Chapter 4
Effects of Aging on Immune Function

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Physiologic changes with age – immune system

Parameter	Change with age	Functional impact of change
T-cells		Increased susceptibility to acute viral infections; increased latent herpesvirus reactivation along with clonally expanded $CD8^+$ T-cells
Memory T cells	Increase	
Thymus gland	Decrease (involutes)	
Naïve T cells	Decrease	
DTH	Decrease	
IL-2 production	Decrease	
Proliferation	Decrease	
Cytotoxicity	Decrease	
B-cells		Increased autoantibodies; decreased antibody production following vaccination
Number	Decreased	
High-affinity antibodies	Decreased	
Non-specific antibodies	Increased	
Inflammation		Increased morbidity and mortality; may play a role in age-related diseases (Alzheimer's, Parkinson's, osteoporosis, atherosclerosis, and type-2 diabetes)
Low-grade inflammation		
Circulating IL-6	Increased	
Circulating TNF-α	Increased	
CRP	Increased	

In this chapter we describe changes in the immune system that are thought to be related to age per se. We subsequently review the clinical implications of these changes, including the effects of surgical trauma on immune function (see the physiology table at beginning of chapter). We then discuss how stress modifies many of these changes. We also describe recent information on persistent infections, in particular latent viral infections and how they may be partly responsible for shaping the aging immune system. We conclude with a discussion of some of the latest research on ways to restore or stimulate immune function in the elderly.

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Changes in Immune Cell Function with Age

T Lymphocytes

Quantitative changes in T cell populations in aging humans and experimental animals include declines in "virgin" (reactive) T cells and increases in "memory" (primed) T cells [1–5]. It is not clear which subpopulations account for the accumulation of memory cells. Some studies have described increases in the population of $CD4^+$ T-helper memory cells [6] and others reported increases in $CD8^+$ T suppressor memory cells as well [1]. Although the number of naive T cells declines in old animals, they appear to produce larger amounts of interleukin-2 (IL-2) than naive cells from young animals [7]. Memory T cells normally produce IL-2; and although aged animals have larger proportions of memory

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cells, many studies have described decreased IL-2 production by aged memory lymphocytes. This paradox of low production of IL-2 despite increased proportions of IL-2-producing cells may be related to a lack of other regulatory cytokine signals, such as IL-4 [8].

A decrease in the proliferative response of lymphocytes to specific antigens or nonspecific mitogens was one of the earliest age-related changes in immune function to be reported [9–12]. Decreased responsiveness to mitogens is due to a number of variables, including reduced numbers of mitogen-responsive cells and decreased vigor of the proliferative response [10]. A smaller percentage of T splenocytes from old mice respond to mitogenic stimulation by entering active phases of cell replication, a defect noted with $CD4^+$ T-helper cells and to a lesser extent with $CD8^+$ T suppressor/cytotoxic cells [13]. Some studies suggest that the type of stimulus may affect the degree of decreased proliferation of lymphocytes from old animals [14]. T-helper cells from old mice generate fewer cytotoxic effector cells involved in delayed hypersensitivity skin reactions [15].

The ability of T cells to support antibody production changes with increasing age. Lymphocytes from old subjects display increased helper activity in vitro for nonspecific antibody production [16, 17], and they proliferate more to nonspecific stimulation [14]. Studies comparing suppressor cells from young and old mice have shown that cells from aged animals have more difficulty in recognizing and exerting suppressive effects against specific antigens from self and other old animals [17–20]. The increased incidence of autoantibodies seen during aging (antibodies directed against parts of the self) may be related to a failure of tonic inhibition by suppressor T cells [21] and has been correlated with the decreased proliferation of T cells to mitogen [22] (i.e., the lower the proliferation of T cells to mitogens, the higher was the level of autoantibodies).

One mechanism that is believed to contribute to the decline in T cell immunity is involution of the thymus, which precedes the age-related decline in T cell function and decreased thymic hormone levels (Fig. 4.1). Thymic function gradually starts declining from the first year of life [23, 24]. The thymic epithelial space, in which thymopoiesis occurs, shrinks to less than 10% of the total thymus tissue by age 70. Despite the reduction in functional thymic area, the aging thymus still demonstrates T-cell output although at a lesser rate [25]. The continual presence of T-cell receptor excision circle-positive T-cells, which represent recent thymic emigrants, were found in the peripheral blood of elderly adults [26]. Thymic atrophy has been speculated to be the result of aging of the T-cell progenitor population [27], loss of self-peptide expressing thymic epithelium [28], defects in TCRβ gene rearrangement [29], and aging of the thymic microenvironment with loss of trophic cytokines such as IL-7 [30].

Another mechanism contributing to T cell immunosenescence is "replicative senescence" [31]. Senescent T cells in vitro exhibit a loss of CD28, a costimulatory molecule critical to the outcome of antigen recognition and signal transduction induced by the T-cell receptor [32]. Similarly, during aging, there is a progressive accumulation of memory CD8 T cells that are CD28-negative, with some elderly adults having more than 50% of their total CD8 T cells being CD28-negative [33, 34]. Notably, CD28 is involved in a number of critical T-cell functions such as lipid raft formation, IL-2 gene transcription, apoptosis, stabilization of cytokine mRNA, and cell adhesion [35–37].

Another observation of CD28-negative T cells is their inability to proliferate, even when using phorbol esters to bypass cell-surface receptors and directly signal proliferation [38]. Extensive research on a variety of cell types have attributed this to the irreversible nature of the proliferative block, which is linked to the upregulation of cell-cycle inhibitors and p53 checkpoints [39]. Once generated, these T cells do not disappear, but show increased expression of bcl2 and are resistant to apoptosis *ex vivo* [40]. Moreover, increased $CD8^+CD28^-$ T cells are often present as a result of oligoclonal expansions that may reduce the overall spectrum of antigenic specificities within the T cell pool [31, 41].

A clinically important implication of large expansions of antigen-specific CD8 T cells in the elderly is that they appear to function as suppressor T cells and affect a number of immune parameters. Poor antibody responses to influenza vaccination in the elderly were significantly correlated with high proportions of $CD8^+CD28^-$ T cells [42, 43]. High levels of $CD8^+CD28^-$ T cells also correlate with greater disease severity in patients with ankylosing spondylitis [44]. $CD8^+CD28^-$ T cells have been implicated as the critical subset in allogeneic organ transplant tolerance, whereby donor-specific $CD8^+CD28^-$ T cells can be found in peripheral blood of stable transplant recipients but not in patients with acute rejection [45]. Notably, $CD8^+CD28^-$ T cells have been shown to induce antigen-presenting cells to become tolerogenic to helper T cells with cognate antigen specificity [45]. Importantly, increased numbers of $CD8^+CD28^-$ T cells (along with low CD4 and poor proliferative responses) were found to predict higher 2-year mortality in a Swedish longitudinal study [46].

B Lymphocytes

Age-related quantitative changes in B cells have become apparent more recently than those described in T cells. The absolute number of B cells does not appear to change appreciably with age [47]. Studies in aged mice have shown a decrease in bone marrow B-cell precursors [48–50] and structural changes in B-cell membranes [51]. B cells from old individuals proliferate less efficiently in response to mitogen stimulation, similar to what has been described for T cells [21]. Also similar to T cells [52], activation of PKC

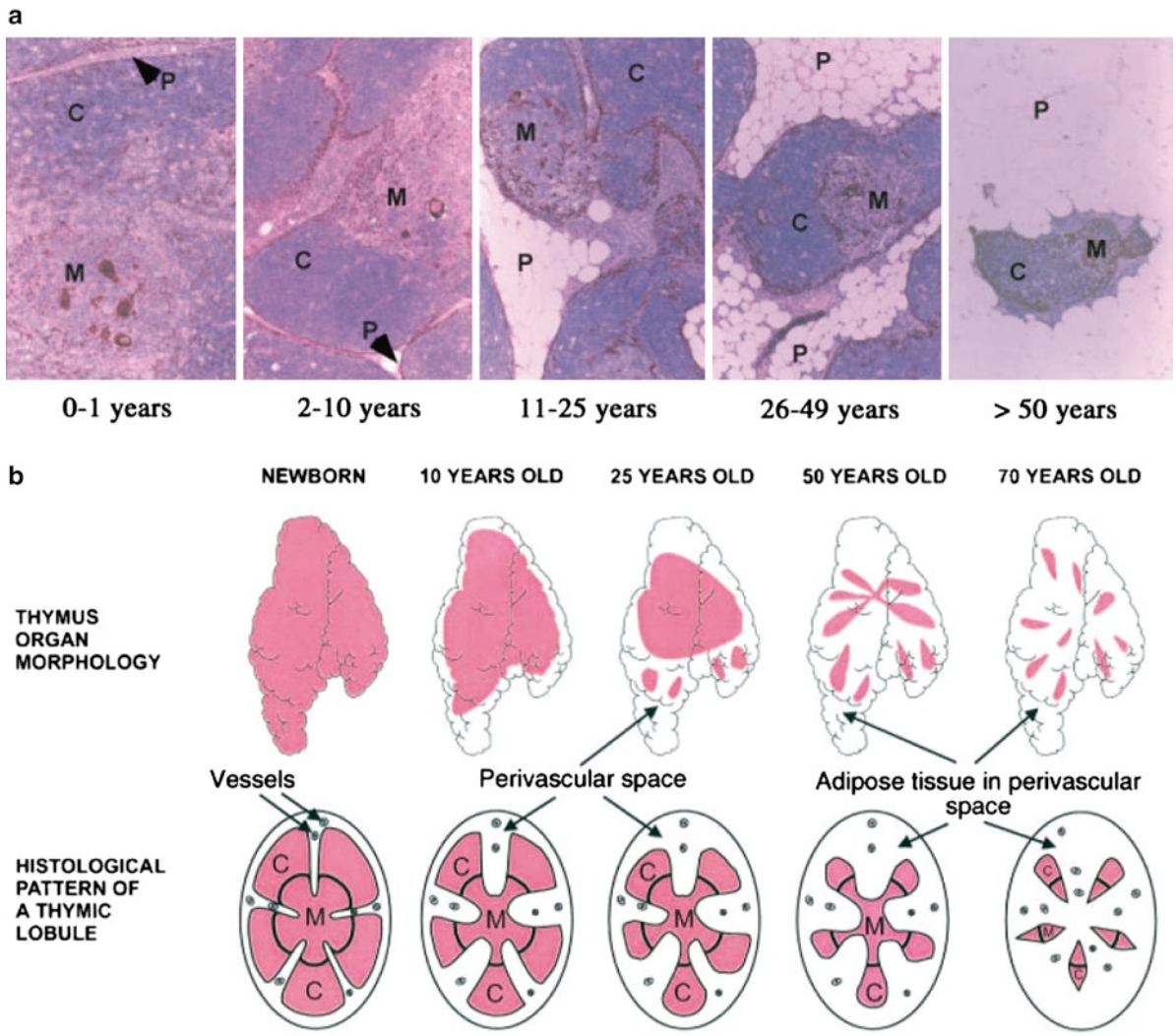


Figure 4.1 The human thymus across the lifespan. (**a**) Representative views of human thymus morphology throughout aging. All tissue was formalin-fixed, paraffin-embedded, and sections stained with haematoxylin and eosin and anti-keratin antibody [*brown*] to determine the percentage thymic epithelial space [each panel, ×25]. C, cortex; M, medulla; P, perivascular space. (**b**) Graphical depiction of the impact of age on human thymus morphology. Thymic epithelial space, *pink*; perivascular space, *white* (reprinted with permission from [267], copyright 2000, The American Association of Immunologists, Inc).

and protein tyrosine kinases is reduced in B cells from old humans [53]. The expression of PKC was not reduced in B cells in this study [54].

The generation of antibody responses by B cells does change with age [55], although much of it is related to changes in T cell function. The distinction between antibody responses to T cell-dependent and T cell-independent antigens is made on the basis of whether there is an absolute requirement for T cell help in the antibody response. The decrease in T cell-dependent antibody responses is obvious in experimental animals, with 80% fewer antibody-forming cells in older animals [2]. The accumulation of anti-idiotypes (antibodies directed against other antibodies) with increasing age may interfere with the production of specific antibody [56].

The ability to respond to specific antigenic challenge with specific antibody production decreases with age [55]. This phenomenon has been described in studies of both primary and secondary antibody responses. When subjects of different ages were immunized with the primary antigen flagellin, similar levels of anti-flagellin antibody were found in both old and young subjects, but the older subjects were unable to maintain the response [57]. In contrast, De Greef et al. immunized old and young subjects with the primary antigen *Helix pomatia* hemocyanin. Compared to young subjects, old subjects had similar numbers of antibody-producing cells after in vitro stimulation with the antigen [58].

Although most investigators agree that changes in antibody production with age are primarily the result of declines in T lymphocyte function, there is also evidence for a decline in intrinsic B cell function. Some studies suggest a diminished ability of purified human B cells to respond to purified T-helper cells, or to T cell-derived helper factors [59, 60].

Studies with murine cells have shown that certain subsets of B cells from old animals function at a much lower level than the same cells from young mice, whereas other subsets produce comparable levels of antibody [61]. Cerny et al. found that the antiphosphorylcholine antibody produced by aged mice did not protect animals against lethal doses of *Streptococcus pneumoniae,* although old animals produced levels of antibody comparable to those in young animals [62]. The genes encoding the variable heavy portions of the antibody molecule were different in the old mice. The resulting antibody had lower affinity for the bacterial antigen and conferred less protection [62, 63].

Macrophage Function

Macrophage function during aging is particularly relevant to the theme of this book, suggesting that "old" macrophages are comparable to "young" macrophages in terms of producing similar levels of cytokines. Differences in function appeared to be modulated through changes in T and B cell responses to the cytokines [64, 65]. Studies of human monocytes have shown decreased secretion of IL-1 with mitogen stimulation [66]. Bone marrow stem cells from senescence-accelerated mice are defective in their ability to generate granulocyte/macrophage precursor cells [67]. In vivo function of macrophages illustrated by cutaneous wound healing in mice, showed that wounds in aged control animals took twice as long to heal as in young ones [68]. When peritoneal macrophages from animals of different ages were added to wounds on old mice, healing was accelerated regardless of the age of the source animal, although, macrophages from young mice accelerated the healing process to the greatest degree [68].

