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Review

Effect of Aging on the Immune System

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Abstract: Host defense mechanisms against microbial and viral infections as well as neoplastic cells constitute a close network, with phagocytes, natural killer (NK) cells, immunocytes including T and B cells, and cytokines released from and interacting with these cells. Although aging is accompanied by many changes in the immune system, it is unlikely that all immune cells and systems age at equal rates. Suffice to say, involution of the thymus plays one of major roles in immune senescence. Related to this event are the altered number and functions of T cell subpopulations involved in immunoregulation, a decrease in the immune response by both cell-mediated and humoral branches of the immune system, and an increase in autoimmune activity. The clinical implications of these changes are the elderly person's increased susceptibility to infections such as pneumococcal pneumonia, influenza and tuberculosis. Other changes include an increased susceptibility to neoplasms and perhaps acceleration of the aging process by increased autoimmune activity and immune complexes. The functions of macrophages, PMN, NK cells, and also the complement system are not seriously impaired with age. The evidence that lymphoid progenitors in bone marrow cells from young animals are able to differentiate into lymphoid cells in the aging animal, and that involution of thymus may be restored by manipulation of the endocrine system, suggest that there may be a potential for reconstitution of some immune defects in aged individuals by grafting or treatment with drugs to control various age-related diseases, including cancer.

Key words: Aging, B cells, T cells, Thymus

INTRODUCTION

Aging is accompanied by characteristic structural and functional alterations in many organs and systems, with the alterations in the immune system being the most pronounced.

Age-associated changes in the immune system have been studied in humans and in experimental animals, and the effect of increase in age on the immune system has been clearly documented (1–6).

Immune senescence in the elderly is usually associated with an increased susceptibility to infections, neoplasia, autoimmune disorders and vascular disease. This hypothesis has led to the investigation of the methodology by which immune system dysfunction might be prevented or restored in an effort to delay the inevitable consequence of aging and age-related disease. The aim of this article is to give an outline of very recent pertinent conclusions concerning the age-related changes in the wide range of the immune system related to the host defense network, as drawn from both human and animal studies. As an introduction, a brief overview of the immune network for host defense will be mentioned.

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THE IMMUNE NETWORK FOR HOST DEFENSE

In the past decade immunologic research has revealed the incredibly complex nature of the interaction between cells involved in host defense and invading microorganisms. It is simplistically devided into two categories. The

first defense is responsible for the control of infections caused by intracellular pathogens and tumors, and rejection on grafts, in terms of cell-mediated immunity. The second is involved in elimination of extracellular organisms in terms of humoral immunity (7).

Killing of prototypical intracellular bacteria such as *Listeria monocytogenes* and the mycobacteria, a number of fungal organisms, certain groups of viruses, and parasites is dependent upon the integrated activity of T lymphocytes and macrophages. Recent studies have defined the roles of various cytokines - interleukin 1 (IL-1) (8), interleukin 2 (IL-2) (9), and γ-interferon (IFN-γ) (10, 11) - in the process leading to macrophage activation or cell-mediated immunity. It has also become increasingly clear that cytotoxic T lymphocytes (CTL) (12, 13) and a separate group of lymphocytes, natural killer (NK) cells (14, 15), participate in defense against tumor cells, certain viruses, and virus-infected cells.

Immunoglobulins and complement factors are the principal elements of humoral immunity, and while a major function of these proteins is the opsonization or killing of extracellular bacteria, they also contribute importantly to defense against viruses and the injurious effects of microbial toxins. Although polymorphonuclear leukocytes (PMN) play a key role in the killing of opsonized bacteria, in the primary (normal) stage of defense, monocytes and macrophages can also eliminate these organisms in the activated stage (11, 16, 17, 18).

To understand the effects of aging on the immune system and its function, the interactions between cells involved in host defense and invading microorganisms and other cells are diagramatically summarized in Figure 1.

AGE-RELATED CHANGES IN THE IMMUNE SYSTEM

Thymus

The work of Good, Miller, and Waksman in the early 1960s revealed the crucial role of the thymus in the immune system. Numerous clinical, biological, and biochemical observations underline the close relations between aging and immunity. In particular, the T cell system and its functions are subjected to age-dependent decline and impairment. The senescence of peripheral immune function is paralleled by the involution of the central organ of the T cell system, the thymus (19).

