Aging, Infections, and the Immune System

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There is increasing clinical and laboratory evidence of decline in the immune system in the elderly patient with a simultaneous rise in the incidence of certain infections. Along with the involution of the thymus gland with age, there is evidence of decline in both T- and B-lymphocyte function and also in delayed hypersensitivity. In addition, there is evidence of an increase in various autoantibodies as a person ages. In recent years evidence has been presented of a genetic basis to this declining system. Because of these changes and because severe infections present more subtly in the elderly patient than in the young, the physician's suspicion for serious infections in the elderly should be heightened and immunization programs in the elderly adhered to.

W hile elderly individuals in the absence of other illness should probably not be considered immunocompromised in the same sense that patients with inherited immunodeficiency or acquired immunodeficiency syndrome are, some clinical and laboratory evidence suggests that the geriatric years of life are a time of at least some immune decline and therefore a period in which susceptibility to infection increases. The decline of the immune system with age actually constitutes one theory as to the cause of biological aging[1] along with the neuroendocrine, DNA repair, free radical, and other theories.[2,3] The purpose of this article is to examine the available evidence for immune decline in the elderly and to describe how the physician might approach infections and immunizations in the aged individual.

THEORETICAL PREMISES

The aging curves in Figure 1[4] show that whereas the average life span of individuals has increased since recorded history, the maximum life span has not. Many gerontologists feel therefore that senility and death will take place in patients in the absence of disease. This assumption contradicts the common notion that modern medicine has lengthened the human life span.[5] It is felt that the

conquest of all remaining diseases without retardation of the basic aging process will add only ten[3] to 20[4,5] years to mean human survival and will not influence maximum survival at all. With the conquest of all remaining diseases, populations should age according to the ideal survival curve (top) in Figure 1. Significant increases in the period of vigorous life will therefore most likely be achieved through biological inhibition of the aging process itself.[3,4]

CLINICAL EVIDENCE FOR ALTERED IMMUNE FUNCTION WITH AGING

The human immune system has been said to reach its optimum functioning capacity at about the time of puberty or somewhat later and then decline to 5 to 30 percent of its original capacity over a person's lifetime, depending on the measurement being assessed.[3] There are some clinical observations that make one suspect that altered immune function accompanies aging. Some of the unusual bacteria that cause meningitis in the newborn and premature infants, such as gram-negative bacteria, listeria, and Staphylococcus aureus, reemerge to cause meningitis in elderly and otherwise debilitated patients. The elderly also have an increased rate of gram-negative colonization and bacteremia.[6] While it is true that many elderly individuals might be expected to be less resistant to infection on the basis of other underlying illness, these clinical trends are nevertheless apparent.

Whereas it has not been documented that there is an increase in the rates of all types of infections in the elderly over the young, increases have been documented in urinary tract infections,[7] respiratory tract infections, and
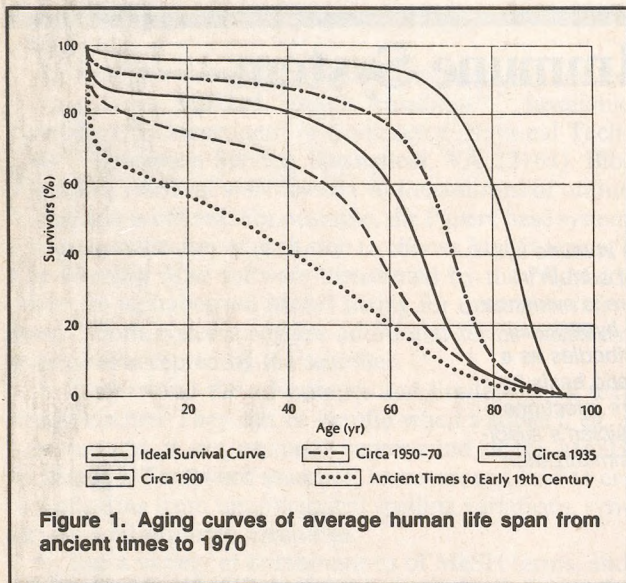
Figure 1. Aging curves of average human life span from ancient times to 1970

wound infections, and a proportionate increase has been shown in nosocomial infections in elderly over young patients.[8] There is also an increase in the mortality rate from influenza and bronchopneumonia in the elderly over the young.[8] Mycobacterium tuberculosis and herpes zoster infections are most common among elderly patients, and tetanus has now become an illness of the elderly.[6]