Studies of macrophage function in aged mice and humans suggest defects in macrophage–T cell interactions. Antigen-sensitized macrophages from old mice stimulated significantly lower levels of T cell proliferation than sensitized macrophages from young mice [14]. Dendritic cells are tissue-fixed macrophages that stimulate formation of germinal centers in lymph follicles where B cell memory develops; they thus play an important role in the secondary immune response. Szakal et al. described serious age-related compromise in this pathway [69]. When macrophages were replaced with other sources for activation (e.g., IL-2, or an activator such as phorbol-12-myristate-13-acetate), T cells from old adults displayed enhanced responses [70]. Macrophages from young adults were able to restore old T cell responses to the level seen in young adults in 70% of the subjects studied. Because the "old" macrophages effectively supported "young" T cells, the authors postulated that the defect resulted from impaired macrophage–T cell communication [70]. In other studies, monocytes from old adults displayed less cytotoxicity against certain tumor cell lines, decreased production of reactive oxygen intermediates (H_2O_2 and NO_2), and lower IL-1 secretion than monocytes from young adults [66, 71].

Natural Killer Cells

Natural killer (NK) cells are cytotoxic cells with the ability to lyse targets without the need for antigenic sensitization, a characteristic that distinguishes them functionally from cytotoxic T cells. Lymphokine-activated killer (LAK) cells, thought to be highly activated NK cells, are able to lyse certain cell lines that are resistant to NK cells. NK cells from mice display a declining ability to lyse spleen cells with increasing age [72, 73]. Most studies using old human subjects have shown little or no change in NK cell cytotoxic ability [74]. There do appear to be differential requirements for maximal activation of NK cells by interferon-α (IFNα). Young NK cells show maximal responses when stimulated with low concentrations of IFNα [75]. The activity of LAK cells from old humans appears to be reduced compared to that of LAK cells from young humans [74, 75].

Changes in Production and Response to Regulatory Factors

Prostaglandins

Prostaglandin E_2 (PGE_2), a metabolite of cell membrane arachidonic acid, is a feedback inhibitor of T cell proliferation in humans [76]. T cells from adults over 70 years of age are a magnitude more sensitive to inhibition by PGE_2 than those from adults less than 40 years of age [9, 77]. Thus PGE_2 may interfere with expansion of antigen-specific T-helper cell clones. T cells from aged mice are not only more sensitive to inhibition by PGE_2, their splenocytes appear to produce more PGE_2 than splenocytes from young mice [78]. Meydani et al. have continued to provide evidence that macrophage production of excess PGE_2 is a significant mechanism in the suppression of T cell proliferation and IL-2 production in old mice [79].

Delfraissey et al. found that PGE_2 suppressed the primary antibody response to trinitrophenylated polyacrylamide beads by lymphocytes from old adults [65]. Removing the monocytes that were the source of PGE_2 production or adding drugs that blocked production of PGE_2, partially reversed

the depressed response [9, 65]. Using a different system of lipopolysaccharide-stimulated versus unstimulated lymphocytes, other investigators have not found increased PGE_2 production in old versus young donors [80]. Polyclonal antibody production was not suppressed by PGE_1 when added to lymphocytes from donors of any age [80].

The increased sensitivity to PGE_2 with age does not appear to be part of a general increase in sensitivity to all immunomodulators. Lymphocytes from subjects over 70 years of age are less sensitive to inhibition by substances such as histamine and hydrocortisone [77].

Interleukins

Interleukins-1 and -2 play a primary role in activation, recruitment, and proliferation of T lymphocytes. Activated T cells then go on to produce a variety of growth and differentiation factors. T-helper (Th) cells can be classified based on the profile of the cytokines they produce and by distinct surface receptors. Th1 cells elaborate IFN-γ, IL-2, IL-12, and tumor necrosis factor-β (TNF-β), leading to the induction of cytotoxic T cells and cellular immunity; Th2 cells elaborate IL-4, IL-5, IL-6, IL-10, and IL-13, which ultimately results in antibody production [81, 82].

A decreased response to IL-2 has been studied extensively as a potential mechanism underlying the age-related defect in cellular immunity. Work from various investigators has demonstrated decreased production of IL-2 after mitogen stimulation, decreased density of IL-2 receptor expression, and decreased proliferation of T cells in response to IL-2 [83–88]. The picture is complicated by variable sensitivity to IL-2 depending on the activation signal [3, 89]. Human memory T cells generally produce low levels of IL-2 when stimulated by mitogen, in contrast to high IL-2 production by young memory T cells [8]. However, production of IL-2 by old cells was greater when a different stimulus was employed [8]. Studies from Nagelkerken's group found no differences in T cell proliferation or IL-2 production when memory T cells from old and young humans were stimulated with a variety of activation signals [3]. $CD4^+$ T cells from old mice accumulate similar levels of IL-2 transcripts, though secretion of IL-2 is lower than that seen in cells from young mice [90].

Increasing evidence has been accumulating that there are age-related declines in lymphocyte production and response to cytokines other than IL-2 [2, 91]. Monocytes from aged humans produce levels of IL-1 precursor comparable to monocytes from young humans, although they secrete less IL-1 [67]. Lymphocytes from old individuals produce higher levels of IL-1, IL-2, and TNF-α than those from healthy young individuals in mixed lymphocyte culture [92].

Li and Miller found a threefold decline in IL-4 production with age when activated murine T cells were immobilized with antibody to the T cell receptor, CD3, and cultured with anti-CD3 and IL-2 [93]. Memory T cells from old donors displayed a sixfold deficit in IL-4 production compared to cells from young donors [93]. In a similar system, $CD4^+$ T cells from young mice were more sensitive to stimulation with exogenous IL-4, producing much higher levels of IL-2 than old $CD4^+$ T cells [8]. Blocking endogenous IL-4 boosted "old" lymphocyte production of specific anti-influenza IgM and IgG1 to levels seen in young animals during a primary antibody response [94]. A similar effect was achieved by blocking endogenous IFN-γ and IL-10 [94]. We have shown that lymphocytes from old adults produce less IL-4 when stimulated with specific antigen than lymphocytes from young adults [95]. When IL-4 is added early during the course of stimulation, old lymphocytes are less inhibited to produce specific antibodies [95], similar to findings described earlier in mice [8].

Other investigators have found no differences between lymphocytes from old and young adults in terms of their ability to produce IL-4 or IL-6 when stimulated with the mitogen phytohemagglutinin [96]. In this system, lymphocytes from old adults produced significantly less IFN-γ [96]. With variation in the activating signals, old human T cells produce larger amounts of IL-4 and IFN-γ [3, 97].

Proinflammatory Cytokines

Aging is associated with elevated levels of circulating inflammatory cytokines such as TNF-α, IL-6, IL-1ra, and the acute phase protein CRP [98–100]. The plasma levels of TNF-α were positively correlated with IL-6, sTNF-RII, and CRP in 126 centenarians indicating an interrelated activation of the entire inflammatory cascade [101]. However, the increased proinflammatory cytokines in healthy elderly adults is not very marked and far from levels observed during acute infection. Thus, aging is associated with chronic low-grade inflammation.

In agreement with low-grade inflammation in aging, aged T cells produce much higher levels of the proinflammatory cytokines TNF-α and IL-6 [102]. Increased production of TNF-α by unstimulated mononuclear cells has been shown [103]. Increased production of IL-6 and IL-1ra by unstimulated mononuclear cells was demonstrated, but no difference was found in levels of TNF-α and IL-1β [104]. However, cells in tissues other than peripheral blood may also contribute to the increased levels of circulating proinflammatory cytokines such as endothelial cells, adipose cells, and macrophage-derived cells in CNS and peripheral tissues.

Clinical Implications of Age-Related Immune Changes

All-Cause Mortality

We have described a variety of immunologic changes with aging. What are the implications of these changes for the occurrence of disease and maintenance of health in older adults? There is little direct causal evidence linking specific changes in immunity to specific clinical diseases or mortality. Most authorities simply assume that a decline in immune function is deleterious, or use theoretic arguments to support this belief. The question of whether decreased immune responses contribute to morbidity and mortality in elderly persons has been addressed mostly by cross-sectional studies looking for associations between a particular abnormal immune response and general health status [105]. For example, the Baltimore Longitudinal Aging Study found that declines in absolute lymphocyte counts predicted mortality after 3 years in aging men [106]. Ferguson et al. found that the presence of two or more suppressed immune parameters predicted poor 2-year survival in a group of adults over the age of 80 [46].

The response to delayed-type hypersensitivity skin tests has been associated with mortality in a number of studies. Delayed-type hypersensitivity skin testing is thought to be the in vivo correlate of in vitro mitogen-stimulated proliferation. Elderly subjects who respond poorly or not at all to a battery of antigens placed intradermally (anergy), have an increased risk of mortality compared to elderly subjects who respond well to one or more antigens [12, 107]. We found a twofold higher mortality rate and incidence of pneumonia during 10 years of follow-up in the one-third of healthy elderly individuals who were anergic at initial testing [107, 108].

We and others have examined mitogen-stimulated lymphocyte proliferation in community-dwelling adults over age 65 years [46, 105, 108, 109]. One study found that 18% of adults seen in an outpatient geriatric clinic had lymphocytes that did not respond to any of the three mitogens [109]. These nonresponders had a 26% mortality rate at 3-year follow-up versus 13% mortality in those whose lymphocytes proliferated to at least one mitogen. The increase in all-cause mortality remained significant after controlling medication use, an indirect indicator of health status. Our own studies showed slightly higher all-cause mortality in old adults with low proliferative responses to the mitogen phytohemagglutinin [105].

Response to Immunization and Infections

Adults over the age of 65 experience greater morbidity and mortality in association with common infections, providing a basis for targeting this population with preventive immunization. Unfortunately, elderly people respond less well to preventive immunizations against common infections compared with young individuals because of the waning of immunity. Epidemiologic evidence suggests that despite decreased efficacy in the elderly, immunizations do reduce morbidity and mortality. The next section focuses on influenza, pneumococcal pneumonia, tetanus, tuberculosis, and herpes zoster, because information is available on disease epidemiology and aging immune responses specific to these entities.

Influenza

Influenza is a common viral respiratory illness that becomes clinically important when complicated by bacterial pneumonia, or when it occurs in debilitated or elderly patients (reviewed by Burns et al.) [110] Individuals who suffer from one or more chronic, systemic illnesses (e.g., chronic obstructive pulmonary disease, diabetes, chronic renal insufficiency) experience a 40- to 150-fold increase in the basal incidence rate for influenzal pneumonia of four cases per 100,000 persons per year. More than 80% of deaths related to influenza epidemics occur in the elderly [111], and the risk of developing influenzal pneumonia or superimposed bacterial pneumonia increases with increasing age. Individuals living in long-term care facilities are at particularly high risk of morbidity and mortality.

After vaccination with influenza, old mice display impaired cytotoxic T cell function and ineffective antibody generation against the virus [112]. When an intranasal viral load is administered after vaccination, old animals are more likely to develop influenzal pneumonia than young animals [112]. Studies in humans have described impaired production of anti-influenza antibodies and impaired influenza-specific cytotoxic activity in old adults compared to that in young adults [113]. Some of the mechanisms mediating this response include reduced IL-2 production and T cell activation in vivo and in vitro [85]. NK cell cytotoxicity is unchanged in old adults after vaccination against influenza, in contrast to increased NK cell activity in young adults [114]. Elderly individuals who do display a significant response to influenza vaccine have increased numbers of T cells capable of responding to the specific viral stimulus, whereas nonresponders have low numbers of such cells [115]. After immunization, IgG and IgG1 antibody production and agglutinating ability were decreased in the elderly compared to that in young subjects [116]. The investigators were able to restore the responses of the elderly subjects to the levels seen in young subjects by doubling the dose of vaccine [116].

Although influenza vaccination is less effective in the higher risk population of old adults, the incidence and severity of influenza infections is clearly reduced by annual usage of the standard preparation [117]. The vaccine confers the highest degree of protection when the epidemic strains are similar to those in the vaccine [118]. Even when the antigenic

determinants of the wild virus have drifted over the course of a year, vaccine utilization can still have a substantial impact on morbidity and mortality [117].

Pneumococcal Pneumonia

An increased incidence of morbidity and mortality due to pneumonia has been recognized in the elderly for years [110]. Hospitalization necessitated by a diagnosis of pneumonia is most often caused by bacteria, primarily (about two-thirds of cases) *S. pneumoniae*. High mortality rates result from the increased incidence of bacteremia and meningitis seen in old adults. Similar to influenza, patients with one or more chronic systemic diseases are at increased risk of complications and mortality from pneumococcal infection.

Most of the information on the immunologic response to pneumococcal vaccination derives from murine studies. After vaccination with phosphocholine, old mice produced levels of antibody similar to those in young mice, but with a molecular shift in the antibody repertoire [62]. The antibody produced by old animals has a lower affinity for its target and is less effective in preventing infection [62]. In old mice, many of the antibodies produced after pneumococcal vaccination cross-react with self-antigens [62]. In humans, serum antibody levels fade more rapidly in old individuals, prompting recommendations to re-vaccinate after 6 years in elderly patients [119]. The vaccine has been estimated to be about 70% effective for reducing morbidity and mortality in the elderly [120].

Tuberculosis and Intracellular Infections

For more than 20 years the risk of active tuberculosis in the Western world is increasingly confined to two populations: those with immunocompromising diseases (e.g., AIDS) and the very elderly [121, 122]. Animal studies show that old mice display increased susceptibility to infection with *Mycobacterium tuberculosis* [123]. The infection containment rate in old mice is similar to that in young animals; but once pulmonary infection is established, there is increased hematogenous spread to other organs [123]. Old animals display decreased $CD4^+$ T cell function, significantly lower levels of IL-12 in the lung [123], and delayed emergence of protective, IFN-γ-secreting $CD4^+$ T cells [124]. The protective cells from old animals were slower to express surface adhesion markers necessary for migration across endothelial linings to sites of active infection [124]. The increased spread of disease in old animals may also be related to alterations in other cytokine levels [123]. Orme has shown that $CD4^+$ cells from young mice protect old mice from infection, suggesting that old macrophages function adequately and the major defect lies in the T cell population [123, 124].

Herpes Zoster

There is a clear positive correlation between age and the incidence of herpes zoster, with an annual incidence rate of 400 cases per 100,000 adults over age 75 [125]. Other surveys suggest an even higher overall incidence [126]. The varicella-zoster virus (VZV) is harbored in dorsal root ganglia for many decades following childhood illness; and when it is reactivated it causes a cutaneous, varicella-type vesicular eruption involving the dermatome of the involved dorsal root ganglion.