The involution of the thymus with age is characterized by a puberty-independent continuous degeneration of the thymic epithelial space (20). It starts in the very first years of life and exhibits a constant velocity during the first decade. The velocity of involution decreases progressively. Remnants of thymic epithelial tissue with a cortical lymphocyte population are preserved beyond 100 years of age (21). Thymic atrophy in the aged involves various types of disorganization of individual lobules with T and B lymphocytes often located outside rather within epithelial remnants. The cause of involution and its impact on the immune status of the aged are far from being understood and remains the subject of speculation. The idea that the age-related involution of the immune apparatus and, in particular, the thymus, may be an adaptive mechanism to protect against autoimmune reactions has already been expressed (22).

Lethally irradiated and thymectomized young animals have been reconstituted with bone marrow cells and thymus grafts from donors of varying ages (23, 24). Thymus grafts from newborn animals permit the most rapid reconstitution of the T lymphocyte population and the most complete recovery of responsiveness to T cell mitogens and to T-cell dependent antigens. When thymus grafts are taken from older animals, the pace of recovery is delayed, and in many cases the level of thymus-dependent immune function never reaches that seen in intact animals or in animals reconstituted with neonatal thymus glands. Thus, the capacity of the thymus to affect the maturation of immature T lymphocytes de-

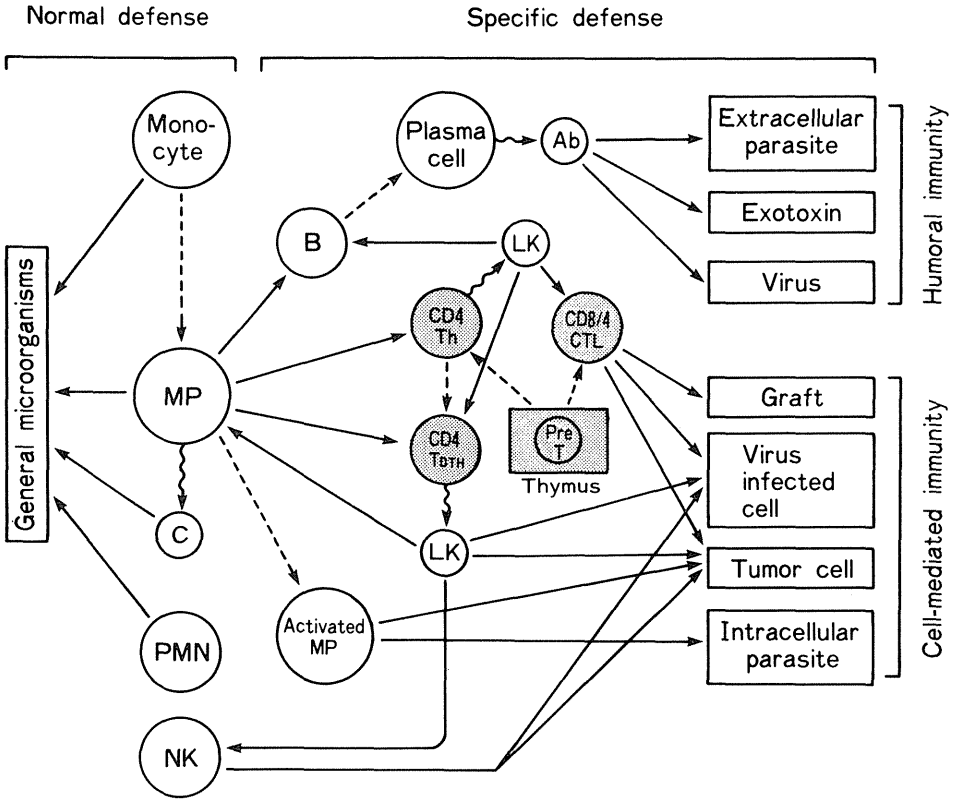

Fig. 1. Schematic diagram of the cellular and molecular interactions in host defense network. —►, interaction; --►, differentiation; ~►, secretion. Ab, antibody; LK, lymphokine; C, complement; shaded parts, sites that are most vulnerable to aging.

creases with age.