IMMUNOBIOLOGICAL EVIDENCE FOR ALTERED IMMUNE FUNCTION WITH AGING

Other sources are best consulted for a review of general immunology.[9,10] The immunobiological evidence for the decline of the immune system with aging is somewhat scattered, and a unified model for the aging of the immune system has not yet been uniformly accepted. Some laboratory observations exist, however, that favor the existence of some immune decline in the elderly.

It is well known that the thymus gland, which is considered necessary for T-lymphocyte maturation, begins to involute around puberty and regresses until only a few remnants of lymphoid tissue are present in senescence.[11,12] The significance of this involution is unclear, since significant loss of immune responsiveness does not immediately follow significant involution, and some workers feel that thymic involution is a necessary stage in the mature immune system. However, levels of thymopoietin, a thymic hormone that acts to stimulate the production of rosetting (mature, postthymic) T cells, begin to decline around the age of 30 years and can no longer be detected in humans over 60 years of age.[11] Other thymic hormones, such as thymosin and facteur thymique serique, start to disappear at an earlier age.[13] While the relationship between thymic hormones and immune responsiveness is not clear, this failure of the thymus to support the differentiation of immature lymphocytes appears to result in an increased number of immature T-lymphocytes in the peripheral blood.[11]

Of the cells making up the immune system, the cell that appears to suffer the most decline in function is the T-lymphocyte.[12] Longitudinal studies of healthy subjects have shown that the total number of lymphocytes in peripheral blood does not change over time. Furthermore, decreasing numbers of cells in the blood may have no bearing on their actual function in tissues. Nevertheless, it has been noted that there is an age-related decline for both the absolute number and percentage representation of peripheral T-lymphocytes.[6,12,14,15] Evidence is conflicting as to whether there is an increase or decrease in suppressor T cell activity or a decrease in helper T cell activity with aging[1,6,12,16,17] and agreement on this issue is as yet forthcoming. It has been shown in vitro, however, that the number of doublings of a population of cultured human peripheral T cells decreases with age of donor.[1] While this occurrence may be unfortunate for the aging immune system, it may not be surprising, since it was demonstrated originally in human fibroblasts in 1965 in a classic series of experiments by Hayflick and has been demonstrated in cells of other tissues since then.[5,18] T-lymphocytes from old human donors are less responsive to plant mitogens such as pokeweed, phytohemagglutinin, and concanavalin A, however.[12,13,16,19] T cells from older subjects when tested in vitro are deficient both in the production of interleukin-2 (or T cell growth factor, which appears to be necessary for T cell proliferation) and in their ability to bind and respond to the factor.[13,16] Finally, a decline in lymphocytotoxic response with age has been demonstrated in mice.[1,11,12] Cytotoxic T-lymphocytes are the effector cells in graft rejection, and impaired graft rejection may reflect a defect in the generation of cytotoxic T-lymphocytes.[11]

It is difficult to judge how much B cell function is impaired because many B cell functions are dependent on T cell function. It is even possible that B cell changes are secondary to age-associated changes in T cell function.[11] Animal evidence exists, however, of suppressor B cells and that suppressor B cell activity increases with age.[20] There has also been shown to be a decrease in mice in vitro of the responsiveness of B cells to bacterial endotoxin from the colon and an associated decrease of Kupffer cell activity.[16,21] The effects of continuous exposure of the immune system to endotoxin constitute one theory of aging.[16] There is also a decrease in the qualitative and quantitative antibody response to both thymus-dependent and thymus-independent antigens.[3] Furthermore, a decrease

in levels of natural antibodies (to foreign blood cells and microbes) in elderly patients has been shown,[16] and the antibody that is produced has reduced antigen avidity.[3,6,16]