Cellular immunity, measured by cutaneous delayed hypersensitivity to varicella zoster, wanes with increasing age, although other factors may be involved in controlling viral latency [127]. Cutaneous zoster is often an indication of immune-compromised status in young persons and those with early recurrence [126], but is not associated with occult malignancy in old adults [128].

Stress, Immunity, and Aging (Table 4.1)

Physical Stress

A number of studies have described the effects of physical stress on the immune system, although most have not analyzed outcomes by age. Time-limited physical stress, such as hypoxia, head-up tilt challenge (approximating conditions of acute hemorrhage), hyperthermia, and exercise, tend to enhance measures of immunity on a transient basis (e.g., increased lymphocyte numbers and increased NK cell activity) [129]. Physical stress associated with tissue injury (e.g., trauma, burns, surgery) is generally characterized by suppressed immune function. $CD4^+$

Table 4.1 Immunologic changes during stress

Type of stress	Parameter	Functional impact of change
Physical (e.g., surgical, trauma, burns)	↓ T-cell number and function	↑ Post-op infections
	↓ NK cell number and function	Delayed wound healing
	↓ PMN function	
	↑ Inflammatory cytokines	
Psychological (e.g., academic exams, major life events, caregiving, spaceflight)	↓ T-cell function	↑ Herpesvirus reactivation
	↓ NK cell function	Delayed wound healing
	↓ Th1 cytokines (e.g., IL-2)	↓ Vaccine responses
	↑ Th2 cytokines (e.g., IL-10)	

and $CD8^+$ cells have been reported to decrease in number [130–132], and T cell activation is decreased [133]. Mitogen-induced lymphocyte proliferation is decreased after surgery and trauma [134–136], and anergy is increased [137]. The presence of anergy has been associated with an increased incidence of postoperative infections [137]. Neutrophil function is adversely affected by surgery, with decreased chemotaxis [137, 138], decreased intracellular killing [139], and disruption of superoxide release [138, 139].

One of the most consistently demonstrated findings is decreased cytotoxicity of NK cells [129, 130, 140–142]. In murine studies, decreased NK activity following surgery is associated with increased tumor metastases [143]. Levels of IL-2, mRNA for IL-2, IFN IL-10, and IL-12 are decreased [131, 135, 137, 144], whereas IL-4 and IL-6 levels are generally increased [131, 133, 136, 137, 144], although some investigators have reported decreased IL-6 [133, 145]. Of clinical relevance are observations that the degree of immune suppression correlates positively with the duration of surgery and volume of blood loss [137, 139].

The mechanisms underlying immune suppression with physical stress are slowly becoming elucidated. Tissue damage results in release of inflammatory substances, including TNF, IL-1, and IL-2 [146–148]. Hypothalamic production of corticotropin-releasing hormone (CRF) and arginine vasopressin (AVP) is stimulated by the locally produced cytokines and by afferent nerve signals from the site of injury. CRF and AVP stimulate pituitary adrenocorticotropic hormone (ACTH) release and subsequent adrenal glucocorticoids, the latter two of which are also directly stimulated by the cytokines from the site of injury [149, 150]. Activation of the hypothalamic–pituitary–adrenal (HPA) axis stimulates transformation of uncommitted Th cells to Th2 cells and inhibits transformation to Th1 cells [151]. The cellular immune responses are thus suppressed partly due to a lack of Th1 cells. The cytokines secreted by the Th2 cells (e.g., IL-1, IL-6, TNF-α) further stimulate the HPA axis and glucocorticoid production [152] and subsequently cause immune suppression [153, 154]. Given the extensive age-related changes in immunity, it is not surprising that old age in surgical patients has been associated with increased postoperative immune suppression and septic complications [139]. It is interesting to speculate that postsurgical immune suppression might be less pronounced in the elderly than expected because of decreased sensitivity to glucocorticoids [76], as mentioned previously.

Psychological Stress

In addition to physical stress from trauma or surgery, psychological stress can have a significant impact on immune system function. Complex and direct links have been described between the immune system and the perceptual capabilities of the central nervous system. Ader and Cohen demonstrated that it was even possible to condition specific immune responses with sensory cues [47]. In a series of taste-aversion learning experiments in rats, saccharin water was initially administered to the animals along with a dose of cyclophosphamide. The rats were subsequently injected with sheep red blood cells with or without readministration of the saccharin solution. Animals who received the saccharin along with the injection had profound suppression of the hemagglutinin response to sheep red blood cells [47].

Carefully controlled experiments with rodents and primates have demonstrated the neurohumorally mediated effects of stress on the immune system [155, 156]. Similar findings are seen in cross-sectional studies with humans, though it is impossible to achieve the same degree of control as in the animal studies. Clusters of illness, from the common cold to cancer, have been reported to occur around the time of major life changes [157]. Strong negative correlations have been seen between loneliness and the proliferative response of lymphocytes to mitogens, NK cell activity, and DNA splicing and repair [157, 158]. We found that healthy old adults with a strong social support system had greater total lymphocyte counts and a stronger mitogen-induced proliferation of lymphocytes than those without a close confidant [159].

Studies of individuals in "naturally occurring" stressful situations have also demonstrated links to suppressed immune function and illness. Mitogen-induced lymphocyte proliferation is suppressed after bereavement [160] and with depression [161]. The stress of taking final examinations has been correlated with recurrence of cold sores, rises in serum antibody titers against herpes simplex type I virus [162], and decreased proliferation of memory T cells [163]. Caregiving for a demented spouse is associated with a poor response to influenza vaccination [164]. Lymphocytes from the caregivers produced less IL-1β and IL-2 when stimulated with influenza virus in vitro compared to age-matched, non-care-giving controls [164]. Caregivers displayed slower wound healing after skin biopsy than did matched controls [165].

Spaceflight

Many studies have reported similarities between spaceflight and aging. The average age of NASA astronauts is early to mid 40s [166–169]. In 1998, however, former Senator John Glenn flew on STS-95 at the age of 77 as a payload specialist (PS2). This afforded a unique opportunity to compare the effects of stress and microgravity in an aged individual to those of six younger astronauts under identical spaceflight conditions. After the 9-day mission, blood and urine samples were collected and neuroendocrine and immune responses were compared to those before flight. As shown in Fig. 4.2, variable levels of plasma and urinary cortisol were observed

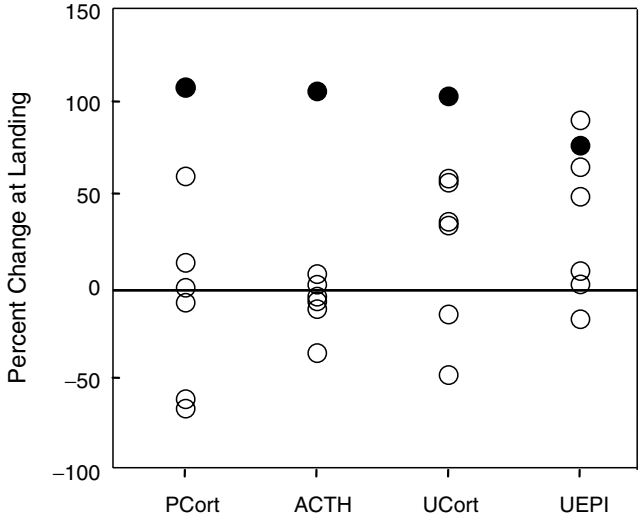


Figure 4.2 Postflight change in plasma cortisol (PCort), ACTH, urinary cortisol (UCort) and urinary epinephrine (UEPI). *Filled circles* indicate values for PS2. *Open circles* indicate individual values for the remaining six STS-95 crewmembers. Data are expressed as the percent change at landing as compared to L-10 values.

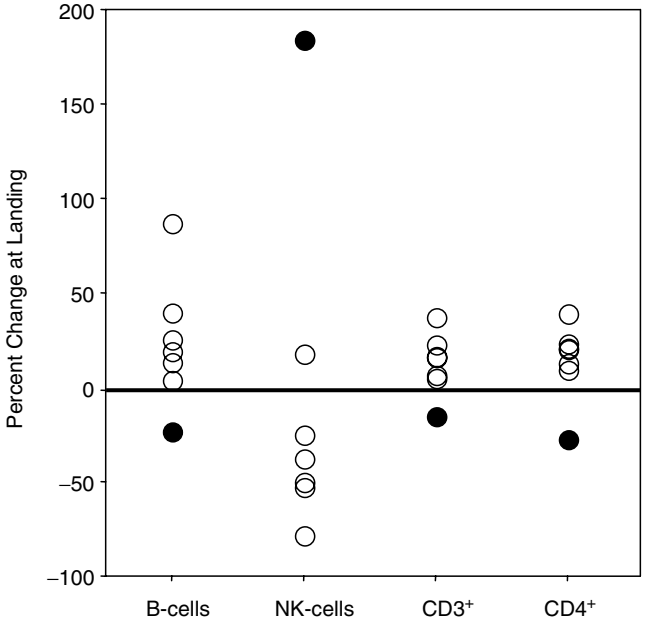


Figure 4.3 Postflight change in circulating lymphocytes. *Filled circles* indicate values for PS2. *Open circles* indicate individual values for the remaining six STS-95 crewmembers. Data are expressed as the percent change at landing as compared to L-10 values.

after spaceflight for all seven crew members. However, PS2 had the greatest increase in both plasma and urinary cortisol. Little change was found in ACTH for the younger astronauts, but once again a significant increase was found in PS2. Postflight levels of urinary epinephrine were mostly increased for the seven astronauts. Again, the aged astronaut had one of the highest epinephrine levels.

Given prior studies of psychological and physical stress on circulating leukocytes and lymphocytes, it would be expected that spaceflight would also result in significant changes in these white blood cell populations. As expected, significant increases in neutrophils were found postflight for all seven astronauts [170]. Excluding PS2 from data analysis, there was a significant increase in circulating B-cells (Fig. 4.3). A non-significant decrease was found in NK cells at landing, while significant increases were found in $CD3^+$ T-cells and $CD4^+$ T-cells. Notably, the magnitude (≥20% difference) and the direction of the shift in lymphocyte subsets for PS2 was opposite from that of the other six crew members. Given the recent explosion in commercial spaceflight and associated opportunities for adults (both young and old) to fly in space, this will be an important area of future research.

Reactivation of Latent Herpesviruses: A Potential Role in Shaping the Aged Immune System

Herpesviruses commonly establish latent infections in the majority of adults. The best known members of this family include herpes simplex virus (HSV), VZV, cytomegalovirus (CMV), and Epstein-Barr virus (EBV). Herpesviruses are medically important viruses; HSV-1 infects 70–80% of all adults and is classically associated with oropharyngeal lesions such as cold sores, pharyngitis, and tonsillitis [171]. EBV infects over 85% of the adult population and is the causative agent of infectious mononucleosis, Burkitt's lymphoma, undifferentiated nasopharyngeal carcinoma, and diffuse polyclonal B-cell lymphoma [172]. Most CMV infections in adults are asymptomatic, but may result in an infectious mononucleosis-like syndrome, central nervous system infections, and febrile illnesses [173]. Notably, CMV infections can be severe in immunocompromised individuals such as AIDS and post transplant patients [174]. VZV causes chicken pox on primary infection and remains latent thereafter; VZV may reactivate resulting in episodes of zoster or "shingles" [175].

Recent work on has focused on herpesviruses, in particular CMV. Numbers of $CD8^+CD28^-$ T cells have been found to positively correlate with CMV seropositivity independent of age [176]. This correlation was also found in the OCTO study [177] as well as the subsequent NONA study [178].

The recent development of MHC tetramers, which allows direct detection of T cells carrying receptors for single peptide epitopes [179], has yielded new information on the way that CMV shapes the immune system. Using tetramers, numerous studies have demonstrated detectable levels of CMV-specific $CD8^+$ T cells present in both healthy and diseased individuals [180–184]. Notably, studies of CMV tetramer-positive cells

have demonstrated the following: (a) CMV tetramer-positive cells are mainly pp65-specific, owing to the fact that pp65 is the most abundant structural protein throughout CMV infection and it is regarded as the dominant antigen recognized by CD8 T cells [185, 186]; (b) the frequency of pp65 tetramer-positive cells can reach 25–50% in healthy individuals and are often present as oligoclonal expansions as determined by TCR-Vβ analysis [181, 187–189]; (c) CMV-specific T cells increase in direct proportion with age [189, 190]; and (d) pp65-positive cells are $CD28^{-}CD57^{+}$ indicating a fully differentiated effector T cell [178, 181, 187, 188, 191].

Importantly, high levels of CMV pp65-specific T cells may downregulate immune responses to other herpesviruses. Recently, Khan and coworkers [192] who found that CMV infection in the elderly impaired the CD8 T cell immunity against EBV, another important member of the herpesvirus family that is known to cause numerous diseases including carcinomas and lymphomas. The authors found aged related increases in the number of EBV-specific T-cells. However, the frequency of EBV-specific $CD8^{+}$ T cells never exceeded 3% in CMV seropositive individuals, whereas in CMV seronegative individuals it was a high as 14%. Additionally, they also found that the proportion of functional EBV-specific $CD8^{+}$ T cells was significantly lower than for CMV-specific $CD8^{+}$ T cells. This study confirmed an earlier report that also demonstrated reduced IFN-γ production by EBV-specific $CD8^{+}$ T cells in the elderly [193]. Subsequently, Vescovini and coworkers [194] showed that several elderly subjects had a predominance of $CD8^{+}$ T cells specific for EBV latent epitopes rather than lytic epitopes typically found in younger subjects. Collectively, these observations suggest a lack of immune control over EBV in the elderly.

It was not known until recently whether the clonally expanded herpesvirus-specific T-cells represented increased viral reactivation or simply reflected an accumulation over time. We showed for the first time direct evidence of increased viral reactivation in the elderly which included increased antiviral antibodies and increased viral load (EBV) in peripheral blood B-cells [195]. In addition, we found plasma viremia (EBV DNA), which was supported by a program of viral gene transcription (e.g., LMP-1, gp350) similar to that found in patients with infectious mononucleosis. CMV DNA was not found in peripheral blood mononuclear cells; however, we did frequently detect CMV DNA in urine. These results were accompanied by clonal expansions of $CD8^{+}$ and $CD4^{+}$ T-cells directed against EBV (Fig. 4.4) and CMV (Fig. 4.5).