The level of thymic hormones in the serum of humans and experimental animals begins to fall soon after the morphologic involution of the thymus gland. Thus, in humans between the ages of 20 and 30, the serum level of thymic hormone begins to fall, and after the age of 60, thymic hormone is no longer detectable in serum (25).

It has been found that thymosin can overcome deficient T helper cell activity and improve *in-vitro* antibody responses of human lymphocytes to influenza vaccine (26), probably as a result of a thymosin-mediated increase in production of IL-2 (27). In another study, thymostimulin, a bovine thymic extract, has been administered parenterally for 3 months to aged hospitalized patients, and although no obvious changes were seen in measured immunologic parameters, patients in the treated group had significantly fewer infections than controls (28).

The thymus, which is grossly atrophied in 12 to 15-month-old male rats, is markedly restored in size 30 days after orchidectomy. The organ then appears normal histologically, having a well-defined cortex and medulla, is vascularized and filled with thymocytes. The regeneration of the thymus after orchidectomy was inhibited in a dose-related fasion by testosterone implants which produced serum concentrations of testosterone within the physiological range. The thymus also increased in size after orchidectomy of 10-week-old rats, and testosterone inhibited the enlargement of the thymus (29). The effects of several steroids

on the regenerating thymus in aging male rats have been studied (30). The results showed the possibility that testosterone and oestradiol may have caused atrophy of the thymus, while 5α-dihydroxy-testosterone may have retarded regeneration of the thymus without any atrophic effects.

Although it is proposed that involution of the thymus gland during the first half of the life span is followed by marked alterations in immune function, cell-mediated immunity and T-cell dependent humoral immune response still remain, if partially, in the aged. The mechanism by which decreased remnant mature lymphocytes in the aged still hold immune function is not clear.

T cells

Contradictory results have been reported regarding the number and proportion of T cells and their subpopulations in the elderly. Regarding the absolute number of peripheral blood, lymphocytes show relatively by constant (31, 32) or little change (33), a decrease in the circulating T lymphocytes (34, 35, 36), and an increase during aging (37). With regard to subpopulations of T lymphocytes, the number of immature T cells is increased in the elderly (38, 39). The number of T helper cells $OKT4^+$ ($CD4^+$) has been reported to be increased (40, 41) or unchanged (41, 42) with age, while the number of T suppressor cells $OKT8^+$ ($CD8^+$) has been reported to be increased (32, 41), decreased (38, 42) or constant (39, 43). Both proportions and absolute numbers of $OKT3^+$ (CD3, pan T cell marker) and $OKT4^+$ (CD4) cells were reduced in the elderly as opposed to those in young control population (44).

By studying 206 apparently healthy aged individuals, a slight decrease in the frequency of $T4^+$ (CD4) and $T8^+$ (CD8) cells has been found (45). Furthermore, these data are also supported by the demonstration that the number of null cells (non-T, non-B lymphocytes) is increased in the peripheral blood of aged individuals (46). Much of the controversy may be accounted for by differences in the technology employed or failure to define properly the subject populations. Regarding the effect of gender, elderly women displayed $T3^+$ (CD3), $T4^+$ and $T8^+$ cell numbers comparable to those seen in young women. Elderly men exhibited a reduction of $T3^+$ and $T4^+$ lymphocytes when compared with either young men or women (44).

Although there is no reduction in the ability of T lymphocytes from the elderly to bind lectin such as phytohaemagglutinin (PHA), PHA-inducible lymphocyte activation declines with age (47, 48). This seems to be due in part to a reduction in the number of PHA responsive lymphocytes and in part to a reduction in the number of sequential cell divisions occuring in lympocytes from elderly vs. young subjects (49). The poor mitogen response of mononuclear cells from elderly volunteers correlated with an increased sensitivity to prostaglandin E_2 (50); this increase was reversed *in vitro* by the addition of the arachidonic cyclo-oxygenase inhibitor, indomethacin, and by lithium carbonate (50, 51). Additional studies in aged experimental animals have also revealed a decrease in the response of T cells to nonspecific mitogens (39, 52, 53).

