living (Ferrucci et al 2002). The declines in functional ability are associated with frailty, and frailty itself is associated with greater risk of institutionalization and mortality (Rockwood et al 2004). Clearly, if exercise shows some benefit with respect to reducing the levels of inflammatory mediators, a reduction in mortality risk as well as functional decline would be expected.

Evidence from several epidemiological studies in older adults have shown that greater levels of physical activity or fitness in terms of walking speed were associated with lower serum levels of several inflammatory markers including IL-6, TNF-α, and CRP (Taaffe et al 2000; Geffken et al 2001; Colbert et al 2004). In addition, greater knee extensor and grip strength as well as larger muscle mass were associated with lower proinflammatory cytokines (Visser et al 2002). It was also recently shown that active older adults demonstrated reduced serum CRP as well as a decrease in LPS-stimulated IL-6, IL-1β, TNF-α, and Toll-like receptor 4 (TLR-4), as compared with inactive older adults (McFarlin et al 2006). These studies suggest that exercise may reduce serum inflammatory markers and this possibility is supported by several exercise intervention trials. For example, studies in middle-aged adults reported that exercise and diet interventions resulting in weight loss reduced serum CRP, IL-6 and IL-18, whereas exercise training alone reduced serum CRP, IL-6, and blood mononuclear cell production of TNF-α and IL-1α in patients at risk for heart disease (Smith et al 1999; Esposito et al 2003; Goldhammer et al 2005). The findings from one exercise intervention study with older adult subjects showed no significant reduction in serum CRP (Hammett et al 2004). Recently, our laboratory has conducted a longer-term intervention (10 months) in older adults, and compared aerobic exercise with flexibility/balance/resistance exercise training. We observed that aerobic exercise training reduced serum IL-6, CRP, IL-18, and both types of training were associated with reduced TNF-α (Kohut et al 2006). These findings suggest that the type and intensity of exercise may be important in reducing inflammatory markers.

Finally, it is important to recognize that although elevated inflammatory markers have been associated with poorer health outcomes, inflammation remains an essential component of immune defense. In fact, it has been suggested that frailty in old age is the net result of the risk of dying from chronic inflammatory disease versus infectious disease (van den Biggelaar et al 2004). A reduction in the ability of LPS-stimulated mononuclear cells to produce inflammatory mediators (IL-6, TNF-α, IL-1β) as well as anti-inflammatory mediators (IL-1Ra, IL-10) was associated with a greater than 2-fold mortality risk. The authors concluded that a malfunctioning innate immune response including lower production of inflammatory cytokines predicts frailty in old age.

## Other benefits of exercise

This review has focused on the immunological outcomes of exercise in older adults; however, the benefits of exercise extend well beyond immunity. These additional benefits encompass both physical and psychosocial realms; for a more thorough treatment, readers should consult (Bean et al 2004).

At the physical level, exercise may improve mobility and motor control in older adults (Whitehurst et al 2005), reducing rates of falls or other ambulation-associated injuries (Schoenfelder and Rubenstein 2004). Exercise improves functional outcomes for disease states such as osteoarthritis (Foy et al 2005) and may positively impact on cancer treatment

and recovery (Galvao and Newton 2005). In one study of older adults acutely hospitalized for various conditions, a one-month exercise program during hospitalization resulted in improved functional outcomes, though it did not shorten length-of-stay (Siebens et al 2000).

At the psychosocial level, exercise programs have been associated with increases in reported vitality (Whitehurst et al 2005) and decreased visits to doctor's offices (Whitehurst et al 2005). Exercise has also been associated with reduced depression, anxiety, and increased sense of coherence (Singh et al 1997; Antunes et al 2005; Barbour and Blumenthal 2005; Kohut et al 2005). Group exercise programs represent a social opportunity to many older adults; the group interaction itself may become a major motivation for exercise program adherence and should not be overlooked in the design of exercise programs for this population.

## Conclusions and potential clinical applications

Results thus far regarding exercise and its impact on immunosenescence in older adults are very promising and encourage further investigations in both clinical and laboratory environs. For these endeavors to be successful, physicians, primary care workers and other health professionals, and patients and their families will need to be educated about the beneficial outcomes of such programs. Once aware of the positive outcomes, adherence to and motivation for these programs will be greatly increased by all parties, which in turn may lead to a proliferation of programs.

## References


Abedin S, Michel JJ, Lemster B, et al. 2005. Diversity of NKR expression in aging T cells and in T cells of the aged: the new frontier into the exploration of protective immunity in the elderly. *Exp Geron*, 40:537–48.

