Hormones and Their Effects in the Aging Body

Changes in the working of the endocrine system have been linked to some of the diseases that diminish the quality of later life

Aging is inevitable—or at least better than the alternative, as the old joke goes. The question, then, is not so much whether aging can be avoided, but whether the physical and mental deterioration that so often accompanies growing old is also inevitable.

At a recent conference* in Bethesda, Maryland, a group of endocrinologists and gerontologists gathered to consider how aging affects the working of the endocrine system. According to conference chairman Stanley Korenman of the University of California at Los Angeles, "Endocrinology is a fountainhead of medical research because it is the study of the molecules that regulate all the body's activities." With the connection between the brain and the endocrine system now firmly established—the brain helps to control hormone secretion and hormones in turn affect the brain's operation—that is not an overstatement.

Changes in the production of hormones or in our bodies' responses to them may contribute to the development of many of the physical ills that diminish the quality of later life. Among the common diseases of the aging that have been linked to endocrine malfunctions are diabetes, high blood pressure, osteoporosis, and some cancers.

One of the inevitable endocrine consequences of aging for women is menopause. Moreover, after menopause, which usually occurs around the age of 50, they face an increased risk of developing breast or uterine cancer. In the view of many investigators, exposure to the female sex hormone estrogen, both during and after reproductive life, may contribute to the development of the cancers, especially if the effects of estrogen are not counteracted by the opposing actions of progesterone.

For example, Barry Sherman, Robert Wallace, and Alan Treloar of the University of Iowa Medical School found that obese women, who have a higher than average risk of breast cancer, begin menstruating earlier and stop later than thinner women. In addition, the obese women tend to have shorter menstrual cycles. All of this means that they have greater estrogen exposures during their reproductive lives, which could contribute to their increased risk of breast cancer. Their obesity could cause the cancer by some other means, but the estrogen hypothesis is consistent with other results.

Estrogen exposure can continue even after menopause. The ovaries no longer produce either estrogen or progesterone, but other tissues, notably adipose tissue, can continue to make estrogen. According to Pentti Siiteri of the University of California Medical School in San Francisco, the continued stimulation of breast and uterine cells by this estrogen, which is no longer opposed by progesterone, may promote the conversion of susceptible cells to the malignant state.

In contrast to breast and uterine cancer, which may be fostered by estrogen, the development of osteoporosis appears to be inhibited by the female sex hormone. In osteoporosis, the bones lose calcium and become fragile, often breaking under stresses that would not fracture normal bones. As many as 190,000 hip fractures, 180,000 vertebral fractures, and 90,000 broken forearms are caused every year by osteoporosis.

Both men and women tend to lose bone mineral beginning around age 35, but the loss accelerates in women at the time of menopause. Because women have a smaller bone mass than men to begin with, they are more prone to the disabling effects of bone calcium loss.

Attempts to determine how estrogen deprivation accelerates bone loss have so far proved frustrating. David Feldman, describing research carried out at the Stanford University Medical School, says that his group could find no evidence for characteristic estrogen receptors on bone cells grown in culture, a result that he thinks militates against a direct effect of the hormone on bone.

Lawrence Raisz of the University of Connecticut Health Center in Farmington agrees: "Estrogens inhibit bone resorption in postmenopausal women but they do not act on bone." He points out that ten or so agents, including hormones, vitamins, and other factors, directly affect bone, causing either deposition or dissolution of bone mineral. Estrogen could enhance or counteract the effects of any of them. It may also indirectly increase calcium absorption by the intestine or decrease its excretion by the kidney, thus making more of the mineral available for bone formation.

Other investigators have evidence suggesting that the net loss of bone mineral may be minimized by giving women either estrogen or calcium supplements. In one such study, Robert Heaney of Creighton University found that premenopausal women or postmenopausal women who are taking estrogen need to consume less calcium to maintain their body calcium content than postmenopausal women not taking the hormone.

By Heaney's calculations, 800 milligrams per day is sufficient to prevent calcium depletion in women who have their own or supplemental estrogens, but estrogen deprivation nearly doubles the required intake to 1500 milligrams per day. (One and a half quarts of milk, either whole or skim, contain about 1500 milligrams of calcium.) This is an encouraging finding because it may mean that osteoporosis is preventable by replacing the estrogens given to postmenopausal women, which have been linked to an increased risk of uterine cancer, with calcium supplements.

Hot flashes are not as life-threatening as cancer or as disabling as osteoporosis, but to some degree they afflict most (about three-quarters) of the women going through menopause. The current therapy is estrogen administration, but the hormone's link to uterine cancer has led researchers to look for substitute therapies, a search that they think will be facilitated if they can find the hitherto elusive cause of the hot flashes.

According to Howard Judd, experiments performed at the University of California Medical School in Los Angeles show that the increase in skin temperature characteristic of a hot flash coincides with an increase in the blood concentration of a pituitary hormone called luteinizing hormone (LH). Other investigators have also observed surges in LH coincident with hot flashes.

The Los Angeles workers do not think that it is the LH itself that produces the unpleasant sensations of the hot flashes, however. Secretion of the pituitary hormone is controlled by a region of the

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brain called the hypothalamus. Judd proposes that both the LH surge and the hot flashes are effects of alterations in hypothalamic function. He points out that the hypothalamic neurons that control LH release are very near a brain center involved in temperature regulation.