Antigen-specific or antigen-nonspecific suppressor cells have received considerable attention in immunogerontology because of their important role in regulating the immune response as well as the induction and maintenance of tolerance to exogenous and self antigens (54, 55). Suppressor cell activity has been found increased (56–58), unchanged (56) or decreased (59–61) in aging mice and humans. The overt controversy as to age-related changes in immunosuppression reflects the large variety of methods used to assess suppressor cell activity. More recently, Doria *et al* (62) reported age-related alterations of antigen-specific T cell-mediated suppression in the 4-hydroxy-3-nitrophenyl acetyl (NP) system, suggesting that aging may affect the recognition repertoire expressed in suppressor T cell

subsets (inducer, transducer and effector suppressor T cells). Moreover, the finding that suppression is less efficient when exerted up on spleen cells from old rather than from young mice provides an explanation for the increased frequency of autoimmune disorders in aging. Studies on *in vitro* induction of Con A-activated T helper cells, T suppressor-inducer cells and T suppressor cells from aged Peyer's patches (PP) indicated that the generation of T suppressor cells was largely impaired, in contrast to minor defect(s) in that of T helper cells (63), suggesting that in aged PP, a T suppressor-inducer cell subset appears to be more selectively impaired during the aging process than the other lymphocyte subpopulations. On the other hand, the ability to generate suppression to newly encountered antigen declines with age, whereas a resident splenic suppressor cell population accumulates over the lifetime of the animals (64).

One hypothesis suggests that defects in the capacity of T cells to produce or respond to T cell growth factor, or IL-2, may be the fundamental cause of the immune deficiency seen with aging. Most evidence from studies of humans supports a decrease in IL-2 production with aging (40, 65, 66). Data from animal studies also support a decrease in IL-2 production with aging (67–69), although one study revealed no difference between IL-2 production in elderly rats and that in young rats (39). Investigations regarding the response of T cells from elderly humans to exogenous IL-2 have given contradictory results, showing intact response (70), or defective responses (40, 65). Similarly, conflicting results have been obtained in studies of the T cell response from aged animals to exogenous IL-2 (39, 60, 67). Further investigations are needed to define the exact role of interleukins in the pathogenesis of immune defects associated with aging.

The level of IFN-γ, another lymphokine thought to be of importance in immunoregulation, resistance to viral infections and also in macrophage activation (11, 16–18), was reportedly normal (71) or decreased (72) in response to antigen or mitogen in elderly subjects. Other investigators reported an age-associated decline in the synthesis and secretion of both IFN-γ and IFN-α by mononuclear cells (73). Whether dificiencies in these lymphokines result in the increased susceptibility of aged humans to viral infection and malignant disease remains to be determined.

Investigation regarding the genetic analysis of Con A-stimulated cultures of spleen cells from old and young mice has been reported to show that aging led to a consistent decline in the level of c-*myc* mRNA in stimulated cells suggesting that these deficits may involve, at least for some gene, alterations in post-transcriptional processing (74).

B cells

Unlike conflicting data on T cell proportion during aging, relative frequency of B lymphocytes is generally unaffected in the elderly, in spite of increased or decreased functional capacities (75). By contrast, an investigation revealed that aged mice are impaired in their ability to generate B cells and that this may be caused in part by a reduction in the frequency of pre-B cells, as well as to a lack of support for these cells in the process of their maturation to B cells (76).

Polyclonal immunoglobulin (Ig) response to pokeweed mitogen (PWM) in a group of aged individuals was either normal or increased (32). By contrast, antigen-specific and polyclonal responses with advancing age was reported to be reduced (77). Antigen-specific response was more reduced than polyclonal response (77). Furthermore, an intrinsic defect of B cell maturation in the elderly has been also postulated (78), which has been confirmed by recent findings showing that both IL-1 and IL-2 are able to enhance signficantly the diminished B cell response of elderly subjects (79). In addition, the decreased expression of surface markers (sIgM and sIgD) and the changes in intracellular structure of aged B

cells analyzed by flow microcytofluorometry strongly support an alteration in B lymphocytes even if their relative frequency remains constant (79). These data suggest that immunosenescence of B lymphocytes leads to a perturbation of their functional and/or phenotypic characteristics.

On the other hand, aged purified B lymphocyte preparations respond to antigen as plaque-forming cells (PFCs) similar to those observed in young healthy donors (80). This suggests that a non-B population is involved in the impaired antibody synthesis; i.e. the negative modulation of B cell responses mediated by T cells during the elderly.