Notably, recent reports have suggested a link between herpesviruses and inflammation. Elevated levels of CMV antibodies have been associated with increased IL-6 and TNF-α levels in older adults [196–198]. The EBV-encoded dUTPase has also been shown to upregulate TNF-α, IL-1β, and IL-6 [199, 200]. EBV and CMV infection also result in a clonal expansion of virus-specific $CD8^{+}$ T-cells [181, 187, 192, 195, 201]. Thus, activation or an increase in the numbers of virus-specific $CD8^{+}$ T-cells, as well as direct interaction with viral antigens, may result in increased levels of circulating inflammatory cytokines. Consistent with this notion, we found increased urinary IL-6 levels in elderly subjects with plasma viremia as compared to those without viremia (Fig. 4.6, unpublished data).

The increased levels of proinflammatory cytokines associated with herpesvirus infection may have important health consequences. CMV, and more recently, EBV have been implicated in the development of coronary artery disease [202, 203]. Strandberg and coworkers [204] found that HSV and CMV were associated with cognitive impairment in elderly adults with cardiovascular disease. A subsequent study identified CMV as a predictor of cognitive impairment even after controlling for numerous covariates including age, education, and health conditions [205]. In perhaps the most striking study, Wikby et al. [197] found that the immune risk phenotype, characterized in part by co-infection with EBV and CMV, was significantly associated with cognitive impairment; the individuals with cognitive impairment were all deceased at follow-up, which was attributed to allostatic overload due in part to multiple herpesvirus infections. Future studies are needed to investigate the role of herpesvirus reactivation in healthy aging.

Reversal of Age-Related Declines in Immune Function

When considering physiologic changes of aging it is important to keep in mind that the changes described do not appear to be synchronized with each other [2, 206]. Defects occur to varying degrees in different systems within a given individual, and immune modulatory substances may affect some systems and not others. It is increasingly clear that there are complex interactions between the nervous, endocrine, and immune systems, although no "global" mechanism has been found that might be the common underlying cause of immune senescence [207]. We conclude with a brief discussion of potential ways to stimulate a failing immune system in elderly persons and review a number of investigations reporting attenuation or reversal of surgically induced immune suppression in animals and humans.

One of the most obvious organ changes that occur with aging is involution of the thymus, loss of thymic hormones, and a subsequent decline in T cell function [208]. In humans and experimental animals, involution begins during adolescence; and the lymphatic mass, particularly in the cortical area, decreases with age [209]. These observations stimulated a number of experiments attempting to enhance lymphocyte function by reestablishing "young" levels of thymic hormone. Exposing lymphocytes of old individuals to thymic hormones in vivo or in vitro, or transplanting young thymic tissue into

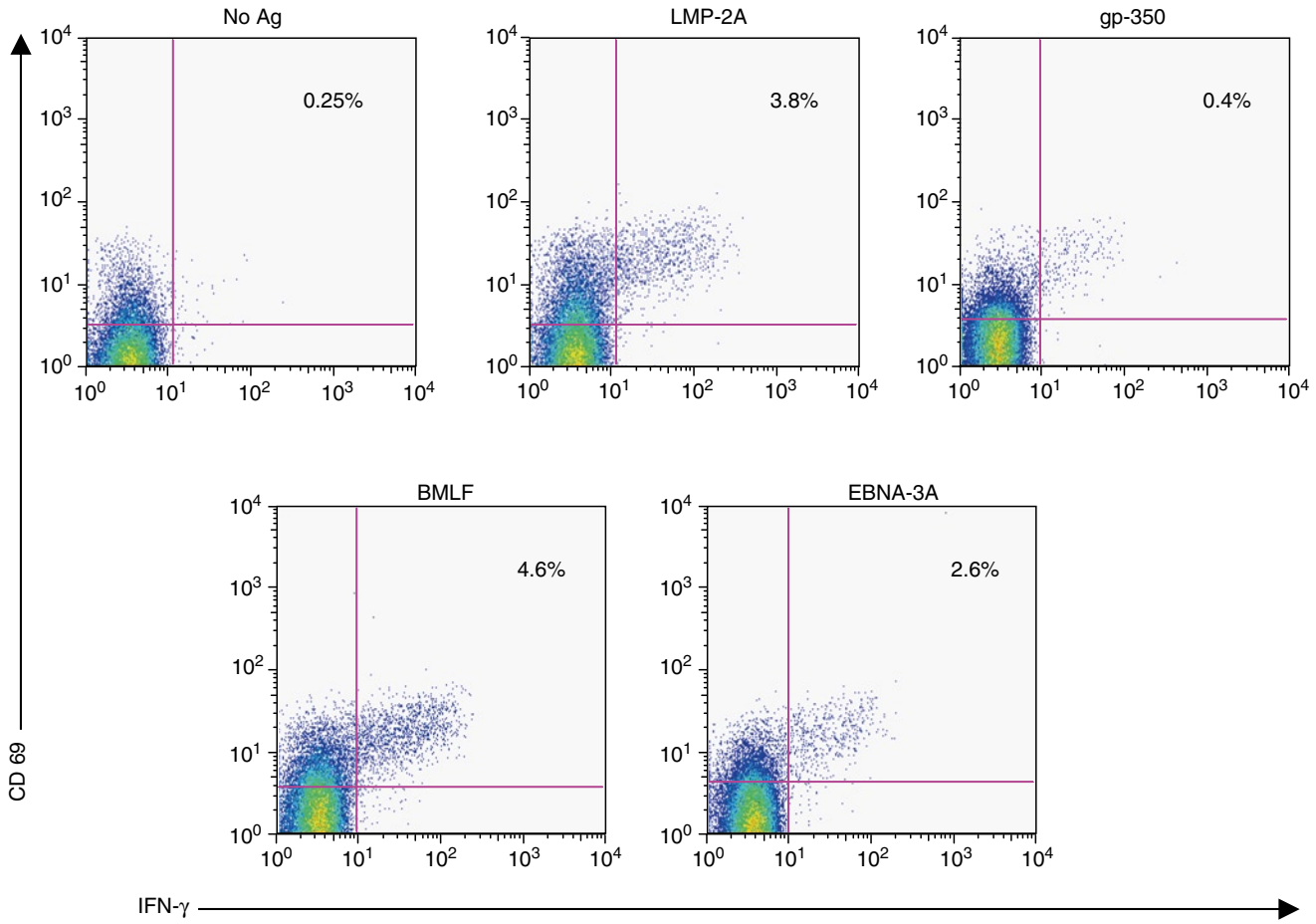
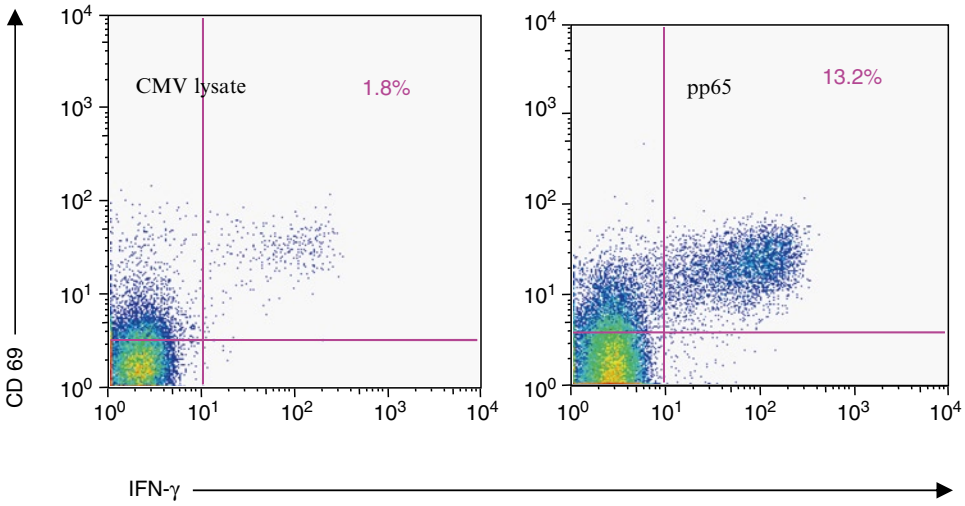


Figure 4.4 Frequency of EBV-specific CD8 T cells in healthy elderly subjects. Fifty thousand cells were included in each analysis. The frequency of $CD8^+$ T cells shown indicate the percentage of CD69 and IFN-γ-positive cells after pulsing with A*0201-restricted peptides to EBV lytic (gp-350; BMLF) and latent proteins (LMP-2A; EBNA-3A).

Figure 4.5 Frequency of CMV-specific CD4 and CD8 T cells in healthy elderly subjects. The frequency of CMV-specific $CD4^+$ or $CD8^+$ T cells shown indicate the percentage of CD69 and IFN-γ-positive cells after incubating with lysates from CMV-infected fibroblasts (CMV lysate) or A*0201-restricted peptides to CMV (pp65), respectively.



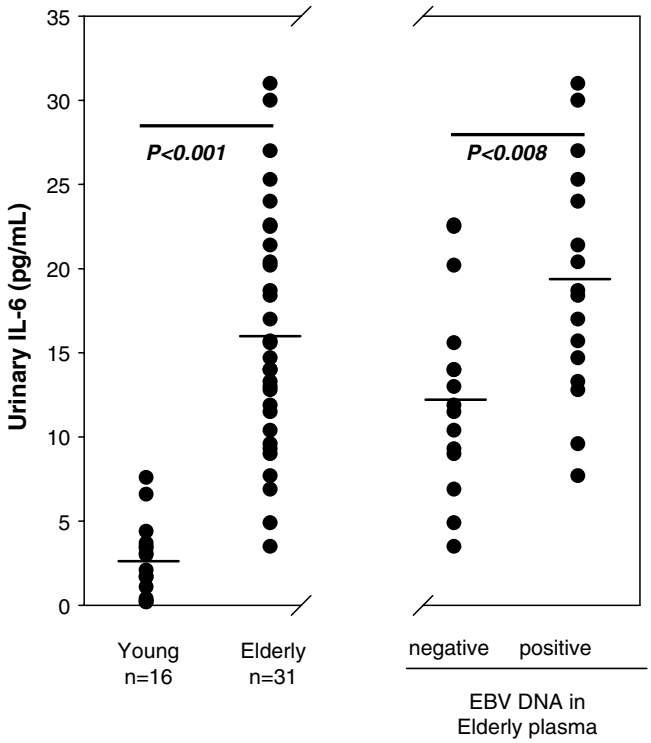


Figure 4.6 Levels of urinary IL-6 in: young versus elderly subjects, and elderly subjects with viremia versus non-viremic subjects.

old animals has resulted in at least partial restoration of immunity on a temporary basis [210–216]. IL-7 therapy alone in old mice can rejuvenate the thymus, but never to the point of the thymic size and output observed in young mice [217, 218]. Although production of IL-7 by thymic epithelial cells and dendritic cells clearly plays a role in murine thymocyte proliferation, attempts to show an age-related change in IL-7 in human studies have failed [219]. Other growth factors have been studied including IL-12, which appears to slow down thymic involution [220], while keratinocyte growth factor may provide critical survival signals for the thymic epithelium [221].

Other hormonal substances being studied for their potential to reverse age-related declines in immunity include melatonin, growth hormone, and adrenal androgens. The pineal hormone melatonin has free-radical-scavenging properties, and its production declines with age [222]. When melatonin has been administered to individuals with a variety of cancers, improved measures of immunity after surgery have been observed (increased number of lymphocytes, T cells, and Th cells) [223] as have partial tumor regression and enhanced 1-year survival of patients with metastatic solid tumors [224]. When melatonin is injected into old mice, it enhances antibody production and increases Th cell activity and IL-2 production [225].

Growth hormone (GH) and its precursor insulin-like growth factor-I (IGF-I) have immune-enhancing effects, including stimulation of phagocyte activity and cytokine production, both of which may help protect against bacterial infection [226]. Elderly patients with GH deficiency have low NK cell activity, but it can be at least partially restored in vitro by exposing NK cells to IGFI [227]. However, healthy old women who were not GH-deficient did not display changes in immune parameters after receiving 6 months of daily supplements [228]. VaraThorbeck et al. gave hypocaloric parenteral nutrition with or without growth hormone supplements to patients undergoing the stress of open cholecystectomy [229]. Those receiving GH had improved responses to delayed hypersensitivity skin testing, a lower incidence of wound infection, and shorter duration of hospital stay than the nonsupplemented group [229, 230]. In a series of experiments by Hinton et al., rats were given total parenteral nutrition with or without IGF-I and were subjected to the stress of a surgical incision or treatment with the synthetic glucocorticoid dexamethasone [231]. IGF-I treatment was associated with restoration of splenic B cell numbers in surgically stressed animals and increased mitogen-stimulated thymocyte proliferation and lymphyocyte-produced IL-6 in the dexamethasone-stressed animals [231].

The adrenal androgen dehydroepiandrosterone (DHEA) has been evaluated as a potential immune stimulant because it antagonizes the actions of cortisol, stimulating increased production of IL-2 and IFN-γ [153]. In vivo administration also augments antibody production by upregulating T cell subsets that are associated with increased antibody production [232]. When aged mice are primed with DHEA, the response to hepatitis B surface antigen vaccination and influenza vaccination is enhanced [233, 234], and the animals are more resistant to infection with influenza [234]. Old humans who received oral DHEA supplements before receiving influenza vaccine displayed a fourfold increase in hemagglutinin inhibition titers compared to elderly individuals who did not take supplements [235].

A few studies in mice have explored the effect of administering cytokines to animals after surgical or burn trauma. In one study, administration of the recombinant cytokine IL-1α 20 h after surgery showed restoration of suppressed NK and LAK cell activity [236]. In another study, mice with 20% burn injuries were treated in vivo with IL-12, which increased splenocyte production of IFN and significantly decreased mortality [144].

The 1990s saw a rapid accumulation of studies investigating links between nutrition and immune function (reviewed by Chandra [237] and Burns and Goodwin) [238]. Work on the effects of nutritional deprivation showed that starvation of experimental animals at young ages results in preservation of normal immune function into old age [238]. It is now known that caloric restriction rather than starvation can achieve the same results [239, 240]. The possibility that lesser amounts of caloric restriction supplemented with

essential nutrients might have similar beneficial effects in humans is being formally tested in primate models [241].