Ahluwahlia N. 2004. Aging, nutrition and immune function. *J Nutr Health Aging*, 8:2–6.

Akbar AN, Fletcher JM. 2005. Memory T cell homeostasis and senescence during aging. *Curr Opin Immunol*, 17:480–5.

Akimoto T, Kumai Y, Akama T, et al. 2003. Effects of 12 months of exercise training on salivary secretory IgA levels in elderly subjects. *Br J Sports Med*, 37:76–9.

Almanzar G, Schwaiger S, Jenewein B, et al. 2005. Long-term cytomegalovirus infection leads to significant changes in the composition of the CD8+ T-cell repertoire, which may be a basis for the imbalance in the cytokine production profile in elderly persons. *J Virol*, 79:3675–83.

Amati L, Cirimele D, Pugliese V, et al. 2003. Nutrition and immunity: laboratory and clinical aspects. *Curr Pharm Des*, 9:1924–31.

Antunes HK, Stella SG, Santos RF, et al. 2005. Depression, anxiety and quality of life scores in seniors after an endurance exercise program. *Rev Bras Psiquiatr*, 27:266–71.

Argentati K, Re F, Donnini A, et al. 2002. Numerical and functional alterations of circulating γδ T lymphocytes in aged people and centenarians. *J Leuk Biol*, 72:65–71.

Aukrust P, Gullestad L, Ueland D, et al. 2005. Inflammatory and anti-inflammatory cytokines in chronic heart failure: potential therapeutic implications. *Ann Med*, 37:74–85.

Aydar Y, Balogh P, Tew JG, et al. 2004. Follicular dendritic cells in aging, a "bottle-neck" in the humoral immune response. *Aging Res Rev*, 3:15–29.

Baik I, Curhan GC, Rimm EB, et al. 2000. A prospective study of age and lifestyle factors in relation to community-acquired pneumonia in US men and women. *Arch Intern Med*, 160:3082–8.

Barbour KA, Blumenthal JA. 2005. Exercise training and depression in older adults. *Neurobiol Aging*, 26:119–23.

Bean JF, Vora A, Frontera WR. 2004. Benefits of exercise for community-dwelling older adults. *Arch Phys Med Rehab*, 85: S31–S42.

Beharka AA, Meydani M, Wu D, et al. 2001. Interleukin-6 production does not increase with age. *J Geron*, 56A:B81–B8.

Bender BS. 2003. Infectious disease risk in the elderly. Immunol Allergy *Clin North Am*, 23:57–64.

Bennekov T, Spector D, Langhoff E. 2004. Induction of immunity against human cytomegalovirus. *Mt Sinai Med J*, 71:86–93.

Ben-Yehuda A, Weksler ME. 1992. Immune senescence: Mechanisms and clinical implications. *Cancer Invest*, 10:525–31.

Bermon S, Philip P, Candito M, et al. 2001. Effects of strength exercise and training on the natural killer cell counts in elderly humans. *J Sports Med Phys Fitness*, 41:196–202.

Boren E, Gershwin ME. 2004. Inflamm-aging: autoimmunity, and the immune-risk phenotype. *Autoimmun Rev*, 3:401–6.

Borrego F, Alonso MC, Galiani MD, et al. 1999. NK phenotypic markers and IL2 response in NK cells from elderly people. *Exper Geron*, 34:253–65.

Bruunsgaard H, Ladelund S, Pedersen AN, et al. 2003. Predicting death from tumour necrosis factor-alpha and interleukin-6 in 80-year-old people. *Clin Exp Immunol*, 132:24–31.

Bruunsgaard H, Pedersen BK. 2000. Effects of exercise on the immune system in the elderly population. *Immunol Cell Biol*, 78:523–31.

Castle S, Uyemara K, Wong W, et al. 1997. Evidence of enhanced type 2 immune response and impaired upregulation of a type 1 response in frail elderly nursing home residents. *Mech Aging Dev*, 94:7–16.

Castle SC. 2000. Clinical relevance of age-related immune dysfunction. *Clin Infect Dis*, 31:578–85.

Castle SC, Uyemara K, Crawford W, et al. 1999. Age-related impaired proliferation of peripheral blood mononuclear cells is associated with an increase in IL-10 and IL-12. *Exper Geron*, 34:243–52.

Chandra RK. 1992. Effect of vitamin and trace-element supplementation on immune responses and infection in elderly subjects. *Lancet*, 340:1124–7.

