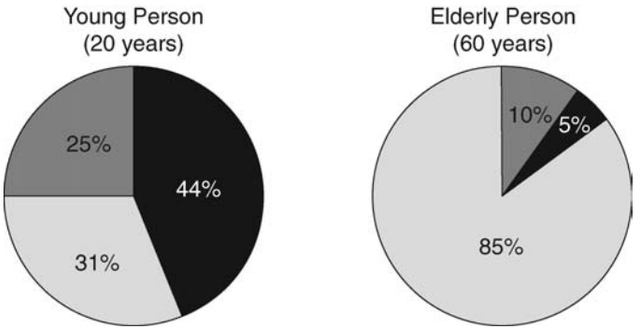

Figure 4 Age-dependent involution of the thymus. During aging, thymic cortex (*black*) and medulla (*grey*) are reduced in size, while adipose tissue (*white*) dominates the thymus in old age. Consequently, thymic output of recent thymic emigrants is decreased from $>10^9$ (1 year) to approximately 1.8×10^8 (>50 years). *Source*: From Ref. 16.

old age may originate from multiple factors, such as an increased post-thymic life span, homeostatic turnover, and/or long-term exposure to harmful environmental factors, which may affect not only the cytotoxic $CD8^+$ T-cell-mediated response to neoantigens in old age but also B-cell-mediated responses that rely on adequate stimulation by $CD4^+$ T-helper cells. While naive T-cell numbers decline with age, the life-long encounter of pathogens leads to the accumulation of antigen-experienced T cells. However, in old age, antigen-experienced T cells frequently display phenotypic as well as functional changes, which especially affect $CD8^+$ T cells (18). The loss of the costimulatory molecule CD28 is one of the most consistent biological indicators of aging of the human immune system. $CD28^-$ T cells are long-lived lymphocytes with short telomeres, an increased resistance to apoptosis and a highly restricted TCR repertoire. The loss of CD28 is accompanied by the loss of another costimulatory molecule, CD27 and by the decreased expression of lymph node homing markers, L-selectin (CD62L), and chemokine receptor 7 (CCR7). The loss of these molecules leads to a decreased stimulation of T cells by antigen-presenting cells (APCs) and to an impaired migration into lymph nodes. In addition, changes in the membrane lipid composition of T lymphocytes during aging lead to an impaired formation of the immunological synapse, which further contributes to decreased T-cell activation and signaling (19). The differentiation into $CD28^-$ T cells is accompanied by the secretion of the type 1 cytokine interferon (IFN)-γ and the loss of IL-2 production. The accumulation of terminally differentiated $CD28^-$ T cells thus contributes at least partly to the increased proinflammatory activity observed in the majority of elderly persons, while low $CD28^-$ T-cell numbers in old age

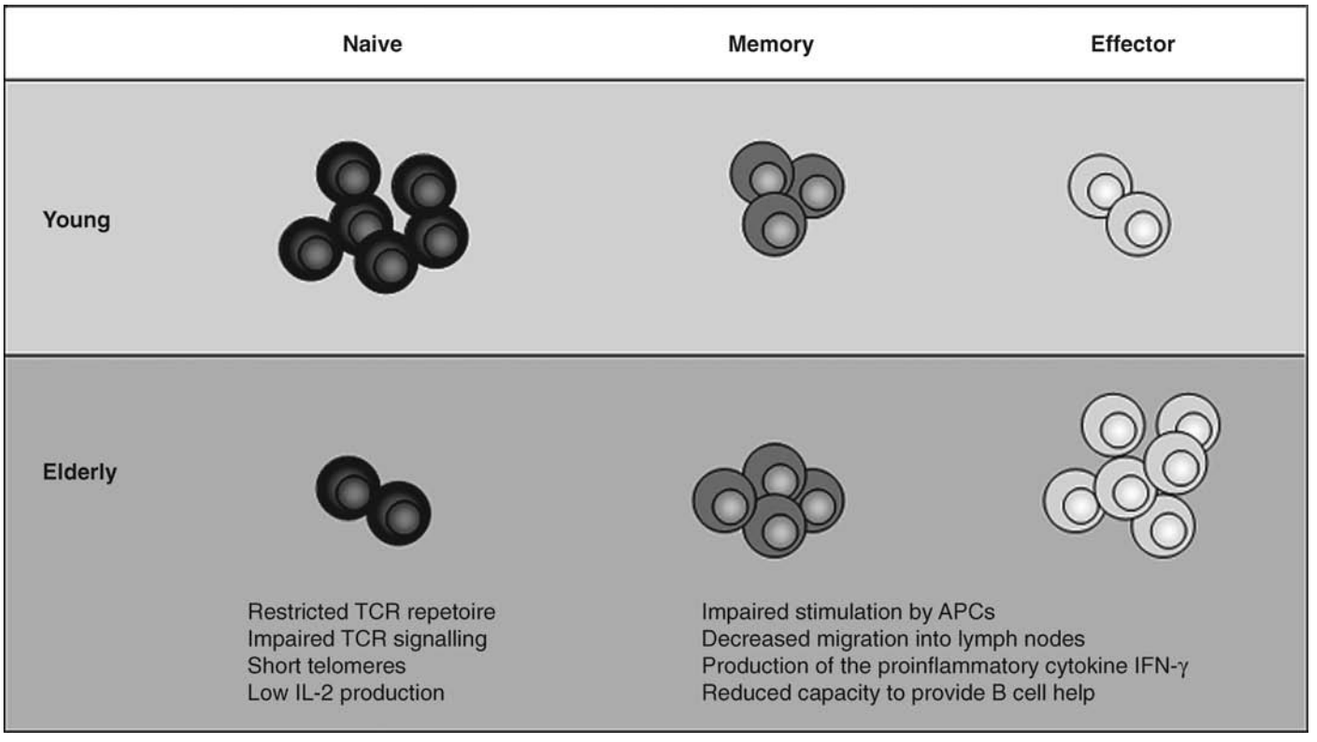

Figure 5 Age-related changes within the peripheral T-cell pool. The number of naive T cells decreases during aging, while antigen-experienced memory and effector T cells increase. In addition, peripheral naive as well as memory/effector T cells exhibit functional deficits in old age.