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*Results from animal and human studies indicate that alterations in the immune system are related to age, but conclusive data supporting direct causal links between immune senescence and most malignancies are limited.*

## Aging, Immunity, and Cancer

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**Background:** *The prime function of the immune system is to protect the entire organism from a variety of insults and illnesses, including the development of cancer. The question of how age-related declines in immune function contribute to an increasing incidence of malignancies continues to be a focus of discussion and speculation.*

**Methods:** *The recent literature from the National Library of Medicine database (1990 through the present) was searched for articles using the medical subject headings (MeSH terms) of aging, immunity, cancer, senescence, and apoptosis. Bibliographies of articles retrieved were also scanned.*

**Results:** *Data from in vitro and in vivo animal and human studies demonstrate clear age-related alterations in both the cellular and humoral components of the immune system, but there is little evidence supporting direct causal links between immune senescence and most malignancies.*

**Conclusions:** *Senescent decline in immune surveillance leads to the accumulation of cellular and DNA mutations that could be a significant factor in the development of malignancy and programmed cell death or apoptosis observed in the elderly.*

### Introduction

It is well established that many aspects of immunity change with increasing age. At the same time, and as described in other articles in this series, there is an

increasing incidence of many cancers with increasing age. The question of how alterations in immune responses contribute to morbidity and mortality from cancer in elderly persons is more difficult to answer. Although a statistical association between some diseases and immune dysfunction has been described in humans of all ages, there is little evidence to support a direct causal relationship between the latter and the former. Most authorities simply have assumed that a decline in immune function is deleterious, or they have used theoretical arguments to support this belief. If a major function of the immune system is to provide "surveillance" against the occurrence of cancer, monitoring for malignant transformation of cells and removing these from the system, then defects or decreased

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efficiency in any one of these steps could contribute to an increased incidence of malignancy. It is likely that age-related changes in immune function affect the expression and progression of malignant conditions. In this article we review changes in immune function that are believed to be related to age per se, focusing on those changes of most relevance to the development and progression of cancer.

## T Lymphocytes

In aging humans and experimental animals, one of the most obvious changes that occur, starting in adolescence, is involution of the thymus with ensuing loss of thymic hormones, such as thymosin.<sup>1,2</sup> Subsequently, changes in T lymphocytes are seen, with declines in "virgin" or reactive T cells and increases in "memory" or primed T cells.<sup>3-7</sup> The accumulation of memory cells occurs in CD4+ T-helper cells<sup>8</sup> and CD8+ T-suppressor cells.<sup>9</sup> While the number of naive T cells declines in old animals, those remaining produce greater amounts of interleukin (IL)-2 than naive cells from young animals.<sup>10</sup> Although memory T cells normally produce IL-2, many studies describe decreased IL-2 production by lymphocytes from old animals and humans. This paradoxically low production may be related to changes in other regulatory cytokine signals, such as IL-4.<sup>11</sup> On a more basic level, there is a loss of stem cell potential to generate T cells, in both mice and humans.<sup>12,13</sup>

A decline in the proliferative response of lymphocytes was one of the earliest age-related qualitative changes in immune function to be reported,<sup>14-17</sup> though recent studies suggest this may be related to the type of stimulus.<sup>18</sup> Hyporesponsiveness to mitogens is due to a reduction in the number of mitogen-responsive cells and vigor of the response.<sup>16</sup> In old compared with young mice, a smaller percentage of T splenocytes respond to mitogenic stimulation by entering active phases of cell replication, a defect noted on CD4+ T-helper cells and, to a lesser extent, on CD8+ T-suppressor/cytotoxic cells.<sup>19</sup> The proportion of cells entering active phases of replication is regulated by a balance between genes stimulating DNA replication and synthesis and genes inhibiting DNA synthesis, leading to apoptosis (programmed cell death).<sup>20</sup> For example, the p53 gene, an important regulator of apoptosis,<sup>21</sup> is underexpressed in active T cells from old donors.<sup>22</sup> Mice bred to be p53-deficient show accelerated aging of the immune system, with early accumulation of memory cells and decreased proliferative responses.<sup>23</sup>