In contrast to findings in the experimental setting, nutritional deficiencies in the clinical setting are generally associated with poor immune responses [237]. In both nutritionally deficient and healthy elderly adults caloric, vitamin, and trace element supplementation has been associated with enhanced immune responses, better responses to vaccines, and fewer days of infectious illness [242, 243]. NK cell activity correlates negatively to the level of polyunsaturated fatty acids in the diet, but there was no effect on NK activity in men who ingested high levels of polyunsaturated fatty acids for 5 weeks [244]. Nutritional supplements given by the enteral or parenteral route have been associated with improved surgical outcomes, but the effects on immune function are not well characterized. Rats receiving total parenteral nutrition display deficits in gut immunity and lymphocyte proliferation [245–249]. In humans, most studies have focused on the role of lipid additives in depressing immune function [247, 249–253]. In contrast to the immune suppression associated with surgery, patients with closed head trauma who receive early parenteral nutrition have preserved or increased $CD4^+$ cell counts and improved lymphocyte proliferation to mitogen stimulation [254].

Antioxidants such as vitamins C (ascorbic acid) and E (tocopherol) have been studied intensively as potential "anti-aging" treatments [255, 256]. When healthy elderly subjects were supplemented with 400–800 IU of vitamin E, delayed-type hypersensitivity skin testing and in vitro lymphocyte production of IL-2 increased [257, 258]. Vitamin E may cause these effects via inhibition of PGE_2 or other suppressive factors [255] (see below). In vitro exposure of T cells from mice to another antioxidant, glutathione, enhanced T cell proliferation at all ages owing at least in part to blockade of eicosanoid production [259]. A placebo-controlled, double-blind trial of vitamin E and β-carotene supplementation in healthy old adults was associated with marked increases in various parameters of immunity, 50% fewer days with infection, and 40% fewer days taking antibiotics during the 1-year trial [242]. Although there is concern over the findings of a higher incidence of lung cancer in heavy smokers, taking β-carotene [260, 261], supplementation with vitamin E was not associated with an increased incidence of lung cancer [260].

Administering drugs or vaccines that in one way or another stimulate immune function are other potential ways of preventing age-related declines in immunity. Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit cyclooxygenase and reduce production of PGE_2, thus stimulating immune responses in vitro and in vivo [76]. For example, an early case report of two anergic patients with an acquired immunodeficiency state showed restoration of the response to delayed-type hypersensitivity skin testing after treatment with indomethacin [262]. The proportion of adults over age 75, displaying a fourfold rise in anti-A/Beijing antibody after influenza immunization was significantly increased by aspirin supplementation [263]. The use of NSAIDs might be especially relevant to elderly persons because their T cells are more sensitive to inhibition by PGE_2 [9].

Cyclooxygenase inhibitors might also reduce the excess autoantibody production that occurs with age [264] and stimulate primary antibody responses to new antigens [22]. Unfortunately, the use of NSAIDs is not without risk, and older adults are at greater risk for experiencing the potential adverse effects of medications.

Suppression of immunity due to psychological stress has been reversed with psychological interventions. Simple relaxation exercises and writing about traumatic events enhanced the measured immune response compared to that in control subjects [265, 266]. The duration of these effects and the mechanisms that underlie them are not fully understood.

References

1. Jackola DR, Ruger JK, Miller RA (1994) Age-associated changes in human T cell phenotype and function. Aging (Milano) 6(1):25–34
2. Miller RA (1991) Aging and immune function. Int Rev Cytol 124:187–215
3. Nijhuis EW, Remarque EJ, Hinloopen B et al (1994) Age-related increase in the fraction of CD27-CD4+ T cells and IL-4 production as a feature of CD4+ T cell differentiation in vivo. Clin Exp Immunol 96(3):528–534
4. Philosophe B, Miller RA (1990) Diminished calcium signal generation in subsets of T lymphocytes that predominate in old mice. J Gerontol 45(3):B87–B93
5. Xu X, Beckman I, Ahern M, Bradley J (1993) A comprehensive analysis of peripheral blood lymphocytes in healthy aged humans by flow cytometry. Immunol Cell Biol 71(Pt 6):549–557
6. Kudlacek S, Jahandideh-Kazempour S, Graninger W, Willvonseder R, Pietschmann P (1995) Differential expression of various T cell surface markers in young and elderly subjects. Immunobiology 192(3–4):198–204
7. Dobber R, Tielemans M, Nagelkerken L (1995) Enrichment for Th1 cells in the Mel-14+ CD4+ T cell fraction in aged mice. Cell Immunol 162(2):321–325
8. Dobber R, Tielemans M, de Weerd H, Nagelkerken L (1994) Mel14+ CD4+ T cells from aged mice display functional and phenotypic characteristics of memory cells. Int Immunol 6(8): 1227–1234
9. Goodwin JS, Messner RP (1979) Sensitivity of lymphocytes to prostaglandin E2 increases in subjects over age 70. J Clin Invest 64(2):434–439
10. Inkeles B, Innes JB, Kuntz MM, Kadish AS, Weksler ME (1977) Immunological studies of aging. III. Cytokinetic basis for the impaired response of lymphocytes from aged humans to plant lectins. J Exp Med 145(5):1176–1187
11. Murasko DM, Weiner P, Kaye D (1987) Decline in mitogen induced proliferation of lymphocytes with increasing age. Clin Exp Immunol 70(2):440–448
12. Roberts-Thomson IC, Whittingham S, Youngchaiyud U, Mackay IR (1974) Ageing, immune response, and mortality. Lancet 2(7877):368–370

13. Ernst DN, Weigle WO, McQuitty DN, Rothermel AL, Hobbs MV (1989) Stimulation of murine T cell subsets with anti-CD3 antibody. Age-related defects in the expression of early activation molecules. J Immunol 142(5):1413–1421
14. Kirschmann DA, Murasko DM (1992) Splenic and inguinal lymph node T cells of aged mice respond differently to polyclonal and antigen-specific stimuli. Cell Immunol 139(2):426–437
15. Vissinga C, Nagelkerken L, Zijlstra J, Hertogh-Huijbregts A, Boersma W, Rozing J (1990) A decreased functional capacity of CD4+ T cells underlies the impaired DTH reactivity in old mice. Mech Ageing Dev 53(2):127–139
16. Crawford J, Oates S, Wolfe LA 3rd, Cohen HJ (1989) An in vitro analogue of immune dysfunction with altered immunoglobulin production in the aged. J Am Geriatr Soc 37(12):1140–1146
17. Kishimoto S, Tomino S, Mitsuya H, Fujiwara H (1979) Age-related changes in suppressor functions of human T cells. J Immunol 123(4):1586–1593
18. Doria G, Mancini C, Frasca D, Adorini L (1987) Age restriction in antigen-specific immunosuppression. J Immunol 139(5):1419–1425
19. Grossmann A, Ledbetter JA, Rabinovitch PS (1989) Reduced proliferation in T lymphocytes in aged humans is predominantly in the CD8+ subset, and is unrelated to defects in transmembrane signaling which are predominantly in the CD4+ subset. Exp Cell Res 180(2):367–382
20. Russo C, Cherniack EP, Wali A, Weksler ME (1993) Age-dependent appearance of non-major histocompatibility complex-restricted helper T cells. Proc Natl Acad Sci USA 90(24):11718–11722
21. Hara H, Negoro S, Miyata S et al (1987) Age-associated changes in proliferative and differentiative response of human B cells and production of T cell-derived factors regulating B cell functions. Mech Ageing Dev 38(3):245–258
22. Hallgren HM, Buckley CE 3rd, Gilbertsen VA, Yunis EJ (1973) Lymphocyte phytohemagglutinin responsiveness, immunoglobulins and autoantibodies in aging humans. J Immunol 111(4): 1101–1107
23. Steinmann GG (1986) Changes in the human thymus during aging. Curr Top Pathol 75:43–88
24. Steinmann GG, Klaus B, Muller-Hermelink HK (1985) The involution of the ageing human thymic epithelium is independent of puberty. A morphometric study. Scand J Immunol 22(5):563–575
25. Douek DC, McFarland RD, Keiser PH et al (1998) Changes in thymic function with age and during the treatment of HIV infection. Nature 396(6712):690–695
26. Jamieson BD, Douek DC, Killian S et al (1999) Generation of functional thymocytes in the human adult. Immunity 10(5):569–575
27. Tyan ML (1977) Age-related decrease in mouse T cell progenitors. J Immunol 118(3):846–851
28. Hartwig M, Steinmann G (1994) On a causal mechanism of chronic thymic involution in man. Mech Ageing Dev 75(2):151–156
29. Aspinall R (1997) Age-associated thymic atrophy in the mouse is due to a deficiency affecting rearrangement of the TCR during intrathymic T cell development. J Immunol 158(7):3037–3045
30. Plum J, De Smedt M, Leclercq G, Verhasselt B, Vandekerckhove B (1996) Interleukin-7 is a critical growth factor in early human T-cell development. Blood 88(11):4239–4245
31. Effros RB (2004) Replicative senescence of CD8 T cells: potential effects on cancer immune surveillance and immunotherapy. Cancer Immunol Immunother 53(10):925–933
32. Lenschow DJ, Walunas TL, Bluestone JA (1996) CD28/B7 system of T cell costimulation. Annu Rev Immunol 14:233–258
33. Boucher N, Dufeu-Duchesne T, Vicaut E, Farge D, Effros RB, Schachter F (1998) CD28 expression in T cell aging and human longevity. Exp Gerontol 33(3):267–282
34. Effros RB (2000) Costimulatory mechanisms in the elderly. Vaccine 18(16):1661–1665
35. Holdorf AD, Kanagawa O, Shaw AS (2000) CD28 and T cell costimulation. Rev Immunogenet 2(2):175–184
36. Sansom DM (2000) CD28, CTLA-4 and their ligands: who does what and to whom? Immunology 101(2):169–177
37. Shimizu Y, van Seventer GA, Ennis E, Newman W, Horgan KJ, Shaw S (1992) Crosslinking of the T cell-specific accessory molecules CD7 and CD28 modulates T cell adhesion. J Exp Med 175(2):577–582
38. Effros RB, Allsopp R, Chiu CP et al (1996) Shortened telomeres in the expanded CD28-CD8+ cell subset in HIV disease implicate replicative senescence in HIV pathogenesis. AIDS 10(8): F17–F22
39. Campisi J (2001) From cells to organisms: can we learn about aging from cells in culture? Exp Gerontol 36(4–6):607–618
40. Posnett DN, Edinger JW, Manavalan JS, Irwin C, Marodon G (1999) Differentiation of human CD8 T cells: implications for in vivo persistence of CD8+ CD28− cytotoxic effector clones. Int Immunol 11(2):229–241
41. Posnett DN, Sinha R, Kabak S, Russo C (1994) Clonal populations of T cells in normal elderly humans: the T cell equivalent to "benign monoclonal gammapathy". J Exp Med 179(2):609–618
42. Goronzy JJ, Fulbright JW, Crowson CS, Poland GA, O'Fallon WM, Weyand CM (2001) Value of immunological markers in predicting responsiveness to influenza vaccination in elderly individuals. J Virol 75(24):12182–12187
43. Saurwein-Teissl M, Lung TL, Marx F et al (2002) Lack of antibody production following immunization in old age: association with CD8(+)CD28(−) T cell clonal expansions and an imbalance in the production of Th1 and Th2 cytokines. J Immunol 168(11): 5893–5899
44. Schirmer M, Goldberger C, Wurzner R et al (2002) Circulating cytotoxic CD8(+) CD28(-) T cells in ankylosing spondylitis. Arthritis Res 4(1):71–76
45. Cortesini R, LeMaoult J, Ciubotariu R, Cortesini NS (2001) CD8+CD28- T suppressor cells and the induction of antigen-specific, antigen-presenting cell-mediated suppression of Th reactivity. Immunol Rev 182:201–206
46. Ferguson FG, Wikby A, Maxson P, Olsson J, Johansson B (1995) Immune parameters in a longitudinal study of a very old population of Swedish people: a comparison between survivors and nonsurvivors. J Gerontol A Biol Sci Med Sci 50(6):B378–B382
47. Makinodan T (1977) Biology of aging: retrospect and prospect. In: Makinodan T, Yunis E (eds) Immunology and aging. Plenum, New York, pp 1–8
48. Ben-Yehuda A, Szabo P, Dyall R, Weksler ME (1994) Bone marrow declines as a site of B-cell precursor differentiation with age: relationship to thymus involution. Proc Natl Acad Sci USA 91(25): 11988–11992
49. Viale AC, Chies JA, Huetz F et al (1994) VH-gene family dominance in ageing mice. Scand J Immunol 39(2):184–188
50. Zharhary D (1988) Age-related changes in the capability of the bone marrow to generate B cells. J Immunol 141(6):1863–1869
51. Callard RE, Basten A, Blanden RV (1979) Loss of immune competence with age may be due to a qualitative abnormality in lymphocyte membranes. Nature 281(5728):218–220
52. Whisler RL, Newhouse YG, Bagenstose SE (1996) Age-related reductions in the activation of mitogen-activated protein kinases p44mapk/ERK1 and p42mapk/ERK2 in human T cells stimulated via ligation of the T cell receptor complex. Cell Immunol 168(2):201–210
53. 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 Ageing Dev 71(1–2):31–46
54. Whisler RL, Newhouse YG, Grants IS, Hackshaw KV (1995) Differential expression of the alpha- and beta-isoforms of protein kinase C in peripheral blood T and B cells from young and elderly adults. Mech Ageing Dev 77(3):197–211
55. Delafuente JC (1985) Immunosenescence. Clinical and pharmacologic considerations. Med Clin North Am 69(3):475–486

