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THE MYSTERY OF MENOPAUSE AND THE ESTROGEN ENIGMA

The menopause is one of the most stressful and puzzling periods of life for females. This inevitable failure of ovarian function around the fifth decade seems to be a uniquely human phenomenon. Birds, butterflies, fishes and all animals, including apes, can reproduce up until the time they die. Why should we be different? From a teleological viewpoint, it has been suggested that this may be a protective evolutionary safeguard to prevent elderly women from bearing children that would be more likely to be defective or inferior.

While this may provide advantages for the human race, it is small consolation for affected individuals. The sudden drop in estrogen is frequently accompanied by annoying symptoms such as hot flashes, sweats, palpitations, cold hands and feet, headaches, and other manifestations of autonomic nervous system instability. Severe insomnia and fatigue are common, as are a variety of emotional and personality changes, including increased nervousness, irritability and anxiety, and disabling depression.

The vagina, breasts and uterus start to shrivel. The weakening and collapse of bones in the spinal column cause a decrease in height and deformities such as the "dowager's" or "widow's" hump. Muscle size and strength shrink, an increase in fat deposits around the abdomen and buttocks contributes to obesity, and wrinkling results from thinning of the skin. Hormonal imbalances may give rise to manifestations of masculinization, such as increased facial hair and a lowering of the voice.

Estrogen replacement prevents or significantly decreases all of these complaints. Hot flashes, sweats, and the pain associated with intercourse or urination promptly and miraculously disappear. However, the long term health rewards with respect to reducing risk for heart attacks, osteoporosis pain and fractures, colon cancer, and Alzheimer's disease are equally impressive and even more important. Despite these benefits, only one in five postmenopausal patients presently opts for treatment! Some feel that their symptoms do not warrant taking daily drugs. However, many more are scared about the risk of cancer, or confused about conflicting statistics.

Cancer And Other Risks

The major concern is cancer of the breast. Earlier this year, a large Harvard study claimed that women taking estrogens for more than five years were almost 50% more likely to develop breast cancer. Most surveys have reported much lower figures. Others have found no increase, and one even showed a reduced risk. In analyz-

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The Newsletter of
**THE AMERICAN INSTITUTE OF
 STRESS**

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ing all the data, it would appear that the most important factor is the length of time that estrogen has been taken. Patients taking estrogen continuously for fifteen years may possibly have a 20 to 25% increased incidence of breast cancer. Women worry more about this than any other health problem, but may be seriously overestimating its significance. In a recent poll of women in their forties, the average respondent believed they had at least a 1 in 5 chance for developing breast cancer over the next ten years. The likelihood is closer to 1 in 50. The chance of dying from breast cancer was estimated to be 1 in 10. The correct figure is actually 1 in 250.

Part of the confusion is the oft quoted statistic of a 1 in 8 *lifetime* chance of developing breast cancer. However, this is based on women who live to age 90. In addition, two out of three patients who develop breast cancer do not die from the disease. Although breast cancer is more common in women over 50, this group paradoxically underestimates their risk and are less likely to obtain mammograms. Yearly mammography after the menopause has been shown to save lives, in contrast to the lack of proof that they significantly reduce death rates in younger women.

Breast cancer is more common in women with a strong family history of malignancy. It is also more frequent in those who never become pregnant, or do so later in life, compared to women who have children before the age of 20 or 30, or have multiple births. Some studies suggest that a high fat diet, particularly saturated

fats, increases risk. In Japan, where fat intake is well below ours, breast cancer rates are very low. When Japanese women emigrate to the U.S., breast cancer rates rise, but several other factors including greater stress could account for this. Breast cancer and heart attack rates are also low in Mediterranean countries, where there is liberal fat intake. This is believed to be due to increased consumption of olive oil and other monounsaturated fats with antioxidant properties that retard the development of malignancy and coronary atherosclerosis. A high fruit and vegetable diet also provides protection, and contain similar nutrients and chemicals that impede the development of cancer in laboratory studies. Soybean products may be particularly effective, possibly because they are composed of phytosterols or plant estrogens that can block the cancer causing activity of natural estrogen.