Cohen HJ, Harris T, Pieper CF. 2003. Coagulation and activation of inflammatory pathways in the development of functional decline and mortality in the elderly. *Am J Med*, 14:180–7.

Cohen HJ, Pieper CF, Harris T, et al. 1997. The association of plasma IL-6 levels with functional disability in community-dwelling elderly. *J Geron A Biol Sci Med Sci*, 52:M201–8.

Colbert LH, Visser M, Simonsick EM, et al. 2004. Physical activity, exercise, and inflammatory markers in older adults: findings from the Health, Aging and Body Composition Study. *J Am Geriatr Soc*, 52:1098–104.

Colonna-Romano G, Aquino A, Bulati M, et al. 2004. Impairment of gamma/delta T lymphocytes in elderly: Implications for immunosenescence. *Exp Geron*, 39:1439–46.

Colonna-Romano G, Potestio M, Scialabba G, et al. 2000. Early activation of γδ T lymphocytes in the elderly. *Mech Aging Dev*, 121:231–8.

Dennett NS, Barcia RN, McLeod JD. 2002. Age associated decline in CD25 and CD28 expression correlate with an increased susceptibility to CD95 mediated apoptosis in T cells. *Exp Geron*, 37:271–83.

Drela N, Kozdron E, Szczypiorski P. 2004. Moderate exercise may attenuate some aspects of immunosenescence. *BMC Geriatr*, 4:8.

Effros RB. 2001. Aging and the immune system. *Novartis Found Symp*, 235:130–49.

El Yousfi M, Mercier S, Breuille D, et al. 2005. The inflammatory response to vaccination is altered in the elderly. *Mech Aging Dev*, 126:874–81.

Ennist DL, Jones KH, St Pierre RL, et al. 1986. Functional analysis of the immunosenescence of the human B cell system: Dissociation of normal activation and proliferation from impaired terminal differentiation into IgM immunoglobulin-secreting cells. *J Immunol*, 136:99–105.

Esposito AL, Clark CA, Poirier WJ. 1988. An assessment of the respiratory burst and bactericidal activity of alveolar macrophages from adult and senescent mice. *J Leuk Biol*, 43:445–54.

Esposito K, Pontillo A, Di Palo C, et al. 2003. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA*, 289:1799–804.

Fagiolo U, Cossarizza A, Scala E, et al. 1993. Increased cytokine production in mononuclear cells of healthy elderly people. *Eur J Immunol*, 23:2375–8.

Fahlman M, Boardley D, Flynn MG, et al. 2000. Effects of endurance training on selected parameters of immune function in elderly women. *Gerontology*, 46:97–104.

Falsey AR, Walsh EE. 2005. Respiratory syncytial virus infection in elderly adults. *Drugs Aging*, 22:577–87.

Ferrucci L, Penninx BW, Volpato S, et al. 2002. Change in muscle strength explains accelerated decline of physical function in older women with high interleukin-6 serum levels. *J Am Geriatr Soc*., 50:1947–54.

Flynn MG, Fahlman M, Braun WA, et al. 1999. Effects of resistance training on selected indexes of immune function in elderly women. *J Appl Physiol*, 86:1905–13.

Foy CG, Penninx BW, Shumaker SA, et al. 2005. Long-term exercise therapy resolves ethnic differences in baseline health status in older adults with knee osteoarthritis. *J Am Geriatr Soc*, 53:1469–75.

Franceschi C, Bonafe M, Valensin S. 2000a. Human immunosenescence: The prevailing of innate immunity, the failing of clonotypic immunity, and the filling of the immunological space. *Vaccine*, 18:1717–20.

Franceschi C, Bonafe M, Valensin S, et al. 2000b. Inflamm-aging: An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci*, 908:244–54.

Frasca D, Riley RL, Blomberg BB. 2005. Humoral immune response and B-cell functions including immunoglobulin class switch are downregulated in aged mice and humans. *Semin Immunol*, 17:378–84.

Froelich CJ, Burkett JS, Guiffaut S, et al. 1988. Phytohemagglutinin induced proliferation by aged lymphocytes: Reduced expression of high affinity interleukin-2 receptors and interleukin-2 secretion. *Life Sci*, 43:1583–90.

Frost KR. 1996. Cytomegalovirus resistance. Public health implications of CMV prophylaxis and treatment in the HIV patient population. *AMFAR Rep*, 1–6.

Galvao DA, Newton RU. 2005. Review of exercise intervention studies in cancer patients. *J Clin Oncol*, 23:899–909.