56. Arreaza EE, Gibbons JJ Jr, Siskind GW, Weksler ME (1993) Lower antibody response to tetanus toxoid associated with higher auto-anti-idiotypic antibody in old compared with young humans. Clin Exp Immunol 92(1):169–173
57. Whittingham S, Buckley JD, Mackay IR (1978) Factors influencing the secondary antibody response to flagellin in man. Clin Exp Immunol 34(2):170–178
58. De Greef GE, Van Staalduinen GJ, Van Doorninck H, Van Tol MJ, Hijmans W (1992) Age-related changes of the antigen-specific antibody formation in vitro and PHA-induced T-cell proliferation in individuals who met the health criteria of the Senieur protocol. Mech Ageing Dev 66(1):1–14
59. Ennist DL, Jones KH, St Pierre RL, Whisler RL (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(1):99–105
60. Whisler RL, Williams JW Jr, Newhouse YG (1991) Human B cell proliferative responses during aging. Reduced RNA synthesis and DNA replication after signal transduction by surface immunoglobulins compared to B cell antigenic determinants CD20 and CD40. Mech Ageing Dev 61(2):209–222
61. Hu A, Ehleiter D, Ben-Yehuda A et al (1993) Effect of age on the expressed B cell repertoire: role of B cell subsets. Int Immunol 5(9):1035–1039
62. Borghesi C, Nicoletti C (1994) Increase of cross(auto)-reactive antibodies after immunization in aged mice: a cellular and molecular study. Int J Exp Pathol 75(2):123–130
63. Miller C, Kelsoe G (1995) Ig VH hypermutation is absent in the germinal centers of aged mice. J Immunol 155(7):3377–3384
64. Delfraissy JF, Galanaud P, Dormont J, Wallon C (1980) Age-related impairment of the in vitro antibody response in the human. Clin Exp Immunol 39(1):208–214
65. Delfraissy JF, Galanaud P, Wallon C, Balavoine JF, Dormont J (1982) Abolished in vitro antibody response in elderly: exclusive involvement of prostaglandin-induced T suppressor cells. Clin Immunol Immunopathol 24(3):377–385
66. McLachlan JA, Serkin CD, Morrey-Clark KM, Bakouche O (1995) Immunological functions of aged human monocytes. Pathobiology 63(3):148–159
67. Izumi-Hisha H, Ito Y, Sugimoto K, Oshima H, Mori KJ (1990) Age-related decrease in the number of hemopoietic stem cells and progenitors in senescence accelerated mice. Mech Ageing Dev 56(1):89–97
68. Danon D, Kowatch MA, Roth GS (1989) Promotion of wound repair in old mice by local injection of macrophages. Proc Natl Acad Sci USA 86(6):2018–2020
69. Szakal AK, Kapasi ZF, Masuda A, Tew JG (1992) Follicular dendritic cells in the alternative antigen transport pathway: microenvironment, cellular events, age and retrovirus related alterations. Semin Immunol 4(4):257–265
70. Beckman I, Dimopoulos K, Xu XN, Bradley J, Henschke P, Ahern M (1990) T cell activation in the elderly: evidence for specific deficiencies in T cell/accessory cell interactions. Mech Ageing Dev 51(3):265–276
71. McLachlan JA, Serkin CD, Morrey KM, Bakouche O (1995) Antitumoral properties of aged human monocytes. J Immunol 154(2):832–843
72. Ho SP, Kramer KE, Ershler WB (1990) Effect of host age upon interleukin-2-mediated anti-tumor responses in a murine fibrosarcoma model. Cancer Immunol Immunother 31(3):146–150
73. Itoh H, Abo T, Sugawara S, Kanno A, Kumagai K (1988) Age-related variation in the proportion and activity of murine liver natural killer cells and their cytotoxicity against regenerating hepatocytes. J Immunol 141(1):315–323
74. Kutza J, Kaye D, Murasko DM (1995) Basal natural killer cell activity of young versus elderly humans. J Gerontol A Biol Sci Med Sci 50(3):B110–B116
75. Kutza J, Murasko DM (1994) Effects of aging on natural killer cell activity and activation by interleukin-2 and IFN-alpha. Cell Immunol 155(1):195–204
76. Goodwin JS, Webb DR (1980) Regulation of the immune response by prostaglandins. Clin Immunol Immunopathol 15(1):106–122
77. Goodwin JS (1982) Changes in lymphocyte sensitivity to prostaglandin E, histamine, hydrocortisone, and X irradiation with age: studies in a healthy elderly population. Clin Immunol Immunopathol 25(2):243–251
78. Hayek MG, Meydani SN, Meydani M, Blumberg JB (1994) Age differences in eicosanoid production of mouse splenocytes: effects on mitogen-induced T-cell proliferation. J Gerontol 49(5): B197–B207
79. Beharka AA, Wu D, Han SN, Meydani SN (1997) Macrophage prostaglandin production contributes to the age-associated decrease in T cell function which is reversed by the dietary antioxidant vitamin E. Mech Ageing Dev 93(1–3):59–77
80. Riancho JA, Zarrabeitia MT, Amado JA, Olmos JM, Gonzalez-Macias J (1994) Age-related differences in cytokine secretion. Gerontology 40(1):8–12
81. Del Prete G, Maggi E, Romagnani S (1994) Human Th1 and Th2 cells: functional properties, mechanisms of regulation, and role in disease. Lab Invest 70(3):299–306
82. Romagnani S (1992) Induction of TH1 and TH2 responses: a key role for the 'natural' immune response? Immunol Today 13(10): 379–381
83. Goonewardene IM, Murasko DM (1993) Age associated changes in mitogen induced proliferation and cytokine production by lymphocytes of the long-lived brown Norway rat. Mech Ageing Dev 71(3):199–212
84. Hara H, Tanaka T, Negoro S et al (1988) Age-related changes of expression of IL-2 receptor subunits and kinetics of IL-2 internalization in T cells after mitogenic stimulation. Mech Ageing Dev 45(2):167–175
85. McElhaney JE, Beattie BL, Devine R, Grynoch R, Toth EL, Bleackley RC (1990) Age-related decline in interleukin 2 production in response to influenza vaccine. J Am Geriatr Soc 38(6):652–658
86. Chopra RK, Holbrook NJ, Powers DC, McCoy MT, Adler WH, Nagel JE (1989) Interleukin 2, interleukin 2 receptor, and interferon-gamma synthesis and mRNA expression in phorbol myristate acetate and calcium ionophore A23187-stimulated T cells from elderly humans. Clin Immunol Immunopathol 53(2 Pt 1): 297–308
87. Negoro S, Hara H, Miyata S et al (1986) Mechanisms of age-related decline in antigen-specific T cell proliferative response: IL-2 receptor expression and recombinant IL-2 induced proliferative response of purified Tac-positive T cells. Mech Ageing Dev 36(3):223–241
88. Vissinga C, Hertogh-Huijbregts A, Rozing J, Nagelkerken L (1990) Analysis of the age-related decline in alloreactivity of CD4+ and CD8+ T cells in CBA/RIJ mice. Mech Ageing Dev 51(2):179–194
89. Ajitsu S, Mirabella S, Kawanishi H (1990) In vivo immunologic intervention in age-related T cell defects in murine gut-associated lymphoid tissues by IL2. Mech Ageing Dev 54(2):163–183
90. Hobbs MV, Ernst DN, Torbett BE et al (1991) Cell proliferation and cytokine production by CD4+ cells from old mice. J Cell Biochem 46(4):312–320
91. Bradley SF, Vibhagool A, Kunkel SL, Kauffman CA (1989) Monokine secretion in aging and protein malnutrition. J Leukoc Biol 45(6):510–514
92. Molteni M, Della Bella S, Mascagni B et al (1994) Secretion of cytokines upon allogeneic stimulation: effect of aging. J Biol Regul Homeost Agents 8(2):41–47
93. Li SP, Miller RA (1993) Age-associated decline in IL-4 production by murine T lymphocytes in extended culture. Cell Immunol 151(1):187–195
94. Dobber R, Tielemans M, Nagelkerken L (1995) The in vivo effects of neutralizing antibodies against IFN-gamma, IL-4, or IL-10 on the humoral immune response in young and aged mice. Cell Immunol 160(2):185–192

95. Burns EA, L'Hommedieu GD, Cunning JL, Goodwin JS (1994) Effects of interleukin-4 on antigen-specific antibody synthesis by lymphocytes from old and young adults. Lymphokine Cytokine Res 13(4):227–231
96. Candore G, Di Lorenzo G, Melluso M et al (1993) Gamma-Interferon, interleukin-4 and interleukin-6 in vitro production in old subjects. Autoimmunity 16(4):275–280
97. Nagelkerken L, Hertogh-Huijbregts A, Dobber R, Drager A (1991) Age-related changes in lymphokine production related to a decreased number of CD45RBhi CD4+ T cells. Eur J Immunol 21(2):273–281
98. Ballou SP, Lozanski FB, Hodder S et al (1996) Quantitative and qualitative alterations of acute-phase proteins in healthy elderly persons. Age Ageing 25(3):224–230
99. Bruunsgaard H, Andersen-Ranberg K, Jeune B, Pedersen AN, Skinhoj P, Pedersen BK (1999) A high plasma concentration of TNF-alpha is associated with dementia in centenarians. J Gerontol A Biol Sci Med Sci 54(7):M357–M364
100. Catania A, Airaghi L, Motta P et al (1997) Cytokine antagonists in aged subjects and their relation with cellular immunity. J Gerontol A Biol Sci Med Sci 52(2):B93–B97
101. Bruunsgaard H, Pedersen M, Pedersen BK (2001) Aging and proinflammatory cytokines. Curr Opin Hematol 8(3):131–136
102. O'Mahony L, Holland J, Jackson J, Feighery C, Hennessy TP, Mealy K (1998) Quantitative intracellular cytokine measurement: age-related changes in proinflammatory cytokine production. Clin Exp Immunol 113(2):213–219
103. Saurwein-Teissl M, Blasko I, Zisterer K, Neuman B, Lang B, Grubeck-Loebenstein B (2000) An imbalance between pro- and anti-inflammatory cytokines, a characteristic feature of old age. Cytokine 12(7):1160–1161
104. Roubenoff R, Harris TB, Abad LW, Wilson PW, Dallal GE, Dinarello CA (1998) Monocyte cytokine production in an elderly population: effect of age and inflammation. J Gerontol A Biol Sci Med Sci 53(1):M20–M26
105. Goodwin JS (1995) Decreased immunity and increased morbidity in the elderly. Nutr Rev 53(4 Pt 2):S41–S44, discussion S44–S46
106. Bender BS, Nagel JE, Adler WH, Andres R (1986) Absolute peripheral blood lymphocyte count and subsequent mortality of elderly men. The Baltimore Longitudinal Study of Aging. J Am Geriatr Soc 34(9):649–654
107. Wayne SJ, Rhyne RL, Garry PJ, Goodwin JS (1990) Cell-mediated immunity as a predictor of morbidity and mortality in subjects over 60. J Gerontol 45(2):M45–M48
108. Goodwin JS, Searles RP, Tung KS (1982) Immunological responses of healthy elderly population. Clin Exp Immunol 48(2): 403–410
109. Murasko DM, Weiner P, Kaye D (1988) Association of lack of mitogen-induced lymphocyte proliferation with increased mortality in the elderly. Aging Immunol Infect Dis 1:1–6
110. Burns EA, Goodwin JS (1990) Immunology and infectious disease. In: Cassel CK, Riesenberg DE, Sorensen LB, Walsh JR (eds) Geriatric medicine, 2nd edn. Springer, New York, pp 312–329
111. Sullivan KM, Monto AS, Longini IM Jr (1993) Estimates of the US health impact of influenza. Am J Public Health 83(12): 1712–1716
112. Ben-Yehuda A, Ehleiter D, Hu AR, Weksler ME (1993) Recombinant vaccinia virus expressing the PR/8 influenza hemagglutinin gene overcomes the impaired immune response and increased susceptibility of old mice to influenza infection. J Infect Dis 168(2):352–357
113. Fagiolo U, Amadori A, Cozzi E et al (1993) Humoral and cellular immune response to influenza virus vaccination in aged humans. Aging (Milano) 5(6):451–458
114. Kutza J, Gross P, Kaye D, Murasko DM (1996) Natural killer cell cytotoxicity in elderly humans after influenza immunization. Clin Diagn Lab Immunol 3(1):105–108
115. Swenson CD, Cherniack EP, Russo C, Thorbecke GJ (1996) IgD-receptor up-regulation on human peripheral blood T cells in response to IgD in vitro or antigen in vivo correlates with the antibody response to influenza vaccination. Eur J Immunol 26(2):340–344
116. Remarque EJ, van Beek WC, Ligthart GJ et al (1993) Improvement of the immunoglobulin subclass response to influenza vaccine in elderly nursing-home residents by the use of high-dose vaccines. Vaccine 11(6):649–654
117. Gross PA, Quinnan GV, Rodstein M et al (1988) Association of influenza immunization with reduction in mortality in an elderly population. A prospective study. Arch Intern Med 148(3):562–565
118. Smith NM, Bresee JS, Shay DK, Uyeki TM, Cox NJ, Strikas RA (1997) Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 46(RR-9):1–25
119. Stein BE (1993) Adult vaccinations: protecting your patients from avoidable illness. Geriatrics 48(9):46, 49–52, 55
120. Sims RV, Steinmann WC, McConville JH, King LR, Zwick WC, Schwartz JS (1988) The clinical effectiveness of pneumococcal vaccine in the elderly. Ann Intern Med 108(5):653–657
121. Stead WW, Lofgren JP, Warren E, Thomas C (1985) Tuberculosis as an endemic and nosocomial infection among the elderly in nursing homes. N Engl J Med 312(23):1483–1487
122. Stead WW, To T (1987) The significance of the tuberculin skin test in elderly persons. Ann Intern Med 107(6):837–842
123. Cooper AM, Callahan JE, Griffin JP, Roberts AD, Orme IM (1995) Old mice are able to control low-dose aerogenic infections with Mycobacterium tuberculosis. Infect Immun 63(9):3259–3265
124. Orme IM (1993) The response of macrophages from old mice to Mycobacterium tuberculosis and its products. Aging Immunol Infect Dis 4:187–195
125. Ragozzino MW, Melton LJ 3rd, Kurland LT, Chu CP, Perry HO (1982) Population-based study of herpes zoster and its sequelae. Medicine (Baltimore) 61(5):310–316
126. Donahue JG, Choo PW, Manson JE, Platt R (1995) The incidence of herpes zoster. Arch Intern Med 155(15):1605–1609
127. Burke BL, Steele RW, Beard OW, Wood JS, Cain TD, Marmer DJ (1982) Immune responses to varicella-zoster in the aged. Arch Intern Med 142(2):291–293
128. Ragozzino MW, Melton LJ 3rd, Kurland LT, Chu CP, Perry HO (1982) Risk of cancer after herpes zoster: a population-based study. N Engl J Med 307(7):393–397
129. Pedersen BK, Kappel M, Klokker M, Nielsen HB, Secher NH (1994) The immune system during exposure to extreme physiologic conditions. Int J Sports Med 15(Suppl 3):S116–S121
130. Tonnesen E, Brinklov MM, Christensen NJ, Olesen AS, Madsen T (1987) Natural killer cell activity and lymphocyte function during and after coronary artery bypass grafting in relation to the endocrine stress response. Anesthesiology 67(4):526–533
131. Vallina VL, Velasco JM (1996) The influence of laparoscopy on lymphocyte subpopulations in the surgical patient. Surg Endosc 10(5):481–484
132. Zedler S, Faist E, Ostermeier B, von Donnersmarck GH, Schildberg FW (1997) Postburn constitutional changes in T-cell reactivity occur in CD8+ rather than in CD4+ cells. J Trauma 42(5):872–880, discussion 880–871
133. Horgan AF, Mendez MV, O'Riordain DS, Holzheimer RG, Mannick JA, Rodrick ML (1994) Altered gene transcription after burn injury results in depressed T-lymphocyte activation. Ann Surg 220(3):342–351, discussion 351–342
134. Keel M, Schregenberger N, Steckholzer U et al (1996) Endotoxin tolerance after severe injury and its regulatory mechanisms. J Trauma 41(3):430–437, discussion 437–438
135. Miller-Graziano CL, De AK, Kodys K (1995) Altered IL-10 levels in trauma patients' M phi and T lymphocytes. J Clin Immunol 15(2):93–104