There is much less controversy about uterine malignancy. Estrogen therapy can be associated with as much as an eight-fold increase in cancer of the uterus. However, this can be effectively prevented by taking progesterone. Although some reports suggest that estrogens may also promote the development of ovarian cancer, the evidence for this is not as strong. On the positive side, estrogen has been shown to inhibit the growth of colon cancer cells in the laboratory. Two large studies have now both reported a 45 per cent reduced risk for colon cancer in women taking estrogen, compared to non-user controls.

Estrogen supplementation can cause fluid retention and weight gain. It may also stimulate the growth of benign uterine fibroid tumors, which normally shrink after the menopause, causing abdominal bloating and cramps, and unpredictable vaginal bleeding. Some forms of estrogen can double the chance of developing gallstones, and aggravate active liver disease. Women on estrogen for 10 or more years are reported to be twice as likely to develop asthma, and in those taking both estrogen and progesterone, the higher the dose, the greater the likelihood of asthmatic attacks.

Benefits For Bones

Despite its apparent permanence and strength, bone is a living tissue that is continually changing. This state of flux results from factors like estrogen, which favor its formation, and others, such as cortisone, which have an opposite effect. Bone is composed of complex calcium salts, and becomes porous and weakened when calcium levels are low, a condition called osteomalacia. However, these calcium salts must be deposited on a

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protein matrix in order to make bone. When this is deficient, a similar situation results, but is referred to as osteoporosis. Taking in extra calcium corrects osteomalacia, but is not very effective for reversing osteoporosis.

The decline in estrogen production following menopause erodes the protein skeleton required for bone formation, resulting in rapid bone loss for the first three to seven years, and a slower decline thereafter. The resultant weakening and collapse of the spinal vertebrae can cause severe pain and disability, and predisposes to these and other fractures. This may occur following minimal trauma, or for no apparent reason, and with few symptoms or warning signs. It is not generally appreciated that complications from osteoporotic fractures are responsible for 3% of all deaths in women over sixty. This is roughly the same number of females in the same age group that succumb to breast cancer. Estrogen replacement is very effective in preventing osteoporosis, and especially these complications. Spine and wrist fractures are reduced as much as 50% and there are 25% fewer hip fractures. Estrogen also lowers the bone loss seen in rheumatoid arthritis, even in women taking drugs like cortisone that cause osteoporosis.

Help For The Heart

Compared to men, relatively few females have heart attacks while they are still having regular menstrual cycles. Most people don't realize that coronary heart disease is still their principal problem. According to a 1995 Gallup poll, four out of five women and even one out of three internists were unaware that coronary heart disease is the leading cause of death in women. Estrogen lowers LDL (bad cholesterol) and increases HDL (good cholesterol). More importantly, like vitamin E, which it resembles structurally, it acts as a powerful antioxidant to block the formation of oxidized LDL, thought to be the real culprit in coronary atherosclerosis. There is also some suggestion that higher serum iron levels are associated with coronary heart disease, and that menstruation helps to prevent this because of periodic blood loss. Postmenopausal coronary heart disease kills one out of three women.

Estrogen can markedly reduce this and other complications of atherosclerosis by an average of 50 per cent. Women on estrogen who undergo excisional atherectomy or angioplasty for clogged coronaries are much less likely to experience recurrent narrowing of these arteries. The physical trauma of such procedures irritates their inner lining, stimulating reparative cell

growth and atherosclerotic deposits that ultimately again restrict blood flow. Estrogen slows down this restenosis, which usually requires additional surgery.

Some studies suggest that synthetic progesterone may reduce estrogen's protective cardiovascular benefits, based on changes in LDL, HDL, and blood clotting factors. A soybean derivative allegedly does not have these effects. It is available in a "micronized" or pulverized form in Europe and Mexico, but has not been approved by the FDA. However, since it is a natural substance, it can be sold directly to the public, provided no medical claims are made. As a consequence, drug companies, mail order pharmacies, and druggists, are now offering their own versions of this capsule. The problem here is that since there is no regulation, dosages may vary, information on possible long term side effects is not available, and it is not clear whether natural progesterone will reduce the risk for uterine cancer as effectively as synthetic preparations.