In conclusion, several factors impair B lymphocyte response during aging, acting either via T cells or directly on B cells even if the regulatory T cell network is taken into consideration.

Macrophages

Macrophages have intrinsic roles for the presentation of antigens for immune response, and phagocytosis and killing of microorganisms. Most animal studies have indicated that the overall number and function of macrophages are unchanged with age. Specifically, chemotaxis, phagocytosis, and intracellular killing have been found to be normal (51, 81, 82). In one study, although monocytes from aged donors showed a normal chemotactic responsiveness to zymosan-activated serum, the chemotactic activity induced by leukocyte-derived chemotactic factor and phagocytosis were depressed (83).

While macrophages from older animals were not impaired in their ability to inhibit either the intracellular growth of *Toxoplasma gondii* or the DNA synthesis of tumor cells, the induction of these capacities was delayed (51, 84). One study of macrophages from aged animals revealed diminished phagocytic activity (77, 85); another detected decreased nonspecific tumor cell cytotoxicity (86). An investigation regarding the respiratory burst and bactericidal activity of alveolar macrophages from adult and senescent mice indicate that the enhanced susceptibility of the senescent host to lower respiratory tract infection cannot be attributed to age-related changes in the nonspecific antimicrobial activity of resident alveolar macrophages (87). The helper function of macrophages from older animals was normal in terms of both T and B cell mitogenesis, the production of plaque-forming cells, and the generation of IL-1 (39). On the other hand, macrophages involved in the production of T cell growth factor, IL-2, from lymphocytes are altered with age (88). The capacity of macrophages of old mice to synthesize IL-1 is also markedly reduced (89, 90).

Polymorphonuclear leukocytes

Polymorphonuclear leukocytes (PMN) represent an important defensive mechanism against infectious agents. Aging does not appear to be associated with granulocytopenia (91). In addition, the adherence of PMN from elderly individuals to nylon fibers is reportedly normal (83) or increased (92, 93). Conflicting data, however, have been reported regarding other PMN functions. Several investigators have demonstrated intact chemotaxis, phagocytosis, and bactericidal activity in the aged (94, 95), whereas others have shown significantly impaired PMN chemotaxis (83, 92, 93). Phagocytosis and the bactericidal activity of PMN were also significantly depressed in several studies of the function of PMN from elderly individuals (83, 92, 93, 96, 97). Specifically, nitroblue tetrazolium reduction (31, 83, 92) and the generation of superoxide anions by PMN stimulated with latex particles (83, 98) were impaired with aging. In addition, PMN chemiluminescence was significantly depressed in one study of individuals exceeding 80 years of age (99). Other investigators, however, reported a specific defect in receptor activation of a key phosphorylating activity (100). Despite these reported defects of PMN from the elderly, there was no association with an

increased incidence of bacterial infections (92).

Natural killer cells

Functional alterations in cytotoxic lymphoid cells also occur with aging. These cells are instrumental in defense against virus-infected cells and tumor cells. There is general agreement that the ability to generate natural killer cells (NK) diminishes with age in animal models of senescence (101, 102). However, results in humans have been conflicting, revealing a marginal increase in NK activity in aged males, but not in females (103), no significant change (104, 105), a moderate increase in NK activity (106), and an increase or lack of increase depending on the parameter of expression (107). Other investigations revealed an increase in NK activity in the majority of healthy elderly (>80 years) and a decrease in mitogenic response to PWM (108–110).

Complement system

The complement system comprises the other major group of serum proteins involved in opsonization, and complement levels and functional activity appear to be intact in elderly subjects (94).

The effects of aging on effector cells and molecules involved in normal defense mechanisms are shown in Table 1.

Table 1. Effects of aging on effector cells and molecules involved in normal defense mechanisms

Effect	Reference(s)
PMN	
Numbers	→ 91
Functions	↓ 31, 83, 92, 93, 96–100
	→ 83, 92–95
Mononuclear phagocytes	
Functions	↓ 77, 83–86, 88
	→ 51, 81, 82, 87
IL-1 production	↓ 89, 90
	→ 39
Natural killer cells	
Number or function	↓ 101, 102
	→ 46, 103–110
Complement levels and function	→ 94

↑, increased; →, unchanged; ↓, decreased.