Gardner EM, Murasko DM. 2002. Age-relatede changes in Type 1 and Type 2 cytokine production in humans. *Biogerontol*, 3:271–89.

Geffken DF, Cushman M, Burke GL, et al. 2001. Association between physical activity and markers of inflammation in a healthy elderly population. *Am J Epidemiol*, 153:242–50.

Girodon F, Galan P, Monget AL, et al. 1999. Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients: a randomized controlled trial. MIN. VIT. AOX. geriatric network. *Arch Intern Med*, 159:748–54.

Goldhammer E, Tanchilevitch A, Maor I, et al. 2005. Exercise training modulates cytokines activity in coronary heart disease patients. *Inter J Cardiol*, 10:93–9.

Gomez CR, Boehmer ED, Kovacs EJ. 2005. The aging innate immune system. *Curr. Opin. Immunol*., 17: 457–62.

Gon Y, Hashimoto S, Hayashi S, et al. 1996. Lower serum concentrations of cytokines in elderly patients with pneumonia and the impaired production of cytokines by peripheral blood monocytes in the elderly. *Clin Exp Immunol*, 106:120–6.

Gregg R, Smith CM, Clark FJ, et al. 2005. The number of human peripheral blood CD4+ CD25high regulatory T cells increases with age. *Clin Exp Immunol*, 140:540–6.

Grubeck-Loebenstein B, Berger P, Saurwein-Teissl M, et al. 1998. No immunity for the elderly. *Nat Med*, 4:870.

Gueldner SH, Poon LW, La Via M, et al. 1997. Long term exercise patterns and immune function in healthy older women: A report of preliminary findings. *Mech Aging Dev*, 93:215–22.

Gupta S. 2000. Molecular steps of cell suicide: An insight into immune senescence. *J Clin Immunol*, 20:229–39.

Hammett CJ, Oxenham HC, Baldi JC, et al. 2004. Effect of six months' exercise training on C-reactive protein levels in healthy elderly subjects. *J Am Coll Cardiol*, 44:2411–13.

Hasler P, Zouali M. 2005. Immune receptor signaling, aging, and autoimmunity. *Cell Immunol*, 233:102–8.

Haynes L, Eaton SM, Burns EM, et al. 2004. Inflammatory cytokines overcome age-related defects in CD4 T cell responses in vivo. *J Immunol*, 172:5194–9.

Henson DA, Nieman DC, Pistilli EE, et al. 2004. Influence of carbohydrate and age on lymphocyte function following a marathon. *Inter J Sport Nutr Exerc Metab*, 14:308–22.

Herndler-Brandstetter D, Schwaiger S, Veel E, et al. CD25-expressing CD8+ T cells are potent memory cells in old age. *J Immunol*, 175:1566–74.

High KP. 2001. Nutritional strategies to boost immunity and prevent infection in elderly individuals. *Clin Infect Dis*, 33:1892–900.

High KP, Bradley S, Loeb M, et al. 2005. A new paradigm for clinical investigation of infectious syndromes in older adults: Assessment of functional status as a risk factor and outcome measure. *Clin Infect Dis*, 40:114–22.

Hong MS, Dan JM, Choi J-Y, et al. 2004. Age-associated changes in the frequency of naive, memory, and effector CD8+ T cells. *Mech Aging Dev*, 125:615–18.

Kapasi ZF, Ouslander JG, Schnelle JF, et al. 2003. Effects of an exercise intervention on immunologic parameters in frail elderly nursing home residents. *J Geron*, 58A:636–43.

Khan N, Hislop A, Gudgeon N, et al. 2004. Herpesvirus-specific CD8 T cell immunity in old age: Cytomegalovirus impairs the response to a coresident EBV infection. *J Immunol*, 173:7481–9.

Koch S, Solana R, Dela Rosa O, et al. 2006. Human cytomegalovirus infection and T cell immunosenescence: a mini review. *Mech Aging Dev*, 127:538–43.

Kohut ML, Cooper MM, Nickolaus MS, et al. 2002. Exercise and psychosocial factors modulate immunity to influenza vaccine in elderly individuals. *J Geron*, 57A:M557–M62.

Kohut ML, Lee W, Martin AE, et al. 2005. The exercise-induced enhancement of influenza immunity is mediated in part by improvements in psychosocial factors in older adults. *Brain Behav Immun*, 19:357–66.

Kohut ML, McCann DA, Russell DW, et al. 2006. Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of beta-blockers, BMI, and psychosocial factors in older adults. *Brain Behav Immun*, 20:201–9.