What Kind Of Hormonal Replacement Is Best?

What kind and how much estrogen should be taken? There is considerable confusion about whether natural preparations are always superior to synthetic products, if progesterone should always be included, or if adding androgens might provide additional benefits for some individuals. Natural estrogens have the chemical configuration of steroids. Some, such as estrone, can be detected in their free state, but most are present in a conjugated form. Conjugation refers to the chemical linkage by a natural process of two compounds in the living body. During pregnancy, huge amounts of conjugated estrogens appear in the urine. In women, these are mostly glucuronide compounds, whereas in other animals, they are primarily sulfate salts. Only compounds which are naturally formed in the body, can be referred to as conjugated estrogens. These are water soluble, highly potent, and are well tolerated orally.

Premarin is the most popular estrogen preparation, and provides the richest and most potent source of natural estrogens like estrone and estradiol. As its name suggests, it is derived from the urine of pregnant mares, which is repulsive to some women. *Estropipate (Ogen)*, a sulfate salt of estrone, is also available, and has activities similar to *Premarin*, but has not been studied as thoroughly. Natural free estrogens, like estrone, are soluble in oil, and while effective when given by injection, they are not absorbed well from the gastrointestinal tract. Other chemically modified and non-steroidal

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substances with estrogenic activity, like stilbestrol and other coal tar derivatives, are also active by mouth, but tend to have undesirable side effects. Chemically modified estrogens, such as ethinyl estradiol have also been synthesized, and are more commonly used in contraceptive pills.

Chemically derived oil soluble estrogens have effects that can last for weeks or months following an injection of slow release formulations. However, these have been discontinued, since absorption is unpredictable, and side effects are difficult to control. Estrogen is now also available in the form of an estradiol skin patch (*Estraderm*). This is applied once or twice a week, although local irritation prevents its use in about 20% of patients. This approach may not provide as much coronary protection, because the product is delivered directly into the blood stream and bypasses the liver, so that it does not produce the same beneficial effects on blood cholesterol components. Also, since synthetic substances and estrogens created by laboratory linkage of chemical compounds are not found in nature, they are considered to be foreign substances.

In addition to estrogen, the majority of postmenopausal women also take a synthetic progesterone, such as medroxyprogesterone (*Provera*), to prevent uterine cancer. It is usually administered for seven or more consecutive days in an effort to mimic the hormonal environment during the normal menstrual cycle. This is apt to result in a resumption of regular periods, as well as cramps, breast tenderness and even migraine headaches in some individuals. Taking smaller doses may eliminate or reduce such complications, but erratic vaginal bleeding usually persists. This is a source of concern, since it could represent an early indication of uterine malignancy that might easily be disregarded.

Non-Hormonal Approaches

A variety of "natural" products are promoted for relieving menopausal complaints, but provide little benefits other than placebo effects. Some of the complications of estrogen deficiency can be mitigated by medications. Hot flashes and sweats may improve with synthetic progesterones (*Provera*, *Megace*), antiestrogens used to treat breast cancer, like tamoxifen (*Nolvadex*), as well as clonidine (*Catapres*), and methyldopa (*Aldomet*), which are antihypertensive drugs. Some claim that taking soy products provides relief, and possibly they are metabolized into progesterone-like compounds. Avoiding caffeine, alcohol, spicy foods and stimulants, regular exercise, meditation, progressive muscular re-

laxation procedures and other stress reduction techniques are also sometimes surprisingly beneficial.