It is ironic with aging that autoimmunity appears to rise while cellular and humoral immune functions appear to decline. The incidence of anti-deoxyribonucleic acid (DNA) antibodies, antithyroid antibodies, rheumatoid factor, and antibodies to smooth muscle, mitochondria,[11] immunoglobulin, thyroglobulin, red cells, and gastric parietal cells[16] have all been shown to increase with age. While the exact role of these autoantibodies is not known, some investigators have felt they might cause slowly progressive tissue damage and in this manner may contribute to physical aging.[1,13] Interestingly, some of these antibodies have been shown to interact with brain neurons.[1,22] One class of autoantibodies, autoantiidiotypic antibody (antibody directed against the binding site of another antibody), may play a role in shutting down the immune response. Old laboratory animals produce more autoantiidiotypic antibody during the immune response than do young animals. This action blocks lymphocyte secretion of specific antibody and therefore may not only reflect immunological aging but may also contribute to its progression.[11] Increases in other products of immune system dysregulation, such as immune complexes and monoclonal gammopathies, have been noted.[13] The explanation for these observations is controversial. Some feel that this observed increase in antibodies with age represents overactivity of the immune system; others feel it is a sign of immune dysregulation and the impairment of one subset of T suppressor cells (which suppress autoimmunity) with age.[3,13]

There is little evidence of macrophage dysfunction with age.[14] In fact, an increase in peritoneal macrophage numbers and activity thought to be secondary to the presence of chemoattractants, possibly endotoxin, has been demonstrated in aged mice.[16]

Some evidence also exists that there is a relative decline in delayed hypersensitivity with aging.[11,12,16,19,21] For example, reactivity to the tuberculin skin test declines after the age of 70 years, the same group in which reactivation of tuberculosis is more common.[18] This impaired response in the elderly to common skin test antigens might reflect an altered response to antigenic challenge, loss of immunologic memory, or both.[11] Some controversy exists, however, in that it is unclear as to how much the decline in these reactions is due to the aging process and how much is due to underlying diseases that are common in the aged population.[6]

OTHER FACTORS CONTRIBUTING TO INFECTIONS IN THE ELDERLY

The decreased responsiveness of the immune system is probably not the only factor that contributes to increased susceptibility to infections in the elderly. Poor nutrition with vitamin deficiency could increase susceptibility to infections in some elderly persons by depressing both humoral and cell-mediated immunity in the same way that it would in other malnourished states, such as in populations with kwashiorkor and marasmus.[6,8,23] With age, alterations in mucosal defense barriers, for example, could increase bacterial adherence and susceptibility of the tracheobronchial tree to colonization. Years of cigarette smoking would probably contribute adversely to the latter problem. Urinary stasis with the onset of benign prostatic hyperplasia with age could contribute to urinary tract infections in male patients. The contribution of environmental factors such as crowded living conditions and psychological stress are likely to play a role, but because they are more difficult to study, have yet to be elicited.[8]

The few available studies appear to show no gross deficiencies in complement levels, and, if anything, show increases in the levels of complement components in the elderly.[8,24]

THE MAJOR HISTOCOMPATIBILITY COMPLEX

Although an area of active investigation, the major histocompatibility complex (MHC) may nevertheless be relevant to discuss, as its potential relationship to immunological aging has been recognized by Walford.[3] The MHC is a collection of genes located on the sixth chromosome in humans (chromosome 17 in mice) that, though it codes for unrelated genetic information, may also exert a regulatory influence on immune function, on self-nonself immunologic recognition, and, Walford submits, aging. (Work by Hayflick[5,18] also suggests that the clock that determines the rate of cellular aging is in the nucleus.) That some diseases characterized by accelerated aging, such as insulin-dependent diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, and some late-life malignancies in mice,[2,25] are MHC influenced or controlled may cloud the possible role of MHC in aging itself.[1] Walford, however, has also put forth evidence that the MHC may in part regulate DNA repair. One may then conceptualize how inadequacies, failure, or errors in the latter may be an important cause in aging, since defective DNA would produce defective cell proteins. He also points to evidence that superoxide dismutase and catalase, which protect against cell damage from free radicals, and the glyoxalase enzyme system, which degrades glyoxal (detrimental to proteins, membranes, and other tissue components), may be MHC linked or controlled. Thus is seen the possible linkage of the free radical, immunologic, and DNA theories of aging. While highly

speculative in nature, this error-immunologic theory is currently the only one of the aging theories with the potential for elucidating the relationship between biologic and pathologic aging.[4]