T-helper cells from old mice are less capable of generating cytotoxic effector cells to participate in delayed hypersensitivity reactions.<sup>24</sup> Cytotoxic lymphocytes

from aged mice are less able to bind targets, though they appear to be equally effective in destroying their targets.<sup>25</sup> In humans, changes in cellular immunity have clinical implications when considered in the context of several infectious entities. The cytotoxic response to influenza vaccine is lower in old adults than in young adults,<sup>26</sup> and old adults are less likely to have T-cell subsets able to respond to the antigen.<sup>27</sup> Some of the mechanisms mediating this response include reduced IL-2 production and T-cell activation in vivo and in vitro.<sup>28</sup> Old mice are more susceptible to developing influenza pneumonia after intranasal inoculation in spite of prevaccination.<sup>29</sup> The old animals have impaired cytotoxic T-cell function and ineffective antibody generation after vaccination.<sup>29</sup> Herpes zoster virus causes the cutaneous condition commonly known as shingles, which occurs predominantly in adults over the age of 75.<sup>30</sup> Factors controlling latency of herpes zoster virus are unclear, although cellular immunity measured by cutaneous delayed hypersensitivity wanes with increasing age.<sup>31</sup> While the disease is recognized as an indication of immunocompromised status in younger persons and those with early recurrence,<sup>32</sup> it is not associated with occult malignancy in older adults.<sup>33</sup>

Suppressor cells from aged animals have more difficulty recognizing and exerting suppressive effects against specific antigens from self and other old animals.<sup>34-37</sup> A failure of tonic inhibition by suppressor T cells may be responsible for the increased incidence of autoantibodies seen in aging.<sup>38</sup> The rise in the presence of autoantibodies in elderly persons has been correlated to decreased proliferation of T cells to mitogen<sup>39</sup> (ie, the lower the proliferation of T cells to mitogens, the higher the level of autoantibodies).

## B Lymphocytes

With increasing age, changes in B cells have recently become more apparent than changes in T cells. The number of circulating B cells does not appear to change appreciably with age.<sup>40</sup> Studies in aged mice have shown structural changes in B-cell membranes<sup>41</sup> and a decrease in estimated numbers of bone marrow B-cell precursors.<sup>42-44</sup> Similar to what has been described for T cells, B cells from old individuals proliferate less efficiently to mitogen stimulation.<sup>38</sup>

The ability of B cells to generate antibody responses changes with age,<sup>45</sup> although much of this is related to declining T-cell function. The decrease in T-dependent antibody responses is obvious in experimental animals, with 80% fewer antibody-forming cells in older animals.<sup>3</sup> The B-cell repertoire changes with age, with

altered ability to recognize antigen.<sup>37,46</sup> A recent study in mice showed that immunization with sheep red blood cells led to a significantly greater rise in the proportion of immunoglobulin-M (IgM)-secreting cells that reacted with self-antigens in old animals.<sup>47</sup> The accumulation of antibodies directed against other antibodies (anti-idiotypes) with increasing age may also interfere with the production of specific antibody.<sup>48,49</sup>

The ability to respond to a novel (primary) or previously encountered (secondary) specific antigen challenge with specific antibody production is decreased in aging.<sup>45,50</sup> We studied a group of healthy older adults participating in a larger study of emotions and health behavior and found they were less likely than a group of healthy young control subjects to mount an *in vivo* response to immunization with the primary antigen keyhole limpet hemocyanin.<sup>51</sup> In a different group of aged subjects meeting rigorous criteria for health,<sup>52</sup> immunization with the novel antigen, *Helix pomatia* hemocyanin, produced numbers of antibody-producing cells in culture comparable to young subjects.<sup>53</sup>