A nasal spray form of calcitonin (*Miacalcin*) and aldrionate (*Fosamax*), an oral drug, have recently been approved for the prevention and treatment of osteoporosis, and fluoride and calcium supplements can also be useful. A major pharmaceutical company recently isolated a critical gene in the cells that cause the protein breakdown responsible for osteoporosis, and are testing chemicals to block or inactivate it. An effective drug would be a breakthrough for genetic engineering, and bring substantial relief to the 25 million suffering from osteoporosis, most of whom are women. Giving up cigarettes may reduce osteoporosis and heart attacks, and regular exercise also helps prevent both of these menopausal complications. Low dose aspirin, a diet high in vegetables, and stress reduction cut the risk of colon cancer and heart attacks. Painful intercourse and urinary tract complaints and infections can be minimized by the application of various hormonal creams and preparations that do not have significant systemic effects.

Preventive Measures

Depression is associated with a higher incidence of osteoporosis, according to German researchers. They used CT scans to measure the thickness or density of lumbar vertebrae in men and women suffering from major depression, and compared them with normal controls. As expected, there was more osteoporosis with advancing age, but even accounting for this, these bones were 15% thinner in depressed individuals. The explanation for this may be that depression is associated with higher levels of cortisol, a stress related hormone that breaks down the protein matrix of bone. It has long been known that cortisol levels are high in patients with anorexia nervosa, who are particularly susceptible to premature osteoporosis, and this is also a frequent complication of long term therapy with cortisone and similar steroids. Other endocrine changes that can accompany depression, such as reductions in growth hormone and gonadal secretions, and abnormalities in thyroid function may be additional contributing factors. Depression may cause poor dietary and exercise habits that could contribute further to osteoporosis, and are also associated with a higher incidence of coronary heart disease, but involve other mechanisms. Whether more aggressive treatment of depression will reduce osteoporosis remains to be seen.

Some studies show an association between breast

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cancer and alcohol consumption. Alcohol is metabolized more slowly in women than men, and this can increase estrogen levels. However, heart disease is a far more common cause of death in females over 55, and daily alcohol, especially wine, can sharply reduce this. A recent study of more than 85,000 nurses revealed that those who consumed two drinks a day had significantly lower mortality rates from coronary heart disease.

Moderate and regular exercise helps prevent breast cancer, according to a study of 1000 premenopausal women. Jogging, playing tennis, or swimming for four hours a week reduced their risk as much as 60 per cent. Exercise can block ovulation and the production of cancer causing hormones, and curbs the development of body fat, which can serve as a source for these steroids. Weight bearing exercise throughout life also stimulates bone growth, and insuring a daily intake of 1500 mg. of calcium can further help to prevent osteoporosis. In addition to lung and other malignancies, smoking has now been linked to breast cancer. Women with deficiencies in an enzyme that detoxifies cancer causing chemicals in tobacco smoke have been found to be eight times more likely to develop breast cancer, compared to those with more efficient enzyme activity. Cancer rates were the highest in those who smoked more than a pack a day, and/or had started in their teens.

Exposure to radiation may be extremely important. It has been estimated that perhaps two thirds of current breast cancer cases may be the result of radiation received over the past 60 years. X-ray therapy for acne and other skin conditions, or for shrinking the tonsils and thymus gland, repeated X-rays to monitor tuberculosis, fluoroscopy of the feet to insure proper fitting shoes in children, and whole body fluoroscopy to check their bone growth have now been abandoned. Safety standards are also now much stricter for routine X-rays. The mammography instrumentation used to detect breast cancer 10 or more years ago often used over 100 times the maximum dose permitted today, and may have caused more problems than it helped. Some experts predict that breast cancer rates will soon start to decline as a result of these improvements.

Women who have had a hysterectomy would appear to derive no benefit from taking progesterone along with estrogen, and there may be disadvantages. Those who still have their uterus may want to weigh any potential protection from cancer, against the problems of vaginal bleeding, abdominal bloating, pain, and cramps. A study now in progress may help to provide some additional guidance. Hysterectomy patients are

randomly assigned to either taking conjugated estrogens or a placebo, and those with an intact uterus, are given either a placebo, or a combination of estrogen and a progesterone derivative. While the major purpose is to determine what the long term effects will be on morbidity and mortality for heart attacks and osteoporotic fractures, we may also gain similar information on breast and other malignancies.

What's The Bottom Line?