Dysfunctional enzyme systems that repair DNA are theorized as the principal sources of spontaneous mutations. Thus both aging and cancer may be the somatic "price" individual organisms have to pay for the terminal mutations that would otherwise contribute to the survival of the species.[4]

EXPERIMENTAL MODALITIES

Mankind's search for ways of increasing his maximum life span have thus far been largely unrewarding. Nevertheless, there have been some experimental modalities that have been shown, probably because of their positive effects on the immune system, to aid in the deceleration of the aging process and to increase life span in laboratory animals. Long-term reduction of core body temperature has been shown to increase maximal life span in some animals. It is speculated that this reduction in temperature plays a role in inhibiting or preventing autoimmunity.[1,26] Caloric restriction without malnutrition, also attempted with some success in animals, appears to delay immune maturation, which consequently allows for less immune decline later in life.[1,27]

RECOMMENDATIONS FOR OBSERVING THE ELDERLY FOR INFECTION

Because of this decline in immune function with concurrent increase in some types of infections, when dealing with elderly patients, the practicing physician is advised to observe and maintain a high index of suspicion for infections, especially with regard to the urinary and respiratory tracts. While the degree to which they are related to immune decline, to chronic illness, or to other mediators is not clear, serious infections do not present classically in the elderly person. Sometimes minor changes in daily function, such as excessive fatigue, mild confusion, and changes in mental status, are the only signs as to the onset of severe infection. Minor changes in vital signs, ie, a mild drop in blood pressure or slight increase in the respiratory rate or pulse, may be early clinical signs of severe infection in institutionalized elderly patients. Also, hypothermia as well as mild hyperthermia may be the first indication of serious infection in the elderly patient. For the physician who has been familiar with an elderly patient for a long time, a high index of suspicion may be the best diagnostic tool to effecting early hospitalization and starting antibiotics.

Partly because of the immune decline but, more importantly, because clinical studies have shown that immunization prevents some infectious diseases in the elderly, immunization schedules should be established for the elderly person as for children, and current recommendations should be adhered to. Patients aged 65 years or older should receive influenza vaccine annually, booster tetanus toxoid every ten years, and pneumococcal vaccine once. Since routine immunization for tetanus in children did not take place until the 1940s, those older patients who have never received a primary series of tetanus immunizations should have it.[6]

If a clinical assessment of a patient's immune status is desirable, delayed hypersensitivity responses to common skin test antigens (mumps, candida, and streptokinase-streptodornase) and total peripheral blood lymphocytes may be measured. These variables tend to correlate with immune competence and have been shown, when depressed, to have predictive value for postoperative sepsis and other complications.[6,28]

It should be mentioned that work has been done on the use of single agents to stimulate immune function. Of these agents, zinc has the most evidence in its favor, showing some improvement both in cell-mediated and humoral immune responses with its use.[6,8,29,30] It is not, however, formally recommended to attempt to enhance immune function in the elderly with zinc or vitamin preparations, and the hazards of zinc toxicity should be considered in prescribing this agent in aged individuals.

FINAL COMMENT

Evidence has been presented of some decline in both the cell-mediated and humoral arms of the immune system in the elderly. This evidence should lead physicians to be more wary of serious infections in the elderly and should also prompt the physician to keep the elderly patient's immunizations current. Because of the increasing knowledge of the human immune system and increased understanding of its genetic connections, the prediction has been made that there will be a major breakthrough in understanding and controlling the aging process before the end of the century. The prospect of being able to control the rate at which a patient ages and thus lengthen his life span is overwhelming, having many social and economic implications. Walford, among others, has expressed the feeling that improvement in international relations and elimination of the possibility of global war is likely to make this prospect a more meaningful one.[31]

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