Kohut ML, Senchina DS. 2004. Reversing age-associated immunosenescence via exercise. *Exerc Immunol Rev*, 10:6–41.

Kohut ML, Senchina DS, Madden KS, et al. 2004. Age effects on macrophage function vary by tissue site, nature of stimulant, and exercise behavior. *Exper Geron*, 39:1347–60.

Kohut ML, Thompson JR, Lee W, et al. 2004. Exercise training-induced adaptations of immune response are mediated by β-adrenergic receptors in aged but not young mice. *J Appl Physiol*, 96:1312–22.

Kostka T, Berthouze SE, Lacour J-R, et al. 2000. The symptomatology of upper respiratory tract infections and exercise in elderly people. *Med Sci Sports Exer*, 32:46–51.

Kudlacek S, Willvonseder R, Stohlawetz P, et al. 2000. Immunology and aging. *Aging Male*, 3:137–42.

Lavery LW, Goyns MH. 2002. Decline in the expression of C4 binding protein alpha-chain gene during aging of the rat liver. *Biogerontol*, 3:207–11.

Leng S, Chaves P, Koenig K, et al. 2002. Serum interleukin-6 and hemoglobin as physiological correlates in the geriatric syndrome of frailty: a pilot study. *J Am Geriatr Soc*, 50:1268–71.

Leng SX, Yang H, Walston JD. 2004. Decreased cell proliferation and altered cytokine production in frail older adults. *Aging Clin Exp Res*, 16:249–52.

Lesourd B. 2004. Nutrition: a major factor influencing immunity in the elderly. *J Nutr Health Aging*, 8:28–37.

Leveille SG, Gray S, LaCroix AZ, et al. 2000. Physical inactivity and smoking increase risk for serious infections in older women. *J Am Geriatr Soc*, 48:1582–8.

Licastro F, Candore G, Lio D, et al. 2005. Innate immunity and inflammation in aging: A key for understanding age-related diseases. *Immunity Aging*, 2:8.

Linton P, Thoman ML. 2001. T cell senescence. *Front Biosci*, 6:D248–D61.

Looney RJ, Falsey AR, Walsh E, et al. 2002. Effect of aging on cytokine production in response to respiratory syncytial virus infection. *J Infect Dis*, 185:682–5.

Lung TL, Saurwein-Teissl M, Parson W, et al. 2000. Unimpaired dendritic cells can be derived from monocytes in old age and can mobilize residual function in senescent T cells. *Vaccine*, 18:1606–12.

Mangge H, Hubmann H, Pilz S, et al. 2004. Beyond cholesterol--inflammatory cytokines, the key mediators in atherosclerosis. *Clin Chem Lab Med*, 42:467–74.

Mangtani P, Cumberland P, Hodgson CR, et al. 2004. A cohort study of the effectiveness of influenza vaccination in older people, performed using the United Kingdom General Practice Research Database. *J Infect Dis*, 190:1–10.

McElhaney J. 2005. The unmet need in the elderly: Designing new influenza vaccines for older adults. *Vaccine*, 23:S1/10–S1/25.

McElhaney J, Gravenstein S, Upshaw CM, et al. 2001. Granzyme B: a marker of risk for influenza in institutionalized older adults. *Vaccine*, 19:3744–51.

McElhaney J, Herre JM, Lawson ML, et al. 2004. Effect of congestive heart failure on humoral and ex vivo cellular immune responses to influenza vaccination in older adults. *Vaccine*, 22:681–8.

McElhaney JE. 2003. Overcoming the challenges of immunosenescence in the prevention of acute respiratory illness in older people. *Conn Med*, 67:469–74.

McFarlin BK, Flynn MG, Campbell WW, et al. 2006. Physical activity status, but not age, influences inflammatory biomarkers and toll-like receptor 4. *J Geron A Biol Sci Med Sci*, 61:388–93.

McGeer EG, Klegeris A, McGeer PL. 2005. Inflammation, the complement system, and diseases of aging. *Neurobiol Aging*, 26(Suppl 1):94–7.

McGeer PL, McGeer EG. 2004. Inflammation and degenerative diseases of aging. *Ann N Y Acad Sci*, 1035:104–16.

McLeod JD. 2000. Apoptotic capability in aging T cells. *Mech Aging Dev*, 121:151–9.

Meyer KC. 2001. The role of immunity in susceptibility to respiratory infection in the aging lung. *Respir Physiol*, 128:23–31.