Age-Related Changes in the Immunity

Cell-mediated immunity

Cell-mediated immunity (CMI) plays an important role in defense against certain infectious agents, in surveillance against cancer, and in immune regulation (111). In aged individuals the susceptibility to infections is increased (112). There is ample evidence that the deterioration of the immune system is related to a decreased function of T cells. This decline in immune function appears to be mainly due to impairment of T helper cell activity (113–116). Helper T cells play an important role in the generation of inducer T cells which participate in the delayed-type hypersensitivity (DTH) reactions and inductions of B-cell responses as well as cytotoxic T-cell response. The inductive helper cells can be characterized on the basis of their surface markers. They have Thy-1 surface markers but lack Lyt-2 (CD8) membrane antigens (117).

The changes in the ability to induce B-cell responses and, to a lesser extent, cytotoxic T-cell responses in aging individuals have been described (118–120). The DTH responses represent the capacity of the immune system to cope with various types of infections of intracellular microorganisms, such as *Mycobacterium tuberculosis* (121), *Salmonella typhimurium* (122), *Listeria monocytogenes* (123), and *Candida albicans* (124). It has been shown that the DTH response to a panel of antigens decreased with increasing age (125). A study employing an experimental mouse model of *Mycobacterium tuberculosis* infection showed that old mice are more susceptible to *M. tuberculosis* in that they are unable to survive an infectious dose that is

sublethal to young abult mice. Passive transfer of adoptive immunity from mice of increasing age revealed that the increased susceptibility of aged mice is associated with a deficient capacity to generate protective T lymphocytes to the *M. tuberculosis* infection (126).

In the animal model of genetic background, it is well known that C57BL/Ka mice are more sensitive to age-related immune disorders than CBA/Rij mice. C57BL/Ka mice show a relatively high frequency of pathological lesions of the immune system with age (127). In both experimental animals and humans, three stages of susceptibility to viral infections are apparent; the neonatal state, characterized by enhanced susceptibility to infections; childhood and adolescence, during which there is decreased susceptibility; and adulthood (sexual maturity), characterized by increased susceptibility to primary viral infections with advancing age (128). Moreover, advanced age is associated with reactions of latent viruses, most notably varicella zoster virus (VZV) (129), and most likely, oncogenic viruses as well. The mechanisms responsible for these alterations in susceptibility to viral infections have not been completely elucidated. Differences in antibody production do not seem to play a role. Most authors feel that depression of CMI, as measured by delayed cutaneous hypersensitivity or lymphocyte stimulation by mitogens and antigens, may be of importance. Recent studies revealed that *in vitro* lymphocyte proliferative resopnses to VZV by lymphocytes of adults aged 12–46 years are mainly by $CD4^+$ T cells and that this subset can lyse VZV-infected cells with HLA-DR surface antigens directly (130). An investigation suggested that mononuclear cells capable of killing VZV-infected target cells persist with aging but that reduced numbers of antigen-responsive and lymphokine-releasing T cells may limit their function (131).

An investigation regarding interferon formation in response to coxsackie virus B3 infection in mice suggested that adult mice produce relatively less interferon in relation to the amount of virus replicated in their tissues than do younger animals (128).

Delayed-type hypersensitivity and graft rejection are two classic manifestations of CMI *in vivo*. In a system producing acquired immunologic tolerance to an allograft by injecting cells from the donor, survival of the allograft is dependent on several factors that include the dose of tolerogenic cells, antigenic disparity between the recipient and donor, and the developmental stage of the recipient (132). The age of adult recipient mice was found to be crucial to the induction of skin allograft tolerance with allogeneic spleen cells plus cyclophosphamide. By contrast, the age of the donor mice used for tolerance induction did not appear to be crucial for the induction of a tolerant state (133).

The ability to mount a mixed lymphocyte reaction (MLR) declines with age in both mice (134) and men (135) as does also antibody-dependent T cell cytotoxicity (136) and cell-mediated cytotoxicity (CTL) (137).

The effects of aging on cell-mediated immune mechanisms are shown in Table 2.

