A new field of Immunogerontology has emerged to study the immune system in the elderly. The immune system was supposed to collapse with age, and several changes have been considered as paradigms of a defective responsiveness: Increased sensitivity to infectious diseases and cancer, decreased antibody production to non-self antigens, and increased levels of auto-antibodies, defective NK activity, and decreased T-lymphocyte proliferation (Miller & Osoba, 1967). Although, large amounts of data are not yet available on some key components of the immune system as it ages. Conclusions drawn from animal studies, tissue culture studies and human studies investigating the same topic often suggest conflicting conclusions, but these discrepancies will probably be resolved once more data become available. Controversy arises in part because gerontologists have not created commonly accepted definitions of when the aging process begins or at what point an individual is considered ‘aged.’ Traditional aging studies merely compared a population of ‘young’ individuals against a population of ‘old’ individuals without attempting to define ‘young’ and ‘old.’ Without a clear definition of these terms it is difficult to determine whether immunological differences observed in the aged group result from age only or are instead

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the results of age-related disease. To work around this problem and develop a definition of what normal aging is for a healthy older population, several studies have focused exclusively on centenarians under the assumption that an individual who lives to be 100 must be exceptionally healthy. Even though this population is extremely limited, the conclusions from these studies have helped to lay the groundwork for broader studies that include a younger elderly population.

When the immune systems of carefully selected, healthy, elderly people were investigated, it was found that physiological aging of the human immune system was probably not as altered as had been thought (Ligthart, Schuit, & Hijnmans, 1989; Ligthart, Schuit, & Hijnmans, 1985). This finding has great biological importance when considering the role of the immune system not only in its specific pathologies but also for other diseases not traditionally included among immune disorders, where immune responses may play an important or even crucial role (e.g., atherosclerosis, dementia, cancer). Last part of human life was a mystery because ‘aged’ individuals were thought to be 65-70 years old. The human lifespan can be considerably longer, i.e., 110-120 years, so that the last three or four decades of human life have been left immunologically and cytometrically unexplored. Moreover, because most studies have simply compared immune parameters from ‘young’ and ‘old’ individuals, the biological significance of the changes as they occur over time have not been fully understood. Human aging is a slow process, and determining when aging begins and choosing appropriate and reliable criteria for assessing it, is difficult.

It is well-documented that immunocompetence declines with age; that is, as people age, the immune system begins to loose some of its functions and cannot respond as quickly or as efficiently to stimuli. Age-related changes in the immune system have been observed at all levels ranging from chemical changes
within the cells, to differences in the kinds of proteins found on
the cell surface, and even to alterations in entire organs. Studied
separately, some of these changes may seem trivial, but when all
of the changes are added up, they radically affect the overall
health of the individual.

One major change that occurs as the body ages is a process
termed “thymic involution.” The thymus, located above the heart
behind the breast bone, is the organ where T cells mature. T cells
are an extremely important, highly-specialized population of
lymphocytes that have many functions ranging from killing
bacteria to assisting other cell types of the immune system. As
humans age, the thymus naturally atrophies. The volume of thymic
tissue in a 60-years-old adult is less than 5% that of a newborn,
and it is postulated that if humans lived to be more than 120, the
thymus would disappear altogether. Although T cells are produced
continuously throughout life, over time this progressive decay of
the thymus causes a sharp decrease in the number and type of T
cells produced. It is not known why the thymus deteriorates in
this fashion. The prevailing theory is that the thymus is an
extremely energy-expensive organ that is most needed in the early
stages of life when the body has not had time to develop resistance
to foreign antigens. Once the immune system fully develops and
can protect the host against a myriad of antigens, the thymus may
be too costly to maintain, so it is evolutionarily advantageous to
decrease the amount of thymic tissue and use the energy that
would have supported the thymus for other purposes. However,
because T cells play such a prominent role in immunity, longer-
lived individuals still need a continuous supply of ‘fresh’ T cells
to protect against newly-encountered antigens, and this slow but
progressive loss of thymic tissue has profound effects on the
entire immune system of the aged.