Sooner or later, every woman must make a choice about whether to take some form of hormonal replacement therapy. This will require consulting their physicians, for whom it may also be a thorny problem. I have had to grapple with it for many patients as well as my wife. At the moment, the benefits would appear to far outweigh any hazards. However, each patient obviously has to be evaluated on a very individual basis. One must take into consideration the importance of known genetic predispositions for malignancy, heart disease and osteoporosis. Past medical history, dietary and exercise habits, current complaints and medications, and other relevant factors such as smoking and drinking can also tip the scales one way or another. The problem is that in trying to balance the benefits against the risks, all of these have different weights, some combinations may be more additive than others, and there is considerable individual variation, about which little is known.

Anyone taking estrogen would be wise to have annual pelvic and breast examinations and mammography, and should immediately report any unusual vaginal bleeding or spotting. For those with an intact uterus, periodic endometrial biopsies may be indicated, especially if progesterone is omitted. Although this is usually an office procedure, it can be very painful, and many patients shy away from taking progesterone because of this. Ultrasonography may actually be superior to biopsy for finding the cause of postmenopausal vaginal bleeding. Ultrasound exams also identify uterine tumors outside the endometrium, and may lead to earlier cancer diagnosis, according to a very recent report.

Unfortunately, too many women view their menopausal complaints as an unavoidable consequence of aging that should be accepted and endured, rather than treated. When they have problems reading or hearing, they readily correct this with glasses and hearing aids, and replacing hips and other joints has become increasingly common. However, when it comes to correcting or replacing hormonal deficiencies, they are much more hesitant, often because of cancer concerns. For many,

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this may have been blown out of proportion.

My personal experience has been that daily estrogen replacement therapy can remarkably improve the quality and length of life in almost all menopausal patients. As indicated in the following abstracts, it may also provide unanticipated rewards ranging from preventing skin aging, tooth loss and the need for dentures, to decreasing depression, memory loss, and even Alzheimer's disease.

Paul J. Rosch, M.D., F.A.C.P.
Editor

"The age of a woman doesn't mean a thing. The best tunes are played on the oldest fiddles."

Sigmund Engel

Preventing Menopausal Depression And Alzheimer's Disease

Depression occurs more often in women than men, and particularly in association with the menopause. "Involutional melancholia" was a well established diagnosis in the psychiatric literature a half century ago. As the term implies, this is a depression or melancholy that appears at the time of involution, or "change of life". In contrast to other depressed patients who were completely withdrawn, such individuals often exhibited increased nervousness and irritability. The recommended treatment was estrogen replacement therapy, which had only recently become available.

The current classification of psychiatric disorders no longer recognizes this, although premenstrual and post partum depression are acknowledged. It is now taught that involutional melancholia and "change of life" depression are forms of agitated depression which can occur at any age. The suggested treatments are antidepressant drugs and electroconvulsive shock therapy. Menopause or the possible use of estrogens are not even mentioned.

The ancient Greeks believed that melancholy had a humoral cause, and resulted from an excess of black bile (*mélas chole*). It now appears that they were on the right track, but that the humoral or endocrine component involves estrogen, which interestingly enough, does influence bile secretion. In a study involving almost 700 women over the age of 60 suffering from major depression, 32% responded to antidepressant drugs, compared to only 18% given a placebo. However, those women

who had been receiving estrogen replacement therapy, were three times more likely to improve than those not taking the hormone. This was true whether or not they had any menopausal symptoms.

Concentrating abilities and memory loss, especially for recent events, are other menopausal complaints that improve with estrogen replacement. In one experimental drug trial designed to improve brain function in Alzheimer's disease, researchers also found that women receiving estrogen were twice as likely to show a favorable response. A very recent report reveals that taking estrogen after the menopause can reduce the risk of dying from Alzheimer's disease by 40% or more.

The use of estrogens was reviewed in 138 patients from a California retirement community who had died from Alzheimer's disease. Each individual was compared with four others the same age who died the same year, but from different causes. The results were quite remarkable.