Humoral Immunity

Infections caused by certain encapsulated bacteria, including *Streptococcus pneumoniae*, group B *Streptococcus*, and *Escherichia coli* K1, appear to occur more frequently in the elderly than in young adults (138, 139) and are suggeated to be due to a decline of humoral immune function that occurs during secescence. Although the total concentration of immunoglobulins remains constant, changes in serum immunoglobulin classes have been noted with age. Most reports reveal a gradual increase in the amount of IgA and IgG, whereas IgM concentrations are unchanged (91) and mortality was higher in a subgroup of volunteers with decreased IgG (140).

In contrast to age-associated alterations in T cell function, those involving B lymphocyte function or humoral immunity are relatively

Table 2. Effects of aging on cell-mediated immune mechanisms

Effect		Reference(s)
Thymic involution		1, 2, 4, 19–21, 24
Thymic hormone levels	↓	25
T cell numbers		
Total T cells	↓	34–36
	→	31–33
	↑	37
Immature T cells	↑	38, 39
T helper cells	↓	44, 45
	→	41, 42
	↑	40, 41
T suppressor cells	↓	38, 42, 45, 63
	→	39, 43
	↑	32, 41
T cell responses		
Proliferative activity	↓	39, 47–49, 52, 53
Suppressor activity	↓	59–61, 63
	→	56
	↑	55, 56–58
Responses to IL-2	↓	40, 65
	→	70
DTH	↓	125
Resistance to infection	↓	126, 128, 131
MLR	↓	134, 135
Resistance to tolerance	↓	133
CTL in number and function	↓	131, 137
Lymphokines		
IL-2 production	↓	40, 65–69
	→	39
IFN-γ production	↓	72, 73, 128
	→	71

↑, increased; →, unchanged; ↓, decreased.

few. Investigations have demonstrated a decreased antibody response to the hepatitis B virus (141) and multivalent influenza vaccines (142, 143) in elderly individuals as well as an impaired adility to sustain the production of IgG when experimentally immunized with monomeric flagellin (144). When infected with influenza virus, elderly persons, particularly those with underlying diseases, are at increased risk for morbidity and mortality (145). In some studies the antibody response in the elderly to pneumococcal vaccine was sufficient to protect against infection (146, 147). Another study demonstrated the ability of the elderly to mount a polyclonal antibody response to pneumococcal polysaccharide vaccine that was similar to the response of healthy younger controls except for the IgM class responses, which were significantly weaker in the elderly (148).

Table 3. Effects of aging on humoral immune mechanisms

Effect	Reference(s)
Reduced antibody responses to:	
Specific antigens	149
Polyclonal activators	77
Vaccines	
Hepatitis B	141
Influenza	142, 143
Pneumococcal polysaccharide	146–148
Tetanus toxoid	151, 152
Enhanced autoantibody	154
Enhanced anti-idiotype antibody	149, 150
B cell function	
Primary defect	78, 79
Defect secondary to regulatory T cell abnormality	
Helper cells	113–116
Suppressor cells	63
Primary B cell defect and regulatory T cell abnormality	39

It has been proposed that auto-anti-idiotypic antibodies that combine with surface immunoglobulin on B lymphocytes to inhibit antibody formation may be responsible for the alterations in the humoral immune response seen in senescence (149, 150).

The highest incidence of tetanus infection occurs in the elderly population. The mortality rate in persons over 65 years old approaches 80 per cent. The age-related decline found in both *in vivo* and *in vitro* synthesis of anti-tetanus toxoid antibody was suggested to be accounted for the impaired tetanus toxoid-specific T-helper cell activity as well as B-cell dysfunction (151, 152).

The effects of aging on humoral immune mechanisms are shown in Table 3.

Autoimmunity

It seems paradoxical that at the time in life

when the activity of the immune system is declining, the incidence of antoantibody production begins to rise. In aging mice an increased resistance to the induction of tolerance has been demonstrated (153). There is little direct evidence that the autoantibodies produced with advancing age have any deleterious effect. The role of antilymphocyte antibodies found with increasing frequency in the elderly is less certain (154). On the other hand, it has been postulated that low-grade tissue damage by a range of age-related autoantibodies may actually contribute to the process of senescence, although there is evidence to suggest that the production of autoantibodies in the elderly represents homeostatic control of the immune system.