Miller RA. 1996. The aging immune system: Primer and prospectus. *Science*, 273:70–4.

Miller RA, Jacobson B, Weil G, et al. 1987. Diminished calcium influx in lectin-stimulated T cells from old mice. *J Cell Physiol*, 132:337–42.

Miyaji C, Watanabe H, Toma H, et al. 2000. Functional alterations of granulocytes, NK cells, and natural killer T cells in centenarians. *Hum Immunol*, 61:908–16.

Mocchegiani E, Malavolta M. 2004. NK and NKT cell functions in immunosenescence. *Aging Cell*, 3:177–84.

Molls RR, Ahluwahlia N, Mastro AM, et al. 2005. Nutritional status predicts primary subclasses of T cells and the lymphocyte proliferation response in healthy older women. *J Nutr*, 135:2644–50.

Mysliwska J, Bryl E, Foerster J, et al. 1999. The upregulation of TNFα production is not a generalised phenomenon in the elderly between their sixth and seventh decades of life. *Mech Aging Dev*, 107:1–14.

Naylor K, Li G, Vallejo AN, et al. 2005. The influence of age on T cell generation and TCR diversity. *J Immunol*, 174:7446–52.

Nichol KL. 2005. Influenza vaccination in the elderly: impact on hospitalization and mortality. *Drugs Aging*, 22:495–515.

Nieman DC. 1998. Exercise and resistance to infection. *Can J Physiol Pharmacol*, 76: 573–80.

Nieman DC, Henson DA, Gusewitch G, et al. 1993. Physical activity and immune function in elderly women. *Med Sci Sports Exer*, 25:823–31.

Njemini R, Lambert M, Demanet C, et al. 2005. Heat shock protein 32 in human peripheral blood mononuclear cells: effect of aging and inflammation. *J Clin Invest*, 25:405–17.

Northfield J, Lucas M, Jones H, et al. 2005. Does memory improve with age? CD85j (ILT-2/LIR-1) expression on CD8+ T cells correlates with 'memory inflation' in human cytomegalovirus infection. *Immunol Cell Biol*, 83:182–8.

Ogawa K, Oka J, Yamakawa J, et al. 2003. Habitual exercise did not affect the balance of type 1 and type 2 cytokines in elderly people. *Mech Aging Dev*, 124:951–6.

Ohkusu K, Du J, Isobe K-I, et al. 1997. Protein kinase Cα-mediated chronic signal transduction for immunosenescence. *J Immunol*, 159:2082–4.

O'Meara ES, White M, Siscovick DS, et al. 2005. Hospitalization for pneumonia in the cardiovascular health study: Incidence, mortality, and influence on longer-term survival. *J Am Geriatr Soc*, 53:1108–16.

Paulus WJ. 2000. Cytokines and heart failure. *Heart Fail Monit*, 1:50–6.

Pawelec G, Effros RB, Caruso C, et al. 1999. T cells and aging (update). *Front Biosc*, 4:D216–69.

Pawelec G, Solana R, Remarque E, et al. 1998. Impact of aging on innate immunity. *J Leuk Biol*, 64:703–12.

Penninx BW, Kritchevsky SB, Newman AB, et al. 2004. Inflammatory markers and incident mobility limitation in the elderly. *J Am Geriatr Soc*, 52:1105–13.

Plackett TP, Boehmer ED, Faunce DE, et al. 2004. Aging and innate immune cells. *J Leuk Biol*, 76:291–9.

Rall LC, Roubenoff R, Cannon JG, et al. 1996. Effects of progressive resistance training on immune response in aging and chronic inflammation. *Med Sci Sports Exer*, 28:1356–65.

Re F, Poccia F, Donnini A, et al. 2005. Skewed representation of functionally distinct populations of Vγ9Vδ2 T lymphocytes in aging. *Exp Geron*, 40:59–66.

Reuben DB, Cheh AI, Harris TB, et al. 2002. Peripheral blood markers of inflammation predict mortality and functional decline in high-functioning community-dwelling older persons. *J Am Geriatr Soc*, 50:638–44.

Riancho JA, Zarrabeitia MT, Amado JA, et al. 1994. Age-related differences in cytokine secretion. *Geron*, 40:8–12.

Rink L, Cakman I, Kirchner H. 1998. Altered cytokine production in the elderly. *Mech Aging Dev*, 102:199–209.