Aging affects the functions of T cells in a myriad of ways.
Several subpopulations of T cells are found in the thymus and in
the blood circulation, among them, naive T cells and memory T cells. Naive T cells are quiescent T cells that have never been exposed to any foreign antigen, while memory T cells are long-lived antigen-activated cells that rapidly respond to a second exposure to the same antigen. When encountering a foreign antigen, naive T cells become activated, stimulate the immune system to eliminate the foreign antigens from the body, and convert into memory T cells. The memory T cells then become dormant and are only reactivated upon a subsequent exposure to that same antigen. A marked difference has been observed between young and old subjects in the subpopulations of naive and memory T cells. In newborns, the ratio of naive to memory T cells is quite high; in adults the ratio is reversed because most of the naive T cells have been exposed to antigen, and hence converted to memory cells. The elderly have almost no naive T cells at all, since as the thymus progressively deteriorates with age, fewer T cells are produced, and the naive T cell subpopulation is not replenished. Consequently, the stock of naive T cells becomes depleted and the aged immune system cannot respond as well as a young person to a ‘new’ antigen.

In addition to the decline of certain subpopulations of T cells, important changes occur at the cell surface of all T cells. When a T cell, using T cell receptor proteins found on the cell surface, binds to an antigen, that environmental stimulus must be communicated to the interior of the T cell. Many molecules are involved in “signal transduction,” the process of transmitting the antigen-binding signal across the cell membrane into the cell. Signal transduction is a cascade of chemical reactions, each dependent upon the preceding event. Aged T cells do not display the CD 28 antigen, a molecule critical for signal transduction and T cell activation, on the cell surface. Without this protein, T cells remain quiescent and do not respond to foreign pathogens. One indication of a malfunctioning signal transduction pathway in T cells is that the presence of CD69 antigen on the cell surface is
lower in elderly individuals. T cells are induced to display CD69 antigen only after antigen binds to the T cell receptor. If the antigen-binding signal is not transmitted to the interior of the T cell, CD69 antigen will not appear on the cell surface, and is an indication that in older people, less signal transduction is occurring.

Another defect of T cell activation among the elderly is characterized by a decrease in calcium. Calcium is a vital element that is absolutely crucial for many biochemical reactions, including signal transduction. A calcium deficiency in T cells effectively halts signal transduction by failing to stimulate enzymes, including protein kinase C, MAPK and MEK, that require calcium for proper function. Decreased amounts of calcium can also inhibit production of cytokines, proteins responsible for coordinating the interaction with antigen and amplifying the immune response.

One cytokine that has been widely studied is interleukin 2 (IL-2), a cytokine produced and secreted by T cells that induces cell proliferation and supports long-term growth of T cells. As T cells age, they lose their capacity to produce and respond to IL-2. When exposed to antigen, memory T cells will rapidly divide and proliferate to make more T cell clones to fight the antigen, but only proliferate upon stimulation with IL-2. If not enough IL-2 is produced, or if the T cells cannot respond effectively to IL-2, T cell function is greatly impaired. Changes in other cytokines such as interleukin 4, tumour necrosis factor-alpha, and gamma-interferon have also been recorded, but it is not yet known to what extent these changes influence the aging immune system.

Age-related genetic alterations occur within T cells as well. In vitro studies of human T cells cultured for long periods have shown that the cell cycle slows and eventually halts, even when the cells are grown in the presence of IL-2; that is, the T cells cease to divide and become too old to function properly. Several problems with the genetic machinery of T cells may account for this slow failure of the cell cycle. Transcription factors (like NF-
KB and AP-1), proteins that use a DNA template to create RNA during the process of manufacturing protein, appear to be impaired or become inactive, which through aging contribute to the decline in T cell responsiveness by failing to activate the genes necessary for T cell stimulation. Aged T cells are more susceptible to apoptosis, or programmed cell death, due in part to the gradual loss of telomeres that cap the ends of the chromosomes to prevent DNA degradation. T cell receptor gene rearrangement problems contribute to thymic involution by making the cells less resistant to apoptosis. Thus it seems that T cells have a limited lifespan, and immunosenescence is genetically programmed.

This reduced function of T cells in the elderly also affects B cell function because T cells act in concert with B cells to regulate the production of antibodies. T cells induce B cells to hypermutate immunoglobulin genes, which in turn create the antibody diversity necessary to recognize a wide range of antigens. Aged helper T cells cannot interact as effectively with B cells, and so in the elderly, the potential antibody repertoire is more restricted than the antibody repertoire of younger people. The production of immunoglobulin M (IgM), one of five classes of antibodies, is especially affected. During infection, IgM is the first class of antibodies to respond. In the elderly the inability to ward off infections easily withstood by younger people could be linked to this diminishing IgM response. The rate of B cell maturation also decreases with age. Although B cells are produced in the bone marrow throughout life, the number of B cells generated declines with age. Having fewer mature B cells contributes to the observed decrease in the amount of antibody produced in response to infection.