B cells from old adults produce less specific antibody when stimulated *in vitro* with specific antigen, such as tetanus toxoid, regardless of the source and type of T-cell help provided in the cultures.<sup>54</sup> Even recently immunized old adults display lower levels of antibody *in vivo*, fewer numbers of B cells producing antibody *in vitro*, and less antibody produced by each B cell. One reason for the decreased response appeared to be lack of precursor cells.<sup>55</sup> Reimmunizing subjects led to an increase in the number of specific antibody-producing B-cells in old and young, but the old adults still had significantly fewer B cells producing specific antibody.<sup>56</sup> Booster immunizations did not alter the mean amount of antibody produced per B cell for either age group. After immunization with influenza vaccine, the antibody isotypes produced that are important in the agglutination response (specifically IgG, IgG1) are decreased in elderly humans compared with young humans.<sup>57</sup>

Although most investigators agree that the changes in antibody production described above are the result of declines in T-lymphocyte function, there is also evidence for a decline in intrinsic B-cell function. Findings from our laboratory and others suggest a diminished ability of purified B cells to respond to isolated T-helper cells or to T-cell-derived helper factors.<sup>58,59</sup> Some murine studies have shown that certain subsets of B cells function at a significantly lower level than the same cells in young mice, while other subsets produce comparable levels of antibody.<sup>60</sup> Old mice produce amounts of antibody comparable to young after vaccination with phosphocholine, but with a molecular shift in the antibody repertoire.<sup>61,62</sup> In the old mice, the

genes encoding the variable heavy portions of the antibody molecule are different from those in young animals. The antibody produced by old mice has diminished affinity for its target and is less effective in preventing infection.<sup>62,63</sup> Vaccination also seems to stimulate production of antibodies that cross-react to self-antigens in old but not young mice.<sup>64</sup>

## Macrophages

Macrophage function in aging has been studied less than other leukocyte subpopulations. Early work suggested that they appear to produce similar levels of cytokines<sup>65,66</sup> and that differences in function may be modulated through changes in T- and B-cell responses to such substances. More recent studies of human monocytes have shown decreased IL-1 secretion with mitogen stimulation.<sup>67</sup> Studies of cutaneous wound-healing in mice also suggest a decline in macrophage function with aging, with prolonged wound healing in aged animals.<sup>68</sup> Adding peritoneal macrophages from animals of different ages to wounds on old mice sped healing, but macrophages from young mice accelerated the healing process to the greatest degree.<sup>68</sup> Other murine studies of bone marrow in senescence-accelerated mice suggested that stem cells are defective in their ability to generate granulocyte-macrophage precursor cells.<sup>69</sup>

Studies of both mouse and human macrophage function in aging suggest defects in macrophage T-cell interactions. Macrophages from old mice that are antigen-sensitized stimulate significantly lower levels of T-cell proliferation than young macrophages.<sup>18</sup> Work from Szakal et al<sup>70</sup> has found serious age-related compromise in the ability of dendritic cells to stimulate the formation of germinal centers in lymph follicles where B-cell memory develops. T cells from old adults are able to function at the same level as T cells from young adults when macrophages are replaced with other sources for activation, suggesting a defect in macrophage T-cell communication.<sup>71</sup> Compared with monocytes from young adults, monocytes from old adults display lower cytotoxicity against certain tumor cell lines, decreased production of reactive oxygen intermediates (H<sub>2</sub>O<sub>2</sub> and NO<sub>2</sub>), and lower IL-1 secretion than monocytes from young adults.<sup>67,72</sup> These findings of decreased secretion were observed when monocytes were stimulated with nonspecific mitogens.<sup>67</sup>

## Natural Killer Cells

Natural killer (NK) cells are cytotoxic cells that differ from cytotoxic T cells by the ability to lyse targets without the need for antigen sensitization. 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. Murine NK cells display an age-related decline in ability to lyse spleen cells.<sup>73,74</sup> Most early studies suggested no change in the cytotoxic ability of NK cells,<sup>75</sup> though more recent studies are contradicting these findings. The number of NK cells appears to increase with aging, but NK activity decreases.<sup>76,77</sup> The decreased activity is caused by increased expression of Ly-49 receptors, which downregulate NK activation.<sup>78</sup> There also seem to be differential requirements for maximal activation of NK by interferon alpha (IFN- $\alpha$ ), with young cells showing maximal responses at lower concentrations.<sup>79</sup> Elderly patients with growth hormone deficiency have lower NK activity, which can be partially restored in vitro by exposing NK cells to the precursor protein.<sup>80</sup> The activity of LAK cells also appears to be reduced in aged compared with young humans.<sup>75,76</sup>