Rockwood K, Howlett SE, MacKnight C, et al. 2004. Prevalence, attributes, and outcomes of fitness and frailty in community-dwelling older adults: report from the Canadian study of health and aging. *J Geron A Biol Sci Med Sci*, 59:1310–17.

Sarkar D, Fisher PB. 2006. Molecular mechanisms of aging-associated inflammation. *Cancer Lett*, 236:13–23.

Saurwein-Teissl M, Blasko I, Zisterer K, et al. 2000. An imbalance between pro-and anti-inflammatory cytokines, a characteristic feature of old age. *Cytokine*, 12:1160–1.

Schleiss MR. 2006. Acquisition of human cytomegalovirus infection in infants via breast milk: natural immunization or cause for concern? *Rev Med Virol*, 16:73–82.

Schmaltz HN, Fried LP, Xue QL, et al. 2005. Chronic cytomegalovirus infection and inflammation are associated with prevalent frailty in community-dwelling older women. *J Am Geriatr Soc*, 53:747–54.

Schnelle JF, Alessi CA, Simmons SF, et al. 2002. Translating clinical research into practice: a randomized controlled trial of exercise and incontinence care with nursing home residents. *J Am Geriatr Soc*, 50:1476–83.

Schoenfelder DP, Rubenstein LM. 2004. An exercise program to improve fall-related outcomes in elderly nursing home residents. *Appl Nurs Res*, 17:21–31.

Schuler PB, Leblanc PA, Marzilli TS. 2003. Effect of physical activity on the production of specific antibody response to the 1998–99 inlfuenza virus vaccine in older adults. *J Sports Med Phys Fitness*, 43:404.

Schwab R, Russo C, Weksler ME. 1992. Altered major histocompatibility complex-restricted antigen recognition by T cells from elderly humans. *Eur J Immunol*, 22:2989–93.

Sebastian C, Espia M, Serra M, et al. 2005. MacrophAging: A cellular and molecular review. *Immunobiol*, 210:121–6.

Semba RD, Margolick JB, Leng S, et al. 2005. T cell subsets and mortality in older community-dwelling women. *Exp Geron*, 40:81–7.

Senchina DS, Macaluso F, Lee W, et al. 2006. T cell CD28 expression in older adults is modulated by exercise training [abstract]. *Med Sci Sports Exerc*, 38:S309.

Shinkai S, Kohno H, Kimura K, et al. 1995. Physical activity and immune senescence in men. *Med Sci Sports Exer*, 27:1516–26.

Shinkai S, Konishi M, Shephard RJ. 1998. Aging and immune response to exercise. *Can J Physiol Pharmacol*, 76:562–72.

Shodell M, Siegal FP. 2002. Circulating, interferon-producing plasmacytoid dendritic cells decline during human aging. *Scand J Immunol*, 56:518–21.

Siebens H, Aronow H, Edwards D, et al. 2000. A randomized controlled trial of exercixe to improve outcomes of acute hospitalization in older adults. *J Am Geriatr Soc*, 48:1545–52.

Singh NA, Clements KM, Fiatarone MA. 1997. A randomized controlled trial of progressive resistance training in depressed elders. *J Geron A Biol Sci Med Sci*, 52:M27–M35.

Smith JK, Dykes R, Douglas JE, et al. 1999. Long-term exercise and atherogenic activity of blood mononuclear cells in persons at risk of developing ischemic heart disease. *JAMA*, 281:1722–7.

Smith TP, Kennedy SL, Fleshner M. 2004. Influence of age and physical activity on the primary in vivo antibody and T cell-mediated responses in men. *J Appl Physiol*, 97:491–8.

Solana R, Alonso MC, Pena J. 1999. Natural killer cells in healthy aging. *Exp Geron*, 34:435–43.

Solana R, Mariani E. 2000. NK and NK/T cells in human senescence. *Vaccine*, 18:1613–20.

Solana R, Pawelec G. 1998. Molecular and cellular basis of immunosenescence. *Mech Aging Dev*, 102:115–29.

Spencer NFL, Daynes RA. 1997. IL-12 directly stimulates expression of IL-10 by CD5+ B cells and IL-6 by both CD5+ and CD5– B cells: Possible involvement in age-associated cytokine dysregulation. *Inter Immunol*, 9:745–54.

Steger MM, Maczek C, Grubeck-Loebenstein B. 1996. Morphologically and functionally intact dendritic cells can be derived from the peripheral blood of aged individuals. *Clin Exp Immunol*, 105:544–50.

Stout RD, Suttles J. 2005. Immunosenescence and macrophage functional plasticity: dysregulation of macrophage function by age-associated microenvironmental changes. *Immunol Rev*, 205:60–71.