Autoantibodies, antibodies that react against ‘self’ antigens, are usually hallmarks of autoimmune disease. However, the presence of autoantibodies is often correlated to age, even in healthy aged individuals who do not have an autoimmune disease. Although interleukin 10 (IL-10) is one molecule that stimulates
production of autoantibodies in patients with autoimmune disease, IL-10 does not seem to have this effect in healthy aged individuals. Instead, autoantibody production in the elderly may be linked to the functional changes in T cells described above. It appears that autoantibody production in small quantities is a normal part of aging, although the reasons behind this are not understood. One possibility is that age-related mutations in T cell genes could create a subpopulation of T cells that recognize host self-antigen. Normally, such T cells would be eliminated in the thymus before they fully matured, but thymic involution allows this destructive population of T cells to persist. These T cells could then induce B cells to produce autoantibodies against self antigens. This theory seems to be supported by a study performed in mice demonstrating that transplantation of a fetal thymus into an aged recipient with an autoimmune disease can restore immune function and thus treat autoimmunity.

Other cells of the immune system are also affected by aging. The activity of leukocytes, including macrophages, monocytes, neutrophils, and eosinophils, is reduced in the elderly, although there are very little data available on the effects of aging on these cell types. Natural killer (NK) cells, cells that secrete cytokines and kill other cells, are one cell type that has been studied extensively. It was once thought that all NK cell functions decline with age, but this theory was based primarily on mouse studies and on human studies performed without using the SENIEUR protocol. In studies where the SENIEUR protocol was employed, it was found that NK cell activity in human’s changes very little over time, although one contradictory study suggests that even though the cytotoxic (cell-killing) function of NK cells is maintained, the cytokine secretory activity is impaired. Since cytokines play an important role in tumour development and warding off infection, immunosenescence of NK cells could have extensive effects on the immune system. More research of NK cells is needed to resolve these discrepancies.
What implications do all of these changes in the aging immune system have for health care of the elderly? Two areas of preventive health care have been widely studied: vaccination and nutrition.

It is well-documented that the elderly do not respond as well to vaccinations as young people. The purpose of a vaccine is to ‘educate’ the immune system against an infectious agent. Vaccines provide a non-infectious substance containing the same antigens as the foreign pathogen to teach the immune system to recognize that foreign pathogen by creating populations of memory T cells and antibody-producing B cells and thus prevent future infection. Some vaccines, like the vaccine for smallpox, only need to be administered once to confer lifetime immunity. Other vaccines, such as vaccines for influenza, need to be administered annually because there are multiple strains of influenza virus and the dominant strain changes each year. Influenza and pneumonia are two diseases that particularly affect the elderly, and providing vaccinations is a high priority in eldercare. However, there are special challenges involved in developing vaccines targeted for older adults. In the elderly, antibody responses to vaccines are slower and not as strong as in younger people, and T cell subpopulations are not very responsive to vaccines. For reasons that are not yet clear, memory T cells from aged individuals do not react as quickly or for as great a duration as cells from younger subjects. Numerous studies have examined means of improving the efficacy of vaccines for the aged. Novel types of vaccine delivery using, for example, liposomes or naked DNA to create a more powerful immune response, are being developed. Alternative adjuvants such as IL-2 are being tested to boost vaccine efficacy. New methods of vaccination, like using nasal sprays or oral vaccines to stimulate mucosal immunity, instead of the traditional injections, are also being explored.

Nutrition plays a prominent role in immune response, and the elderly often suffer from malnutrition. Reduced caloric intake is known to slow the aging process and help maintain higher numbers
of naive T cells and levels of IL-2. Vitamin E and zinc in particular are important nutrients for the proper functioning of the immune system. Long-term zinc deficiency in the elderly causes a decrease in cytokine production and impaired regulation of helper T cell activity. Vitamin E has recently been in the news as a possible treatment for Alzheimer’s and it seems that vitamin E supplements may also boost the immune system. In both mice and humans, a daily dose of vitamin E significantly higher than the U.S. Recommended Daily Allowance improved T cell function in cell-mediated immunity. Vitamin E is also an antioxidant that can protect lymphocytes, the brain, and other tissues from destructive free radicals (Whitman, 1999).

REFERENCES


Ligthart, G.J., Schuit, H.R.E., & Hijmans, W. (1989). Natural killer function is not diminished in the healthy aged and is proportional to the number of NK cells in the peripheral blood. *Immunology, 68*, 396-402.