RESTORATION OF IMMUNE FUNCTIONS OF THE AGED

Various attempts have been made to restore immune functions of aged animals to levels approaching those of younger mature individuals. Studies attempting to potentiate immune functions of old mice revealed that the loss of normal immune functions with age is associated with changes in antigen-/mitogen-responsive T cells, the inability of the involuted thymus to synthesize T cell maturation factor(s), changes in precursor cells in the bone marrow, and emergence of deleterious factors with age (6). When long-lived old mice were grafted with both young bone-marrow stem cells and newborn thymic lobes, their immune functions were restored to levels approaching those of younger adult mice, and the restorative effect was observed for 6 to 11 months after grafting in mice with a mean life span of 28 months (an equivalent of about 16–28 human years) (155).

The sulfhydryl compound most commonly used by immunologists is 2-mercaptoethanol (2-ME). Studies on its immunorestorative actions on aging mice show that it enhances the antibody-forming capacity of old mice preferentially over that of young mice (156). Thus, the effect of 2-ME on the T cell-dependent antibody-forming capacity of old spleen cells *in vitro* was an order of magnitude greater than that on young spleen cells (157). That 2-ME is also an effective immunorestorative agent in intact old mice was demonstrated by restoration of the T cell-dependent antibody-forming capacity of long-lived old mice to that of young mice by administration of this compound (156). More recently, in a preliminary study, young and old mice were subjected to immunotherapy by injecting either saline or dithiothreitol, a potent *in vitro* immunostimulant, following inoculation with melanoma cells (158). The results revealed that dithiothreitol could reduce the incidence of pulmonary metastasis 38 days after inoculation of melanoma cells. Moreover, augumentation of intracellular glutathione concentraions in lymphocytes may enhance immune function in depressed immune states (159). The mode of action of these chemicals is not known. It is well known that the function of sulfhydryl compounds ranges from R-SH to R-S-S-R' exchange reactions at the membrane level, to antioxidant and metal chelating effects (160).

Many recent reports point out the relationship between nutrition and immunocompetency in the elderly. The use of certain drugs such as cholestyramine, anticonvulsant drugs, and thiazide diuretics may reduce the immune system by inducing nutrient depletion (161). An important role is played by zinc depletion. Previous results have demonstrated that mice fed a zinc-supplemented diet maintain thymic hormone levels better than mice fed a normal diet (162). The effect mediated by zinc seems to be selective for B cells. In fact, zinc addition in culture augments specific antibody response or polyclonal antibody synthesis (163, 164). On the basis of the well-known capacity of zinc to activate B lymphocytes, the above-described effects are likely due to a modulation of early events involved in the activation of antibody forming

cells.

The relation between zinc level and thymic hormones has also prompted many studies on the beneficial effects of thymic hormone administration in elderly individuals. In this context, it has been observed that injection of thymosin is able to restore T cell-dependent immune functions (165). With regard to the mechanism of action of thymosin, the enhancement of IL-2 production cannot be excluded (2).

Conclusion

In the present review, we have summarized the changes in immunocytes and discussed their functions in relation to the host defense network that are coupled with aging. It is proposed that increased susceptibility of elderly people to infectious and neoplastic diseases may be a consequence of immune senescence.

It is unlikely that all immune cells and systems age at equal rates. Although a plethora of frequently conflicting evidence has accumulated from studies in both animals and humans, the most visible cellular target of aging appears to be the T cells, and changes in their subpopulations involved in immunoregulation are highly prominent. These evidence appear to be related to thymic function which declines with age as assessed by a reduction in thymic hormone levels, thymic involution and its reduced activity. The functions of macrophages, PMN, NK cells, and also the complement system are not seriously impaired with age.

While it appears that impaired immune responsiveness is a consequence of the aging process, the possibility that altered immunity plays a primary role, if not wholly, in the senescence process remains to be solved. The evidence that lymphoid progenitors in bone marrow cells from young animals are able to differentiate into lymphoid cells in aging animals suggests that there may be a potential for reconstitution of some immune defects in aged individuals.

A recent study suggested that in addition to a central role for immune mechanisms, the thymus appears to be closely related to the function of the endocrine system of the pituitary and the hypothalamus. In fact, involution of the thymus may not be irreversible but could be restored by manipulating the endocrine system (166). This hypothesis has led to the investigation of an effective manipulative methodology including grafting and treating with chemical agents by which immune system dysfunction might be prevented, retarded or restored in an effort to delay the inevitable consequences of age and age-related diseases.

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