136. Wlaszczyk A, Adamik B, Durek G, Kubler A, Zimecki M (1996) Immunological status of patients subjected to cardiac surgery: serum levels of interleukin 6 and tumor necrosis factor alpha and the ability of peripheral blood mononuclear cells to proliferate and produce these cytokines in vitro. Arch Immunol Ther Exp (Warsz) 44(4):225–234
137. Meakins JL (1989) Host defense mechanisms in surgical patients: effect of surgery and trauma. Acta Chir Scand Suppl 550:43–51, discussion 51–43
138. Redmond HP, Watson RW, Houghton T, Condron C, Watson RG, Bouchier-Hayes D (1994) Immune function in patients undergoing open vs laparoscopic cholecystectomy. Arch Surg 129(12):1240–1246
139. Shigemitsu Y, Saito T, Kinoshita T, Kobayashi M (1992) Influence of surgical stress on bactericidal activity of neutrophils and complications of infection in patients with esophageal cancer. J Surg Oncol 50(2):90–97
140. Blazar BA, Rodrick ML, O'Mahony JB et al (1986) Suppression of natural killer-cell function in humans following thermal and traumatic injury. J Clin Immunol 6(1):26–36
141. Pollock RE, Lotzova E, Stanford SD (1991) Mechanism of surgical stress impairment of human perioperative natural killer cell cytotoxicity. Arch Surg 126(3):338–342
142. Pollock RE, Lotzova E, Stanford SD (1992) Surgical stress impairs natural killer cell programming of tumor for lysis in patients with sarcomas and other solid tumors. Cancer 70(8):2192–2202
143. Oka M, Hazama S, Suzuki M et al (1994) Depression of cytotoxicity of nonparenchymal cells in the liver after surgery. Surgery 116(5):877–882
144. O'Sullivan ST, Lederer JA, Horgan AF, Chin DH, Mannick JA, Rodrick ML (1995) Major injury leads to predominance of the T helper-2 lymphocyte phenotype and diminished interleukin-12 production associated with decreased resistance to infection. Ann Surg 222(4):482–490, discussion 490–482
145. Trokel MJ, Bessler M, Treat MR, Whelan RL, Nowygrod R (1994) Preservation of immune response after laparoscopy. Surg Endosc 8(12):1385–1387, discussion 1387–1388
146. Hauser CJ, Zhou X, Joshi P et al (1997) The immune microenvironment of human fracture/soft-tissue hematomas and its relationship to systemic immunity. J Trauma 42(5):895–903, discussion 903–894
147. Traynor C, Hall GM (1981) Endocrine and metabolic changes during surgery: anaesthetic implications. Br J Anaesth 53(2):153–160
148. Wilmore DW (1991) Homeostasis: bodily changes in trauma and surgery. In: Sabiston DC (ed) Textbook of surgery: the biological basis of modern surgical practice, 14th edn. Saunders, Philadelphia, pp 19–33
149. Besedovsky HO, del Rey A, Klusman I, Furukawa H, Monge Arditi G, Kabiersch A (1991) Cytokines as modulators of the hypothalamus-pituitary-adrenal axis. J Steroid Biochem Mol Biol 40(4-6):613–618
150. Gaillard RC (1994) Neuroendocrine-immune system interactions the immune-hypothalamo-pituitary-adrenal axis. Trends Endocrinol Metab 5(7):303–309
151. Rook GA, Hernandez-Pando R, Lightman SL (1994) Hormones, peripherally activated prohormones and regulation of the Th1/Th2 balance. Immunol Today 15(7):301–303
152. Blalock JE (1994) The syntax of immune-neuroendocrine communication. Immunol Today 15(11):504–511
153. Hassig A, Wen-Xi L, Stampfli K (1996) Stress-induced suppression of the cellular immune reactions: on the neuroendocrine control of the immune system. Med Hypotheses 46(6):551–555
154. Ottaviani E, Franceschi C (1996) The neuroimmunology of stress from invertebrates to man. Prog Neurobiol 48(4–5):421–440
155. Borysenko M, Borysenko J (1982) Stress, behavior, and immunity: animal models and mediating mechanisms. Gen Hosp Psychiatry 4(1):59–67
156. Rosenberg LT, Coe CL, Levine S (1982) Complement levels in the squirrel monkey (Saimiri sciureus). Lab Anim Sci 32(4):371–372
157. Minter RE, Kimball CP (1978) Life events and illness onset: a review. Psychosomatics 19(6):334–339
158. Glaser R, Thorn BE, Tarr KL, Kiecolt-Glaser JK, D'Ambrosio SM (1985) Effects of stress on methyltransferase synthesis: an important DNA repair enzyme. Health Psychol 4(5):403–412
159. Thomas PD, Goodwin JM, Goodwin JS (1985) Effect of social support on stress-related changes in cholesterol level, uric acid level, and immune function in an elderly sample. Am J Psychiatry 142(6):735–737
160. Schleifer SJ, Keller SE, Camerino M, Thornton JC, Stein M (1983) Suppression of lymphocyte stimulation following bereavement. JAMA 250(3):374–377
161. Bartoloni C, Guidi L, Antico L et al (1991) Psychological status and immunological parameters of institutionalized aged. Panminerva Med 33(3):164–169
162. Glaser R, Kiecolt-Glaser JK, Speicher CE, Holliday JE (1985) Stress, loneliness, and changes in herpesvirus latency. J Behav Med 8(3):249–260
163. Glaser R, Pearson GR, Bonneau RH, Esterling BA, Atkinson C, Kiecolt-Glaser JK (1993) Stress and the memory T-cell response to the Epstein-Barr virus in healthy medical students. Health Psychol 12(6):435–442
164. 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 USA 93(7):3043–3047
165. Kiecolt-Glaser JK, Marucha PT, Malarkey WB, Mercado AM, Glaser R (1995) Slowing of wound healing by psychological stress. Lancet 346(8984):1194–1196
166. Stowe RP, Pierson DL, Barrett AD (2001) Elevated stress hormone levels relate to Epstein-Barr virus reactivation in astronauts. Psychosom Med 63(6):891–895
167. Stowe RP, Pierson DL, Feeback DL, Barrett AD (2000) Stress-induced reactivation of Epstein-Barr virus in astronauts. Neuroimmunomodulation 8(2):51–58
168. Stowe RP, Sams CF, Mehta SK et al (1999) Leukocyte subsets and neutrophil function after short-term spaceflight. J Leukoc Biol 65(2):179–186
169. Stowe RP, Sams CF, Pierson DL (2003) Effects of mission duration on neuroimmune responses in astronauts. Aviat Space Environ Med 74(12):1281–1284
170. Stowe RP, Mehta SK, Ferrando AA, Feeback DL, Pierson DL (2001) Immune responses and latent herpesvirus reactivation in spaceflight. Aviat Space Environ Med 72(10):884–891
171. Miller CS, Danaher RJ, Jacob RJ (1998) Molecular aspects of herpes simplex virus I latency, reactivation, and recurrence. Crit Rev Oral Biol Med 9(4):541–562
172. Okano M, Thiele GM, Davis JR, Grierson HL, Purtilo DT (1988) Epstein-Barr virus and human diseases: recent advances in diagnosis. Clin Microbiol Rev 1(3):300–312
173. Alford CA, Britt WJ (1993) Cytomegalovirus. Raven, New York
174. Komanduri KV, Feinberg J, Hutchins RK et al (2001) Loss of cytomegalovirus-specific CD4+ T cell responses in human immunodeficiency virus type 1-infected patients with high CD4+ T cell counts and recurrent retinitis. J Infect Dis 183(8):1285–1289
175. Arvin AM (1996) Varicella-zoster virus. Clin Microbiol Rev 9(3):361–381
176. Looney RJ, Falsey A, Campbell D et al (1999) Role of cytomegalovirus in the T cell changes seen in elderly individuals. Clin Immunol 90(2):213–219
177. Olsson J, Wikby A, Johansson B, Lofgren S, Nilsson BO, Ferguson FG (2000) Age-related change in peripheral blood T-lymphocyte subpopulations and cytomegalovirus infection in the very old: the

Swedish longitudinal OCTO immune study. Mech Ageing Dev 121(1–3):187–201
178. Wikby A, Johansson B, Olsson J, Lofgren S, Nilsson BO, Ferguson F (2002) Expansions of peripheral blood CD8 T-lymphocyte subpopulations and an association with cytomegalovirus seropositivity in the elderly: the Swedish NONA immune study. Exp Gerontol 37(2–3):445–453
179. Altman JD, Moss PA, Goulder PJ et al (1996) Phenotypic analysis of antigen-specific T lymphocytes. Science 274(5284):94–96
180. Komanduri KV, Viswanathan MN, Wieder ED et al (1998) Restoration of cytomegalovirus-specific CD4+ T-lymphocyte responses after ganciclovir and highly active antiretroviral therapy in individuals infected with HIV-1. Nat Med 4(8):953–956
181. Gillespie GM, Wills MR, Appay V et al (2000) Functional heterogeneity and high frequencies of cytomegalovirus-specific CD8(+) T lymphocytes in healthy seropositive donors. J Virol 74(17): 8140–8150
182. Jin X, Demoitie MA, Donahoe SM et al (2000) High frequency of cytomegalovirus-specific cytotoxic T-effector cells in HLA-A*0201-positive subjects during multiple viral coinfections. J Infect Dis 181(1):165–175
183. Komanduri KV, Donahoe SM, Moretto WJ et al (2001) Direct measurement of CD4+ and CD8+ T-cell responses to CMV in HIV-1-infected subjects. Virology 279(2):459–470
184. Sester M, Sester U, Gartner B et al (2002) Sustained high frequencies of specific CD4 T cells restricted to a single persistent virus. J Virol 76(8):3748–3755
185. Wills MR, Carmichael AJ, Mynard K et al (1996) The human cytotoxic T-lymphocyte (CTL) response to cytomegalovirus is dominated by structural protein pp 65: frequency, specificity, and T-cell receptor usage of pp65-specific CTL. J Virol 70(11): 7569–7579
186. Kern F, Bunde T, Faulhaber N et al (2002) Cytomegalovirus (CMV) phosphoprotein 65 makes a large contribution to shaping the T cell repertoire in CMV-exposed individuals. J Infect Dis 185(12):1709–1716
187. Khan N, Shariff N, Cobbold M et al (2002) Cytomegalovirus seropositivity drives the CD8 T cell repertoire toward greater clonality in healthy elderly individuals. J Immunol 169(4):1984–1992
188. Lang KS, Moris A, Gouttefangeas C et al (2002) High frequency of human cytomegalovirus (HCMV)-specific CD8+ T cells detected in a healthy CMV-seropositive donor. Cell Mol Life Sci 59(6):1076–1080
189. Ouyang Q, Wagner WM, Wikby A et al (2003) Large numbers of dysfunctional CD8+ T lymphocytes bearing receptors for a single dominant CMV epitope in the very old. J Clin Immunol 23(4): 247–257
190. Komatsu H, Sierro S, Cuero AV, Klenerman P (2003) Population analysis of antiviral T cell responses using MHC class I-peptide tetramers. Clin Exp Immunol 134(1):9–12
191. Papagno L, Appay V, Sutton J et al (2002) Comparison between HIV- and CMV-specific T cell responses in long-term HIV infected donors. Clin Exp Immunol 130(3):509–517
192. 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(12): 7481–7489
193. Ouyang Q, Wagner WM, Walter S et al (2003) An age-related increase in the number of CD8+ T cells carrying receptors for an immunodominant Epstein-Barr virus (EBV) epitope is counteracted by a decreased frequency of their antigen-specific responsiveness. Mech Ageing Dev 124(4):477–485
194. Vescovini R, Telera A, Fagnoni FF et al (2004) Different contribution of EBV and CMV infections in very long-term carriers to age-related alterations of CD8+ T cells. Exp Gerontol 39(8): 1233–1243
195. Stowe RP, Kozlova EV, Yetman DL, Walling DM, Goodwin JS, Glaser R (2007) Chronic herpesvirus reactivation occurs in aging. Exp Gerontol 42(6):563–570
196. 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(25–26):3826–3836
197. Wikby A, Ferguson F, Forsey R et al (2005) An immune risk phenotype, cognitive impairment, and survival in very late life: impact of allostatic load in Swedish octogenarian and nonagenarian humans. J Gerontol A Biol Sci Med Sci 60(5):556–565
198. Wikby A, Nilsson BO, Forsey R et al (2006) The immune risk phenotype is associated with IL-6 in the terminal decline stage: findings from the Swedish NONA immune longitudinal study of very late life functioning. Mech Ageing Dev 127(8):695–704
199. Glaser R, Litsky ML, Padgett DA et al (2006) EBV-encoded dUTPase induces immune dysregulation: implications for the pathophysiology of EBV-associated disease. Virology 346(1): 205–218
200. Glaser R, Padgett DA, Litsky ML et al (2005) Stress-associated changes in the steady-state expression of latent Epstein-Barr virus: implications for chronic fatigue syndrome and cancer. Brain Behav Immun 19(2):91–103
201. Tan LC, Gudgeon N, Annels NE et al (1999) A re-evaluation of the frequency of CD8+ T cells specific for EBV in healthy virus carriers. J Immunol 162(3):1827–1835
202. Kendall TJ, Wilson JE, Radio SJ et al (1992) Cytomegalovirus and other herpesviruses: do they have a role in the development of accelerated coronary arterial disease in human heart allografts? J Heart Lung Transplant 11(3 Pt 2):S14–S20
203. Waldman WJ, Williams MV Jr, Lemeshow S et al (2007) Epstein-Barr virus-encoded dUTPase enhances proinflammatory cytokine production by macrophages in contact with endothelial cells: evidence for depression-induced atherosclerotic risk. Brain Behav Immun 22(2):215–223
204. Strandberg TE, Pitkala KH, Linnavuori KH, Tilvis RS (2003) Impact of viral and bacterial burden on cognitive impairment in elderly persons with cardiovascular diseases. Stroke 34(9):2126–2131
205. Aiello AE, Haan M, Blythe L, Moore K, Gonzalez JM, Jagust W (2006) The influence of latent viral infection on rate of cognitive decline over 4 years. J Am Geriatr Soc 54(7):1046–1054
206. Cinader B, Thorbecke GJ (1990) "Aging and the Immune System". Report on Workshop #94 held during the 7th international congress of immunology in Berlin on August 3, 1989. Aging Immunol Infect Dis 2:45–53
207. Fabris N (1990) A neuroendocrine-immune theory of aging. Int J Neurosci 51(3–4):373–375
208. Song L, Kim YH, Chopra RK et al (1993) Age-related effects in T cell activation and proliferation. Exp Gerontol 28(4-5):313–321
209. Lewis VM, Twomey JJ, Bealmear P, Goldstein G, Good RA (1978) Age, thymic involution, and circulating thymic hormone activity. J Clin Endocrinol Metab 47(1):145–150
210. Cillari E, Milano S, Perego R et al (1992) Modulation of IL-2, IFN-gamma, TNF-alpha and IL-4 production in mice of different ages by thymopentin. Int J Immunopharmacol 14(6):1029–1035
211. Duchateau J, Servais G, Vreyens R, Delespesse G, Bolla K (1985) Modulation of immune response in aged humans through different administration modes of thymopentin. Surv Immunol Res 4(Suppl 1):94–101
212. Ershler WB, Moore AL, Hacker MP, Ninomiya J, Naylor P, Goldstein AL (1984) Specific antibody synthesis in vitro II. Age-associated thymosin enhancement of antitetanus antibody synthesis. Immunopharmacology 8(2):69–77
213. Frasca D, Adorini L, Doria G (1987) Enhanced frequency of mitogen-responsive T cell precursors in old mice injected with thymosin alpha 1. Eur J Immunol 17(5):727–730

