Aging Research (II): Pacemakers for Aging?

Loss of physiological adaptability is one of the hallmarks of old age. As people grow older, their bodies can no longer cope with stress or environmental change as easily as they once could. Because the immune and neuroendocrine systems are intimately involved with adaptation, they have increasingly caught the attention of gerontologists looking for the causes of aging. The declining efficiency of these systems with increasing age has been well documented.

Unfortunately for investigators who are trying to sort out the causes of senescence, old age is accompanied by increases in the incidence of a number of diseases. This makes it difficult to determine whether the changes associated with old age cause the diseases or whether the reverse is true. It is clear, for example, that immune function reaches a maximum in young adults and then declines with age. Equally clear is the rise in the susceptibility of older persons to conditions such as cancer and autoimmune diseases that appear to be associated with immune deficiency. What is not so clear is whether these diseases compromise immune functions or whether the fall in immune functions predisposes an individual to the illnesses.

Evidence can be marshalled in favor of both points of view. Most investigators, however, have adopted the latter assumption as a working hypothesis—at least until further evidence proves it to be incorrect.

The activities of both B cells (bone marrow–derived) and T cells (thymus-derived) decrease in aged animals. When properly stimulated, B cells differentiate into plasma cells that secrete antibodies; antibodies provide immunity against many types of disease-causing microorganisms. The T cells form "killer" lymphocytes that kill foreign cells and, probaby, tumor cells. They also help to regulate immune responses, including those of B cells. As regulators, T cells act both as B cell "helpers" that are needed for B cell differentiation and as suppressors of B cell activity. It is not known whether one cell can perform both functions.

According to Takashi Makinodan of the Gerontology Research Center in Baltimore, Maryland, soon to be a branch of the National Institute on Aging (*Science*, 20 December, p. 1106), the age-related decline in immunological activities is due partly to changes in the environment of T and B lymphocytes, but mostly to changes in the cells themselves. Makinodan compared the activities of cells from young donor mice transplanted into young and old recipients with those of old cells also transplanted into young and old recipients. From the data, he calculated that about 90 percent of the total decline in immune function was due to changes in the cells of old animals.

The question then is whether the changes occur primarily in T cells or B cells or whether both are affected. At present most evidence favors the T cells as the ones changed.

Thymus Atrophy and Aging

Investigators such as MacFarlane Burnet, now at the University of Melbourne, Australia, have suggested that the thymus gland, which is necessary for the differentiation of T cells from their precursors, is the biological clock that determines how fast we age. This idea is analogous to that of Leonard Hayflick of Stanford University, Stanford, California, who thinks that cells have an intrinsic program that limits their capacity to divide (*Science*, 20 December, p. 1105). Here, the thymus would be the pacemaker for the whole body, and its atrophy would be the programmed event that leads to aging of the animal.

The thymus begins to atrophy at an early age, shortly after puberty in humans. A number of studies in humans and rodents indicate that B cell functions begin to decline shortly afterward. Makinodan points out that this suggests that aging affects antibody responses indirectly through its effects on the T cells that regulate B cell differentiation.

With W. H. Adler, also at the Gerontology Research Center, he has evidence that at least one activity of T cells declines with age much faster than does a similar activity of B cells. These investigators found that the capacity of T cells from a long-lived strain of mice to divide in response to agents that stimulate mitosis had already declined markedly by the time the mice were 8 months old; by 24 months, it was only 10 percent of that of cells from 3-month-old animals. In contrast, the response of B cells from 24-month-old animals was 90 percent of that of cells from 3-month-old mice.

A decline in T cells activity could produce the immunological changes associated with aging by causing a decline in B cell differentiation to antibody-producing cells. Alternatively, loss of suppressor activities of T cells on antibody secretion by B cells could result in the increased autoimmunity (destruction by the immune system of the body's own tissues) known to occur in the aged. Old people have elevated levels of autoantibodies (antibodies directed at their own cells), and some of the pathologic characteristics of senescence resemble those of autoimmune conditions. The aged are also more susceptible than the young to a number of diseases, including rheumatoid arthritis and "maturity-onset" diabetes, that are thought to be of autoimmune origin.

A number of theories, in addition to those involving suppressor activities of T cells, have been proposed to account for the development of autoimmunity. Some investigators have suggested that cell antigens that are normally shielded from the immune system in the cell interior are exposed and recognized as foreign, possibly as a result of viral infection. Others, such as Roy Walford of the University of California School of Medicine in Los Angeles, have suggested that loss of control of immunological tolerance for self may cause an increase in autoimmunity and, consequently, aging. He is interested in the possibility that loss of histocompatibility antigens (cell surface antigens that elicit transplant rejections), which appears to occur in cultured cells before other degenerative changes, could cause defects in the capacity of lymphocytes to recognize "self."

The immune system is a major target of investigators who would like to devise ways to retard aging. Two strategies that may act through the immune system involve restricting caloric intake, especially in young animals, and lowering body temperatures. Both have worked with experimental animals, but neither are practical for humans at this time.

Forty years ago, C. M. McCay observed that caloric restriction prolonged the lives of rats by 50 to 100 percent; this has been confirmed in a number of laboratories, including that of Morris Ross at the Fox Chase Institute for Cancer Research in Philadelphia, Pennsylvania. The diets, although low in calories, must be nutritionally adequate.