Strasser A, Teltscher A, May B, et al. 2000. Age-associated changes in the immune system of German Shepherd dogs. *J Vet Med A Physiol Pathol Clin Med*, 47:181–92.

Taaffe DR, Harris TB, Ferrucci L, et al. 2000. Cross-sectional and prospective relationships of interleukin-6 and C-reactive protein with physical performance in elderly persons: MacArthur studies of successful aging. *J Geron A Biol Sci Med Sci*, 55:M709–15.

Trzonkowski P, Mysliwska J, Szmit E, et al. 2003. Association between cytomegalovirus infection, enhanced proinflammatory response and low level of anti-hemagglutinins during the anti-influenza vaccination--an impact of immunosenescence. *Vaccine*, 21:3826–36.

Tsukamoto K, Suzuki K, Machida K, et al. 2002. Relationships between lifestyle factors and neutrophil functions in the elderly. *J Clin Lab Anal*, 16:266–72.

Utsuyama M, Hirokawa K, Kurashima C, et al. 1992. Differential age-change in the numbers of $CD4^+CD45RA^+$ and $CD4^+CD29^+$ T cell subsets in human peripheral blood. *Mech Aging Dev*, 63:57–68.

van Baarle D, Tsegaye A, Miedama F, et al. 2005. Significance of senescence for virus-specific memory T cell responses: Rapid aging during chronic stimulation of the immune system. *Immunol Lett*, 97:19–29.

van den Biggelaar AHJ, Huizinga TW, de Craen AJ, et al. 2004. Impaired innate immunity predicts frailty in old age. The Leiden 85-plus study. *Exp Geron*, 39:1407–14.

Vescovini R, Telera A, Fagnoni FF, et al. 2004. Different contribution EBV and CMV infections in very long-term carriers to age-related alterations of CD8+ T cells. *Exp Geron*, 39:1233–43.

Villanueva JL, Solana R, Alonso MC, et al. 1990. Changes in the expression of HLA-class II antigens on peripheral blood monocytes from aged humans. *Dis Markers*, 8:85–91.

Visser M, Pahor M, Taaffe DR, et al. 2002. Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the Health ABC Study. *J Geron A Biol Sci Med Sci*, 57:M326–32.

Volpato S, Guralnik JM, Ferrucci L, et al. 2001. Cardiovascular disease, interleukin-6, and risk of mortality in older women: the women's health and aging study. *Circulation*, 103:947–53.

Waitumbi JN, Donvito B, Kisserli A, et al. 2004. Age-related changes in red blood cell complement regulatory proteins and susceptibility to severe malaria. *J Infect Dis*, 190:1183–91.

Whisler RL, Grants IS. 1993. Age-related alterations in the activation and expression of phosphotyrosine kinases and protein kinase C (PKC) among human B cells. *Mech Aging Dev*, 71:31–46.

Whisler RL, Newhouse YG. 1985. Immunosenescence of the human B cell system: Impaired activation/proliferation in response to autologous monocytes pulsed with Staph Protein A and the effects of interleukins 1 and 2 compared to interferon. *Lymphokine Res*, 4:331–7.

Whitehurst MA, Johnson BL, Parker CM, et al. 2005. The benefits of a functional exercise circuit for older adults. *J Strength Cond Res*, 19:647–51.

Wick G, Jansen-Durr P, Berger P, et al. 2000. Diseases of aging. *Vaccine*, 18:1567–83.

Wisse BE. 2004. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. *J Am Soc Nephrol*, 15:2792–800.

Woods JA, Ceddia MA, Wolters BW, et al. 1999. Effects of 6 months of moderate aerobic exercise training on immune function in the elderly. *Mech Aging Dev*, 109:1–19.

Xu X, Beckman I, Dimopoulos K, et al. 1992. Age-related changes in the expression of T cell activation antigens following phytohaemagglutinin stimulation. *Exp Clin Immunogenet*, 9:203–11.

Yan H, Kuroiwa A, Tanaka H, et al. 2001. Effect of moderate exercise on immune senescence in men. *Eur J Appl Physiol*, 86:105–11.

Zheng B, Han S, Takahashi Y, et al. 1997. Immunosenescence and germinal center reaction. *Immunol Rev*, 160:63–77.

Zissel G, Schlaak M, Muller-Quernheim J. 1999. Age-related decreases in accessory cell function of human alveolar macrophages. *J Invest Med*, 47:51–6.