## Lymphocyte DNA

The longer individuals live, the more time their genetic material has to undergo somatic mutations, from a combination of epigenetic factors combined with environmental exposure to a variety of toxic or potentially damaging substances (eg, free oxygen radicals).<sup>81</sup> Changes in activation or inactivation of cellular DNA, such as by methylation, result in differential expression of various genes that have roles in suppression of tumor activity.<sup>81,82</sup> The ability of cells to repair damage to DNA interacts with these factors to affect the development of cancer.<sup>82,83</sup> Genes regulating the process of apoptosis (or programmed cell death) may counteract malignant progression.<sup>83,85</sup>

The increasing fragility of lymphocyte DNA with age may predispose to or compound immunosenescence. Chromosomes of T cells from old adults are more fragile than those from young adults,<sup>86</sup> and certain sites on the X chromosome have been shown to be more sensitive to chemical insults. Atomic bomb survivors who were over 55 years of age when exposed to radiation have lymphocytes that mount poorer cellular responses than survivors who were under 15 years of age at the time of exposure.<sup>87</sup> These results may reflect the increased susceptibility of the aging immune system to radiation. With in vitro exposure to irradiation, there are fewer breaks in double-stranded DNA in lymphocytes from old adults, but the cells are unable to repair these breaks as effectively as lymphocytes from young donors.<sup>88</sup> Other investigators have looked at sister chromatid exchange (a measure of DNA damage) in healthy old individuals and newborns and found a 10-fold greater basal frequency of exchange in lymphocytes from the old subjects.<sup>89</sup>

Because of the rapid accumulation of evidence implicating free radicals in the processes of aging and neoplasia,<sup>90</sup> there has been a tremendous upsurge in research on antioxidants as potential immune stimulants or anticancer and "anti-aging" treatments.<sup>91,93</sup> In vitro exposure of T cells from old mice to the antioxidant glutathione enhances T-cell proliferation at all ages, due at least in part to blockade of eicosanoid production.<sup>94</sup> Supplementation with vitamin E in healthy elderly subjects results in enhanced responses to delayed-type hypersensitivity skin testing and also increased in vitro lymphocyte production of IL-2.<sup>95,96</sup> It has been postulated that vitamin E causes these effects via inhibition of suppressive factors such as prostaglandin E2.<sup>92</sup> A placebo-controlled trial of vitamin supplementation in healthy elderly individuals was associated with marked increases in various parameters of immunity and lower rates of infection.<sup>97</sup> The 1-year trial did not show any effect on cancer incidence.

## Interleukins

The response to IL-2 has been extensively studied as one potential mechanism underlying the age-related defect in cellular immunity. Several laboratories have demonstrated decreased production of IL-2 after mitogen stimulation, decreased density of IL-2 receptor expression, decreased expression of IL-2 mRNA, and decreased proliferation of T cells in response to IL-2.<sup>28,98-102</sup> Additional experiments suggest that the picture might be more complex, with defects in production of or sensitivity to IL-2 varying with the activation signal.<sup>5,103</sup> Some investigators have found no difference in T-cell proliferation or IL-2 production when memory T cells from old and young humans were stimulated with a variety of activating signals.<sup>5</sup> CD4+ T cells from old mice accumulate similar levels of IL-2 transcripts, though secretion of IL-2 is lower than in cells from young mice.<sup>104</sup>