The hypothalamus controls the secretion not only of LH but also of follicle-stimulating hormone, a pituitary hormone that stimulates the ovaries to produce mature egg follicles, which in turn produce estrogen. As Paola Timiras of the University of California at Berkeley pointed out, the ovaries of rats stop producing estrogen and progesterone not because of some intrinsic defect but because of changes in the hypothalamus. She and her colleagues have found that if they inject an inhibitor of serotonin synthesis into the hypothalamus of young rats, it produces a condition similar in some respects to human menopause.

Work from Timiras's and other laboratories suggests that a delicate balance between serotonin and other neurotransmitters in the brain is needed to maintain the normal cycling activities of rat ovaries. Slight disturbances in this balance can greatly alter ovarian activity.

The cause of the shift in neurotransmitter balance is unknown, but Caleb Finch of the University of Southern California has suggested that it is the cumulative impact on the brain of the ovarian hormones that eventually signals the brain to bring an end to a female's reproductive period. He visualizes this as a counting mechanism that may terminate ovarian cycles at various ages depending on the extent of hormone exposure.

Men do not experience the dramatic changes in sex hormone production that women do. Whether the production of testosterone, the principal hormone made by the testes, falls off gradually with age, possibly leading to a decline in sexual vigor, is still an open question. Moreover, it is a question that touches on a pivotal issue in gerontology today: Is there a basic—and thus unavoidable—decrease in function with age, or is the deterioration an indirect effect of repeated insults to our health?

Alex Vermeulen of the University of Ghent, Belgium, had originally thought everyone would agree that testosterone production decreases with age. But the results of a trial conducted at the Gerontology Research Center in Baltimore caused him to wonder whether there was such agreement.

Research carried out by Vermeulen and his colleagues has shown decreases in testosterone concentrations in aging men, with some falloff perhaps as early as age 50. Moreover, other researchers have shown that the volume of the testes, the number of living sperm per ejaculate, and the ease with which conception may be achieved all decrease as a man grows older. Vermeulen says that older men also produce more estrogens, which are formed from certain androgens, than do younger individuals. Changes such as these could contribute to the decrease in sexual activity that has often been noted as men age.

The trial conducted at the Gerontology Research Center also sought to answer the question of what happens to testosterone production in older men. It included 76 men, 69 of whom are enrolled in the long-term Baltimore Longitudinal Study on Aging, which is aimed at defining, by following specific individuals for many years, just what does happen as people grow older.

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The Baltimore workers found that testosterone concentrations are no lower and may even be slightly higher in older men than in younger men. As S. Mitchell Harman of the Center emphasized, however, the men they studied are unusual in that they have more education and are more prosperous than the general population. People who are well educated and members of the higher socioeconomic classes tend to take better care of themselves and to receive better medical attention than those who are less fortunate.

And the men in the Baltimore study were exceptionally healthy. All those with evidence of cardiovascular disease, obesity, excessive drinking, or other health problems were eliminated from the study population. This difference may help to account for the discrepancy between the results obtained in Baltimore and elsewhere. The Baltimore results may also carry the encouraging message that a decline in testosterone production need not be inevitable, provided good health can be maintained.

Some aspects of endocrine aging are more difficult to understand than simple changes in hormone production. An example is the decrease with age of the ability of the body's tissues to use glucose, a major source of chemical energy. Most studies, says Mayer Davidson of the University of California School of Medicine in Los Angeles, do not show an age-related reduction in the production of insulin, which is needed for glucose metabolism. A more likely explanation, according to Ralph de Fronzo of Yale University Medical School, is that insulin's activity is somehow impaired or antagonized.

Most individuals who develop diabetes late in life also have normal or even elevated insulin production. De Fronzo said that reduced tissue sensitivity to the hormone may account for the impaired ability of these "maturity-onset" diabetics to use glucose. This may be because their cells have fewer receptors for binding insulin than do normal cells.

Binding to receptors is the first step in the action of all hormones. It is the receptor-hormone complex that initiates the chain of cellular events that bring about the characteristic effects of a hormone. The receptor is also one of the first places endocrinologists look for an explanation of the many situations where a particular hormonal response is impaired but the hormone production appears normal.

According to George Roth of the Gerontology Research Center, there are some well-documented examples in which a reduction in receptor number can account for loss of responsiveness to a hormone during aging. One of these is the loss of receptors on the fat cells of aging rats that bind an adrenal steroid hormone called cortisol. In other cases of reduced responsiveness, no receptor loss can be detected, however. "The point," says Roth, "is that you cannot ascribe all changes to receptors."

In addition to alterations in hormone and receptor concentrations, a number of other possible explanations for altered hormonal activity must be considered, such as those affecting the "second messengers" that transmit many hormonal signals to the cell interior or the enzymes needed to carry out the activities regulated by the hormone. "So many steps influence the final result," Korenman points out, "that it is almost too hard to do the right experiments."

Nevertheless, as Timiras maintained, "Aging is not a disease or a sickness but a period in the life-span with its own physiological characteristics, which are still largely unknown." The researchers who gathered in Bethesda this October hope that by better understanding the endocrine aspects of those characteristics they can help to head off some of the deterioration we all face as we grow older.—JEAN L. MARX