- Women who had used estrogen in any form at any time, including pill, patch or even vaginal cream, had a 30% lower death rate from Alzheimer's compared to non-users.
- Those on the most common regimen, .625 mg. of conjugated estrogens (Premarin) were 41% less likely to die from Alzheimer's.
- The longer estrogen had been taken, the lower the death rate.

Laboratory studies have shown that estrogen stimulates the production of substances like cholinesterase and serotonin that keep brain cells healthy and increases their communication links, and help prevent depression and dementia.

Internal Medicine News-May 1, 1995

USA Today, 11/20/95

"There are three classes into which all the women past seventy that ever I knew were to be divided: 1. That dear old soul; 2. That old woman; 3. That old witch."

Samuel Taylor Coleridge

Anti-Aging Effects Of Estrogen On Skin And Teeth

Belgian researchers utilized a computerized skin suction device to compare aging characteristics in post-menopausal women taking estrogen, with controls who were not. Following menopause, the skin becomes less thick due to the loss of connective tissue and there is also diminished elasticity. Both of these contribute to in-

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creased slackness, as can be readily demonstrated by pinching the skin on the back of the hand and lifting it up. The instrumentation, which provides a method of measuring this slackness, confirmed that it was significantly less in those receiving hormones.

A survey of 4000 women in a retirement community, showed that estrogen replacement can also benefit oral health. Prior studies have shown a relationship between osteoporosis and tooth loss, gum, and other age related dental problems. Although less than 1% of people under the age of 45 are toothless, the proportion shoots up to 40% in those 65 and older. In addition, denture replacement is often unsatisfactory because of progressive gum resorption. While local factors may play a role, recent studies have shown no consistent relationship between periodontal disease and tooth loss, and systemic factors such as osteoporosis may be more important. Women with severe osteoporosis are three times more likely than age matched controls to lose all their teeth.

Researchers found that women taking estrogens had more natural teeth than those not receiving replacement therapy, and that this increased with the duration of treatment. The estrogen group was also much less likely to have lost all their teeth or to wear dentures. Tooth loss and gum resorption may be one of the earliest signs of osteoporosis in otherwise apparently healthy postmenopausal women, and should signal the need to explore this possibility and hormonal replacement therapy.

J. Am. Geriatr. Society-June 1995

Arch. Int Med.-November 1995

Old age puts more wrinkles in our minds than on our faces.

Michel de Montaigne

Is There A Male Menopause?

Some studies support the notion of a male climacteric, or "menopause" which affects men in their sixties or later. Some men in this age group do occasionally complain of menopausal vasomotor symptoms such as cold hands, palpitations, and even hot flashes and sweats. Even more have other common complaints, such as memory loss, depression and decreased libido. Although this is usually attributed to a decline in the production of testosterone, many affected individuals have normal values. Unlike estrogen, which plummets in postmenopausal women, testosterone levels do not decrease dramatically in men. However, as noted in a prior report on the "viropause", some seem to become

resistant to testosterone, and experience a marked improvement in virility and sense of well-being when receiving testosterone supplementation.

Further support comes from a recent study of 10 apparently healthy men aged 60-75, who received low doses of testosterone weekly or twice a month for 2 years. Most reported increased energy, sexual desire and activity, and also showed evidence of greater muscle strength, less fat, and lower cholesterol. Careful monitoring revealed no indication of any increased tendency for prostate cancer. Similar results have been seen following replacement of DHEA, a weak androgen made in the adrenal gland, which also declines with age.

Science News-July 1, 1995

Testosterone And Coronary Heart Disease

Testosterone has traditionally been considered to be a major contributor to coronary heart disease. The effectiveness of estrogen in reducing female heart attacks, has led to suggestions that it might provide similar benefits for men, and it has been used in the past with varying success, but often annoying side effects. However, it now appears that testosterone may actually protect men from heart attacks. Men and women produce different amounts of both hormones. Many of their biological actions, such as building up protein, are similar. Both are vasodilators, and years ago, were even used to treat angina.