IL-1 and -2 play a primary role in activation, recruitment, and proliferation of T lymphocytes. Activated T cells go on to produce a variety of cell growth and differentiation factors such as IL-4, IL-6, and IFN- $\gamma$ . Evidence has been accumulating that there are age-related declines in lymphocyte production and response to other cytokines, such as IL-1 and tumor necrosis factor (TNF).<sup>3,105</sup> Monocytes from aged humans secrete less IL-1 when stimulated with lipopolysaccharide, although they appear to produce comparable amounts of IL-1 precursor.<sup>67</sup> Under conditions of mixed lymphocyte culture, lymphocytes from old individuals produce higher levels of IL-1, IL-2, and TNF- $\alpha$  than those from healthy young individuals.<sup>106</sup> In some studies, lymphocytes from old animals are not stimulated to the same

extent by IL-4 as lymphocytes from young mice<sup>107</sup> or by a combination of IL-4 and anti-IgM.<sup>108</sup>

Murine memory T cells from old animals produce less IL-4 than is produced from cells of young animals.<sup>109</sup> CD4+ T cells from young mice were more sensitive to stimulatory effects of exogenous IL-4 (producing much higher levels of IL-2 than old CD4+ T cells) in a similar system.<sup>11</sup> Blocking the effects of endogenous IL-4 boosted levels of specific anti-influenza IgM and IgG1 to levels seen in young animals in a primary antibody response, an effect also seen by blocking endogenous IFN- $\gamma$  and IL-10.<sup>110</sup> We found that lymphocytes from old adults produce less IL-4 with specific antigen stimulation than lymphocytes from young adults and are less sensitive to inhibition of specific antibody production when IL-4 is added early in the course of stimulation with specific antigen,<sup>111</sup> similar to the findings described in mice.<sup>11</sup>

Other investigators found no differences between lymphocytes from old and young adults in the ability to produce IL-4 or IL-6 when stimulated with the mitogen phytohemagglutinin.<sup>112</sup> In this model, lymphocytes from old adults produced significantly less IFN- $\gamma$ .<sup>112</sup> Some studies of human T-cell cultures utilizing different activation signals demonstrated increased IL-4 production and increased IFN- $\gamma$  production by old cells.<sup>5,113</sup>

Depending on donor age, NK cell cytotoxicity is differentially affected by IFN- $\gamma$ .<sup>114</sup> NK cells incubated with IL-2 secreted less IFN- $\gamma$  than those from young adults with unchanged cytotoxic activity.<sup>115</sup> Other investigators have reported increases of IFN- $\gamma$  in human lymphocyte<sup>116</sup> and CD4+ T-cell cultures.<sup>113</sup> In aging rats, lymphocytes demonstrate increased interferon and decreased IL-2 production with concanavalin-A stimulation.<sup>102</sup> Other laboratories have found no correlation between level of lymphocyte proliferation to mitogens and production of interferon.<sup>117</sup> Compared with cells of young donors, cells from old donors were more sensitive to a combination of IL-2 and IFN- $\gamma$ .<sup>117</sup> IFN- $\gamma$  mRNA and synthesis of IFN- $\gamma$  increase in T cells from old donors.<sup>118</sup>

Several investigators have described elevated circulating levels of IL-6 in old mice, monkeys, and adult humans,<sup>119-121</sup> while others observed no differences in circulating levels.<sup>122</sup> Old mouse peritoneal macrophages and human B cells cultured in vitro produce higher levels of IL-6 than macrophages from young mice when stimulated with mitogens.<sup>38,123</sup> IL-6 levels are elevated in unstimulated cultures of lymphocytes from old humans and mice.<sup>119</sup> Other studies failed to show differences in IL-6 production by lymphocytes from old adults in vitro.<sup>112</sup>

Changes in production of the neutrophil chemoattractant IL-8 have been described in comparisons of old and young adults. Lymphocytes from old adults produce less IL-8 spontaneously, a difference that appears to be due primarily to unresponsiveness of cells from old men.<sup>124</sup> When the lymphocytes were stimulated with the mitogen lipopolysaccharide, cells from the old men increased IL-8 production over eight-fold, while cells from old women showed no increase. Lymphocytes from young subjects of both sexes increased production of IL-8 but to a much smaller degree.<sup>124</sup>