A low-calorie, low-protein diet depressed both cellular and humoral immunity in weanling mice kept on the diet for 5 weeks, according to D. G. Jose, now at the Royal Children's Hospital Research Foundation in Melbourne, Australia, and Robert Good of the Sloan-Kettering Memorial Institute in New York. Walford, with Richard Liu, also at the UCLA School of Medicine, found that such a diet delays the maturation of immune responses so that they appear low in young animals; in older animals, however, the responses are actually greater than those of mice fed the control diet. Walford hypothesizes that this immunosuppression in early life may delay the appearance of autoantibodies and thus aging.

Lowering the body temperature of fish prolonged their lives, according to Walford and Liu. They do not think that the prolongation was simply due to a general slowing of metabolism because the growth rate and eventual size of the fish were actually greater at the lower temperatures. Cooling the animals by about 5°C did depress their immune responses, however.

Hormones and Enzyme Induction

Since the endocrine and nervous systems act, often together, to enable an organism to adapt to environmental changes, these systems are also being examined as possible sites of aging pacemakers. The role of hormones in aging may be studied by means of their effects on enzyme induction. A number of stimuli, many of them acting indirectly by stimulating the release of hormones, induce the synthesis of enzymes by animal tissues. As animals age, their ability to respond to the stimuli may be modified in a variety of ways. The response may be slowed and decreased in magnitude; or it may be diminished or enhanced but not altered in rate; or it may be delayed but eventually reach the same magnitude as in young animals.

In many of these cases, the change producing the altered response does not appear to reside in the cells that synthesize the enzymes. For example, Caleb Finch of the University of Southern California in Los Angeles found that exposure of young mice to cold produced a rapid induction of the synthesis of the enzyme tyrosine aminotransferase in liver. In mice older than 24 months, the enzyme concentration eventually reached the same level as in young animals but only after a lag period. Injection of insulin and corticosterone, hormones known to act directly on liver, induced the enzyme in young and old animals with equal speed. Finch concluded that basic cellular function of liver is maintained throughout life when the appropriate stimuli are present.

Another system that has been extensively investigated is the induction of the enzyme glucokinase in liver in response to glucose. The glucose acts indirectly by stimulating insulin secretion by the pancreas. Richard Adelman of the Temple University School of Medicine, Philadelphia, Pennsylvania, observed that, as male rats aged from 2 to 24 months, the time required for glucose to increase glucokinase activity in liver also increased progressively. Again, the response to injection of insulin was just as fast in old as in young rats. In order to minimize the influences of environment and disease on their results, both Finch and Adelman use only healthy animals that have been maintained in special colonies under closely controlled conditions for their investigations.

Since aging does not appear to impair the capacity of the liver to respond to insulin, Adelman is now attempting to trace the effects of aging on insulin secretion and activity. A number of possibilities are under investigation. One of them is that insulin secretion decreases as animals age. Adelman found that, as rats aged from 12 to 24 months, there was a marked decrease in the insulin concentration in the vein that leads directly from the pancreas to the liver. There was no change in the concentration between 2 and 12 months. Adelman said that the biological activity of isolated insulin does not decrease with age; it was the same whether isolated from young or old animals.

Another possibility is a decrease in insulin binding to membrane receptors, which is necessary if the hormone is to exert its effects on sensitive cells. The binding capacity of preparations of cell membranes decreased by 50 percent as rats aged from 2 to 12 months and only slightly thereafter. Thus, decreased insulin secretion and binding may both contribute to age-dependent modifications in regulation of liver enzymes.

A number of hormone systems are ultimately under the control of the nervous system. Finch is especially interested in the possibility that aging pacemakers are located in the brain. He points out that other investigators have established that the marked decline in hormone output by the ovary during menopause is not due to intrinsic incapacity of the gland to secrete the hormones. For example, Joseph Meites of Michigan State University in East Lansing was able to reinitiate ovarian activity and estrous cycles (analogous to menstrual cycles in primates) in aged rats by stimulating an area of the brain known to control reproductive hormone secretion.

Finch thinks that functional alterations in selected populations of neurons in the brain may regulate aging. He has been investigating the effects of age on the concentrations of monoamine neurotransmitters (serotonin, dopamine, and norepinephrine are monoamines) in brain. Finch did not detect any changes in them in whole mouse brains. But when he looked at specific brain regions, Finch found that the concentration of dopamine in the striate body declined by 25 percent.

Parkinsonism, Dopamine, and Aging

This is interesting because dopamine deficiency in certain regions of the brain has been associated with Parkinson's disease. Finch hypothesizes that the age-related increase in the incidence of Parkinson's disease and related syndromes may result from the tendency of the mammalian brain to lose dopamine stores during aging.

This may occur because the metabolism of monoamines is altered in the brains of senescent animals in such a way that their concentration declines. When Finch injected precursors of monoamines into the animals, the precursors reached the brains of young and old animals with equal facility but their conversion to monoamines was reduced in four brain regions of old animals. Finch does not know the exact mechanism underlying this observation but decreased synthesis and increased breakdown of monoamines are possibilities.

These articles have examined a number, but by no means all, of the current theories by which gerontologists are trying to explain the too familiar deterioration of aging. Some investigators have suggested that aging, whether caused by intrinsic or extrinsic factors, is a generalized property of all normal cells. Others have proposed that a limited population of cells controls the course of aging throughout the body. Many think that a combination of mechanisms causes the complex phenomenon of senecence.—JEAN MARX