In one study of men with heart attacks, it was found that testosterone levels were surprisingly low, leading researchers to suspect that high levels might help prevent coronary atherosclerosis. To test this, they studied 55 men with angina or other symptoms of coronary disease who had undergone angiography to evaluate the degree of atherosclerotic obstruction. The results confirmed that those with low testosterone levels were significantly more likely to have seriously clogged coronaries, compared to those with high concentrations. While this hardly proves that low testosterone causes atherosclerosis, or that its administration could slow it down, male hormones might be as beneficial to men as estrogen is for women.

Science News-Vol. 145, pg. 340, 1995

Men have a much better time of it than women. For one thing, they marry later, for another thing, they die earlier. - H.L. Mencken

.....
I love the male body, it's better designed than the male mind. - Andrea Newman

Book Reviews • Meetings and Items of Interest

Book Review

Hormones and Aging, Timiras, P. S., Quay, W. D., and Vernadakis, A., eds., CRC Press, Boca Raton, FL, 438 pgs., \$110.00 (over 141 illustrations and tables)

The aging process is accompanied by significant declines in the levels of many hormones and humoral agents, including specific sex steroids in men and women, growth hormone (somatotropin, somatotropin) and insulin-like growth factors (somatomedin-1, somatomedin-C). In addition, since many age related symptoms and signs are similar to those seen in endocrine deficiency disorders, various attempts have been made to retard the aging process or promote rejuvenation, as outlined in this issue's Editorial. The role of the endocrine system and neurotransmitters in the aging process has received increased attention in recent years for other reasons. Among these are growing evidence that most of the stigmata of aging, such as gray hair, wrinkled skin, cataracts, advanced atherosclerosis, and malignancies associated with depressed immune system function, are caused by oxidative stress.

There is also evidence that emotional and physical stress can accelerate the aging process. Possible mechanisms of action include excess stimulation of the hypothalamic—pituitary—adrenal axis, increased production of free radicals, and depression of immune system function. There may also be relevant stress related influences on neuropeptides, especially melatonin, which Russel Reiter, who contributed to the Preface, has shown to be a powerful antioxidant and scavenger of the highly toxic hydroxyl free radical.

A vivid illustration of the influence of stress on aging is provided by the Pacific salmon and the Atlantic eel. During the spawning process, both of these fish seem to age biologically in a remarkably short period of time. They die shortly after spawning, and exhibit adrenal cortical hyperactivity and other characteristic pathologic changes associated with exposure to severe stress. This is undoubtedly due to the tremendous physical exertion required to swim

upstream against rapids, since if spawning is prevented, both of these fish continue to live for several years. Indeed, in books directed to the general public, Hans Selye redefined stress in as "the rate of wear and tear on the body", which is also a fairly accurate definition of biological aging.

The senior editor contributed 6 of the 21 chapters in this book, including the very valuable Introduction in Part I dealing with definitions and theories of the aging process. Part II, Aging of the Endocrine Glands, includes chapters devoted to changes in steroid and amine secreting glands, and others that discuss hormonal changes in the reproductive system, and relevant therapies. Part III, Pathology and Hormonal Action in the Aged, addresses the role of nutrition in aging, osteoporosis, and diabetes, and there is a particularly valuable chapter outlining the relationships between stress, glucocorticoids, and aging. Part IV is entitled, Molecular Regulatory Mechanisms, and covers oxidative stress, growth factors, target cell responses, and the role of the immune system and defense mechanisms in aging. Part V, which was also written by the senior author, is a remarkable overview entitled, Neuroendocrinological Theories of Aging.

This attractive volume covers not only hormonal secretions from endocrine glands, but other relevant humoral chemicals arising from diverse cells in the nervous and immune systems. The fields of interest of the more than two dozen contributors from North and South America, Europe, and Japan, reflect the multi-disciplinary approach that this topic mandates. The numerous graphs, diagrams, and tables are of high quality, and the references are extremely comprehensive. This book is should be of extreme interest to anyone remotely involved in the study of endocrine function, neurotransmitters, the immune system, and especially their contribution to the aging process.

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