The increased susceptibility to infection with *Mycobacterium tuberculosis* displayed by old mice is associated with lower levels of IL-12 in the lung, postulated to be related to decreased CD4+ T-cell function.<sup>125</sup> They have a delay in the emergence of protective, IFN- $\gamma$ -secreting CD4+ T cells.<sup>126</sup> These cells are slower to express surface adhesion markers that allow migration across endothelial linings to sites of active infection.<sup>126</sup> Alterations in other cytokines with aging may also contribute to the increased spread of disease in old animals.<sup>127</sup> Further work suggests that the major defect lies in the T-cell population: CD4+ cells from young mice protect old mice from infection, suggesting adequate function of old macrophages.<sup>128,129</sup> At this point it is not clear which of the age-related changes in interleukins is the "most critical." Certainly the defects described in IL-2 are some of the fundamental mechanisms underlying changes in early lymphocyte activation and function, and they have been linked to increased susceptibility to illness. It may be that changes in the steps leading to commitment of lymphocytes to produce a specific "profile" of cytokines will prove more important than changes in any particular interleukin, although there continue to be conflicting reports as to which pathways are predominant in aging.<sup>130,131</sup>

## Cell Activation and Membrane Signal Transduction

The proliferative response of T cells to various stimuli results from a complex set of interactions involving T cells and macrophages or other antigen-presenting cells. Mitogens or antigens are processed by antigen presenting cells and then bind to and cross-link with the T-cell antigen receptor. This results in activation of phospholipase C, cleavage of membrane phosphatidylinositol phosphates, and liberation of inositol triphosphate and diacylglycerol. Inositol triphosphate and perhaps inositol tetrakisphosphate play a key role in raising intracellular free calcium, which opens calcium channels.<sup>132-134</sup> Diacylglycerol binds to and activates protein kinase C, which is further activated by the increased

free calcium. A number of other protein kinases have also been identified and play a role in cell activation.

Activation of protein kinases leads to increased transcription and subsequent translation of the gene coding for IL-2 and of receptors for IL-2. IL-2 is thus an autocrine as well as a paracrine growth factor, produced by the same cells that respond to it. Exposure of IL-2 receptor-bearing T cells to IL-2 results in proliferation. Antigen-presenting cells such as monocytes help T cells to produce and respond to IL-2 by presenting antigen that occupies and cross-links T-cell receptors. These antigen-presenting cells secrete IL-1 and other monokines that provide additional signals necessary for complete activation of T cells.

Several laboratories have hypothesized that the decreased proliferative response of lymphocytes in aging is due to impaired membrane signal transduction in response to various stimuli. Studies in some strains of old mice have found decreased calcium metabolism associated with defective proliferation.<sup>4,135</sup> Mitogen stimulation leads to smaller rises in mean intracellular calcium levels than in young mouse T cells.<sup>136</sup> This is correlated to the shift from naive to memory phenotype, with memory cells displaying more resistance to mitogens, decreased tyrosine phosphorylation of phospholipase C-gamma 1, and a decreased ability to produce and respond to IL-2.<sup>136</sup> In these studies, no changes in inositol triphosphate production were found. However, inositol triphosphate formation was reduced in a system utilizing human peripheral blood neutrophils.<sup>137</sup>

T lymphocytes from aged animals that retain the ability to proliferate to mitogens have normal or enhanced mobilization of calcium compared with lymphocytes from young animals.<sup>138</sup> Similar results have been found with human peripheral blood lymphocytes and isolated T cells, where decreased calcium mobilization was a factor in defective proliferation in some T-cell subpopulations but not others.<sup>3,139,140</sup> A recent study found decreased cell-cell binding (a calcium/magnesium-dependent reaction) in monocyte-depleted lymphocytes from old donors compared with young donors.<sup>141</sup> This was believed to be secondary to altered activation of the lymphocyte adhesion molecule leukocyte function-associated antigen-1 (LFA-1) in the cells from old adults.