214. Goso C, Frasca D, Doria G (1992) Effect of synthetic thymic humoral factor (THF-gamma 2) on T cell activities in immunodeficient ageing mice. Clin Exp Immunol 87(3):346–351
215. Hirokawa K, Utsuyama M, Kasai M, Kurashima C (1992) Aging and immunity. Acta Pathol Jpn 42(8):537–548
216. Meroni PL, Barcellini W, Frasca D et al (1987) In vivo immunopotentiating activity of thymopentin in aging humans: increase of IL-2 production. Clin Immunol Immunopathol 42(2):151–159
217. Aspinall R (2006) T cell development, ageing and Interleukin-7. Mech Ageing Dev 127(6):572–578
218. Plum J, De Smedt M, Leclercq G (1993) Exogenous IL-7 promotes the growth of CD3-CD4-CD8-CD44+CD25+/- precursor cells and blocks the differentiation pathway of TCR-alpha beta cells in fetal thymus organ culture. J Immunol 150(7): 2706–2716
219. Henson SM, Pido-Lopez J, Aspinall R (2004) Reversal of thymic atrophy. Exp Gerontol 39(4):673–678
220. Li L, Hsu HC, Stockard CR et al (2004) IL-12 inhibits thymic involution by enhancing IL-7- and IL-2-induced thymocyte proliferation. J Immunol 172(5):2909–2916
221. Min D, Taylor PA, Panoskaltsis-Mortari A et al (2002) Protection from thymic epithelial cell injury by keratinocyte growth factor: a new approach to improve thymic and peripheral T-cell reconstitution after bone marrow transplantation. Blood 99(12): 4592–4600
222. Reiter RJ (1994) Pineal function during aging: attenuation of the melatonin rhythm and its neurobiological consequences. Acta Neurobiol Exp (Wars) 54(Suppl):31–39
223. Lissoni P, Brivio F, Brivio O et al (1995) Immune effects of preoperative immunotherapy with high-dose subcutaneous interleukin-2 versus neuroimmunotherapy with low-dose interleukin-2 plus the neurohormone melatonin in gastrointestinal tract tumor patients. J Biol Regul Homeost Agents 9(1):31–33
224. Lissoni P, Barni S, Fossati V et al (1995) A randomized study of neuroimmunotherapy with low-dose subcutaneous interleukin-2 plus melatonin compared to supportive care alone in patients with untreatable metastatic solid tumour. Support Care Cancer 3(3):194–197
225. Caroleo MC, Frasca D, Nistico G, Doria G (1992) Melatonin as immunomodulator in immunodeficient mice. Immunopharmacology 23(2):81–89
226. Saito H, Inoue T, Fukatsu K et al (1996) Growth hormone and the immune response to bacterial infection. Horm Res 45(1–2):50–54
227. Auernhammer CJ, Feldmeier H, Nass R, Pachmann K, Strasburger CJ (1996) Insulin-like growth factor I is an independent coregulatory modulator of natural killer (NK) cell activity. Endocrinology 137(12):5332–5336
228. Bonello RS, Marcus R, Bloch D, Strober S (1996) Effects of growth hormone and estrogen on T lymphocytes in older women. J Am Geriatr Soc 44(9):1038–1042
229. Vara-Thorbeck R, Guerrero JA, Rosell J, Ruiz-Requena E, Capitan JM (1993) Exogenous growth hormone: effects on the catabolic response to surgically produced acute stress and on postoperative immune function. World J Surg 17(4):530–537, discussion 537–538
230. Vara-Thorbeck R, Ruiz-Requena E, Guerrero-Fernandez JA (1996) Effects of human growth hormone on the catabolic state after surgical trauma. Horm Res 45(1–2):55–60
231. Hinton PS, Peterson CA, Lo HC, Yang H, McCarthy D, Ney DM (1995) Insulin-like growth factor-I enhances immune response in dexamethasone-treated or surgically stressed rats maintained with total parenteral nutrition. JPEN J Parenter Enteral Nutr 19(6): 444–452
232. Swenson CD, Gottesman SR, Belsito DV, Samanich KM, Edington J, Thorbecke GJ (1995) Relationship between humoral immunoaugmenting properties of DHEAS and IgD-receptor expression in young and aged mice. Ann N Y Acad Sci 774:249–258
233. Araneo BA, Woods ML 2nd, Daynes RA (1993) Reversal of the immunosenescent phenotype by dehydroepiandrosterone: hormone treatment provides an adjuvant effect on the immunization of aged mice with recombinant hepatitis B surface antigen. J Infect Dis 167(4):830–840
234. Danenberg HD, Ben-Yehuda A, Zakay-Rones Z, Friedman G (1995) Dehydroepiandrosterone (DHEA) treatment reverses the impaired immune response of old mice to influenza vaccination and protects from influenza infection. Vaccine 13(15):1445–1448
235. Araneo B, Dowell T, Woods ML, Daynes R, Judd M, Evans T (1995) DHEAS as an effective vaccine adjuvant in elderly humans. Proof-of-principle studies. Ann N Y Acad Sci 774: 232–248
236. Shen RN, Wu B, Lu L, Kaiser HE, Broxmeyer HE (1994) Recombinant human interleukin-1 alpha: a potent bio-immunomodifier in vivo in immunosuppressed mice induced by cyclophosphamide, retroviral infection and surgical stress. In Vivo 8(1):59–63
237. Chandra RK (1990) Nutrition is an important determinant of immunity in old age. Prog Clin Biol Res 326:321–334
238. Burns EA, Goodwin JS (1994) Aging: nutrition and immunity. In: Forse RA, Bell SJ, Blackburn GL (eds) Diet, nutrition and immunity. CRC, Boca Raton, FL, pp 57–72
239. Effros RB, Walford RL, Weindruch R, Mitcheltree C (1991) Influences of dietary restriction on immunity to influenza in aged mice. J Gerontol 46(4):B142–B147
240. Ershler WB, Sun WH, Binkley N et al (1993) Interleukin-6 and aging: blood levels and mononuclear cell production increase with advancing age and in vitro production is modifiable by dietary restriction. Lymphokine Cytokine Res 12(4):225–230
241. Kemnitz JW, Weindruch R, Roecker EB, Crawford K, Kaufman PL, Ershler WB (1993) Dietary restriction of adult male rhesus monkeys: design, methodology, and preliminary findings from the first year of study. J Gerontol 48(1):B17–B26
242. Chandra RK (1992) Effect of vitamin and trace-element supplementation on immune responses and infection in elderly subjects. Lancet 340(8828):1124–1127
243. Chandra RK, Puri S (1985) Nutritional support improves antibody response to influenza virus vaccine in the elderly. Br Med J (Clin Res Ed) 291(6497):705–706
244. Rasmussen LB, Kiens B, Pedersen BK, Richter EA (1994) Effect of diet and plasma fatty acid composition on immune status in elderly men. Am J Clin Nutr 59(3):572–577
245. Alverdy JA, Aoys E, Weiss-Carrington P, Burke DA (1992) The effect of glutamine-enriched TPN on gut immune cellularity. J Surg Res 52(1):34–38
246. Alverdy JC, Aoys E, Moss GS (1988) Total parenteral nutrition promotes bacterial translocation from the gut. Surgery 104(2):185–190
247. Hamawy KJ, Moldawer LL, Georgieff M et al (1985) The Henry M Vars Award. The effect of lipid emulsions on reticuloendothelial system function in the injured animal. JPEN J Parenter Enteral Nutr 9(5):559–565
248. Mainous M, Xu DZ, Lu Q, Berg RD, Deitch EA (1991) Oral-TPN-induced bacterial translocation and impaired immune defenses are reversed by refeeding. Surgery 110(2):277–283, discussion 283–274
249. Shou J, Lappin J, Daly JM (1994) Impairment of pulmonary macrophage function with total parenteral nutrition. Ann Surg 219(3):291–297
250. Gogos CA, Kalfarentzos FE, Zoumbos NC (1990) Effect of different types of total parenteral nutrition on T-lymphocyte subpopulations and NK cells. Am J Clin Nutr 51(1):119–122
251. Jensen GL, Mascioli EA, Seidner DL et al (1990) Parenteral infusion of long- and medium-chain triglycerides and reticuloendothelial system function in man. JPEN J Parenter Enteral Nutr 14(5):467–471

252. Salo M (1990) Inhibition of immunoglobulin synthesis in vitro by intravenous lipid emulsion (Intralipid). JPEN J Parenter Enteral Nutr 14(5):459–462
253. Sedman PC, Somers SS, Ramsden CW, Brennan TG, Guillou PJ (1991) Effects of different lipid emulsions on lymphocyte function during total parenteral nutrition. Br J Surg 78(11):1396–1399
254. Sacks GS, Brown RO, Teague D, Dickerson RN, Tolley EA, Kudsk KA (1995) Early nutrition support modifies immune function in patients sustaining severe head injury. JPEN J Parenter Enteral Nutr 19(5):387–392
255. Meydani M (1995) Vitamin E. Lancet 345(8943):170–175
256. Meydani M, Hayek M (1992) Vitamin E and immune response. In: Chandra RK (ed) Proceedings of international conference on nutrition and immunity. ARTS Biomedical, St. John's Newfoundland, pp 105–128
257. Meydani SN, Barklund MP, Liu S et al (1990) Vitamin E supplementation enhances cell-mediated immunity in healthy elderly subjects. Am J Clin Nutr 52(3):557–563
258. Meydani SN, Meydani M, Blumberg JB et al (1997) Vitamin E supplementation and in vivo immune response in healthy elderly subjects. A randomized controlled trial. JAMA 277(17): 1380–1386
259. Wu D, Meydani SN, Sastre J, Hayek M, Meydani M (1994) In vitro glutathione supplementation enhances interleukin-2 production and mitogenic response of peripheral blood mononuclear cells from young and old subjects. J Nutr 124(5): 655–663
260. Albanes D, Heinonen OP, Taylor PR et al (1996) Alpha-Tocopherol and beta-carotene supplements and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: effects of base-line characteristics and study compliance. J Natl Cancer Inst 88(21):1560–1570
261. Omenn GS, Goodman GE, Thornquist MD et al (1996) Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. J Natl Cancer Inst 88(21):1550–1559
262. Goodwin JS, Bankhurst AD, Murphy SA, Selinger DS, Messner RP, Williams RC Jr (1978) Partial reversal of the cellular immune defect in common variable immunodeficiency with indomethacin. J Clin Lab Immunol 1(3):197–199
263. Hsia J, Tang T, Parrott M, Rogalla K (1994) Augmentation of the immune response to influenza vaccine by acetylsalicylic acid: a clinical trial in a geriatric population. Methods Find Exp Clin Pharmacol 16(9):677–683
264. Ceuppens JL, Rodriguez MA, Goodwin JS (1982) Non-steroidal anti-inflammatory agent inhibit the synthesis of IgM rheumatoid factor in vitro. Lancet 1(8271):528–530
265. Kiecolt-Glaser JK, Glaser R, Williger D et al (1985) Psychosocial enhancement of immunocompetence in a geriatric population. Health Psychol 4(1):25–41
266. Pennebaker JW, Kiecolt-Glaser JK, Glaser R (1988) Disclosure of traumas and immune function: health implications for psychotherapy. J Consult Clin Psychol 56(2):239–245
267. Sempowski GD, Hale LP, Sundy JS et al (2000) Leukemia inhibitory factor, oncostatin M, IL-6, and stem cell factor mRNA expression in human thymus increases with age and is associated with thymic atrophy. J Immunol 164(4):2180–2187