Other aspects of signal transduction are altered with aging. The level and duration of protein kinase activation by mitogens is significantly reduced in old humans.<sup>142</sup> Protein analyses have shown that levels of the isoenzyme protein kinase C alpha are significantly reduced in old T cells, although functional properties are comparable to those in young cells.<sup>143</sup> In old mouse

T cells, a decrease has been found in phosphorylation of all 16 phosphoproteins that are vigorously phosphorylated in young mouse cells.<sup>144</sup> In addition to the protein phosphokinases, there is impaired phosphorylation of protein tyrosine kinases in both CD4+ and CD8+ T cells from old animals.<sup>145</sup> As with T cells, the activation of protein kinase C and protein tyrosine kinases is reduced in B cells from old humans.<sup>146</sup> The actual expression of protein kinase C does not appear to be reduced in these cells.<sup>143</sup> Transcription of nuclear factors is decreased in old cells, correlating with decreased IL-2 production.<sup>147</sup> This is postulated to be due to impaired signal transduction, as expression of the nuclear factors is preserved with aging.<sup>148</sup>

## Immune-Deficiency and Disease

### *All-Cause Mortality*

There is not much direct causal evidence linking age-specific changes in immunity to clinical illnesses or mortality. The question of whether decreased immune responses contribute to morbidity and mortality in elderly persons has been addressed for the most part by studies looking for associations between abnormalities in a particular immune response and general health status.<sup>149</sup> Elderly subjects who display declines in absolute lymphocyte counts,<sup>150</sup> have two or more suppressed immune parameters,<sup>151</sup> display decreased proliferative lymphocyte responses<sup>15,149</sup> or are anergic<sup>14,152,153</sup> have higher mortality rates anywhere from 2 to 7 years after measuring the immune parameter.

### *Cancer*

One function of the immune system is postulated to be protection of the organism against the development of malignancy. The theory of "immune surveillance" proposes that the cellular immune system is constantly surveying for and eliminating malignancies when they arise and that clinical cancer represents a failure of this system.<sup>154-156</sup> Thus, elderly persons or other individuals with depressed immune function should have a higher incidence rate of malignancy, and advanced age is indeed the greatest risk factor for the development of cancer.<sup>157,158</sup> Recently, the lack of a generalized increase in most malignancies among immunosuppressed humans and experimental animals has placed this theory into relative disrepute. There was also no evidence of an increased incidence of cancer in older adults with impaired immune function over a 10-year period.<sup>149</sup>

Observations in a variety of murine species show an association between altered immunity with age and

the occurrence of cancer. For example, the majority of normally short-lived New Zealand black (NZB) mice develop expansions of malignant B-cell clones by 12 months of age, similar to the malignant B-cell transformation seen in human chronic lymphocytic leukemia.<sup>159,160</sup> The rare NZB mouse having a longer-than-expected life span has greatly expanded clones of T cells (CD8+, CD4+, and CD5+) compared with its shorter-lived brethren and also has markedly different patterns of cytokine production (more IFN- $\gamma$  and less IL-10).<sup>161</sup> Mice whose T cells carry mutations of genes controlling apoptosis also develop B-cell malignancies.<sup>162</sup> Deficiencies in such genes are also associated with "switching" of cells from a Th2 to a Th1 profile, ie, fewer cells secreting IL-4, IL-6, and IL-10.<sup>163</sup>

The factor of time may be of major importance in explaining why cancer is more common in older people. Those who live longer may develop cancer because there has been enough time to progress through a sequence of mutations ultimately resulting in malignancy, eg, from normal colon to hyperproliferation (loss of adenomatous polyposis coli), to early adenoma (DNA hypomethylation), to intermediate (activation of *k-ras*) and late adenoma (loss of DCC), to carcinoma (loss of p53), to metastatic disease.<sup>164</sup> There is increased variability in DNA methylation patterns with increasing time, a phenomenon seen in aging cells and neoplasms.<sup>82</sup> Normal age-related changes in susceptible tissues may permit the development of certain tumors such as the hormone-dependent cancers of the breast, ovary, and endometrium, and also non-Hodgkin's lymphoma.<sup>165,166</sup> Some changes in the aging immune system may actually result in more indolent tumor growth and lower levels of metastases than are seen in younger individuals, as in breast and prostate cancer.<sup>167,168</sup> However, although cancer incidence increases with age, aging changes in the biological nature of tumors may permit an elderly person to die with, rather than of, malignancy.

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