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DHEA AND THE FOUNTAIN OF YOUTH

DHEA (dehydroepiandrosterone) has attracted markedly increased media attention, where it has been described as the "youth hormone". Levels rise steadily until they peak in the mid-twenties, following which there is a progressive decline. DHEA is manufactured in the adrenal cortex, but for years, was viewed as little more than a weak androgen. However, the fact that it is the most abundant steroid hormone in the circulation suggests that it may have important physiological functions not previously appreciated. When converted in the liver to DHEAS (dehydroepiandrosterone sulfate), it reaches blood concentrations in humans and primates that are 10 times higher than cortisol. Stress stimulates the production of both hormones, but unlike cortisol, DHEA secretion falls off sharply in older individuals. By age 70, concentrations are only 10% of peak values.

A variety of studies have shown a clear correlation between very low DHEA levels and various age related afflictions, including osteoporosis, impotence, premature heart attacks, deaths from coronary heart disease, severity of atherosclerosis, obesity and maturity onset diabetes, Alzheimer's disease, and certain malignancies. The reason for this is not clear. However, since DHEA blocks the ability of glucocorticoids to suppress immune system responses, low concentrations could facilitate the well established accelerating effects of stress and cortisol on the aging process. It has also been found to be significantly diminished in depression and other disorders associated with neuroendocrine disturbances which can occur at any age. There are similar deficiencies in diseases due to immune system dysfunction, including rheumatoid arthritis and lupus, that may have important clinical implications. Both in humans and animal models of lupus, there is a deficiency of Interleukin-2 (IL-2), an important cytokine that activates certain immune system lymphocytes. This deficit is thought to be due to low DHEA levels, since following its administration, IL-2 values return to normal. In experimental animals, there is a concomitant and dramatic reversal in the usual downhill, fatal course.

The crucial question is whether these observations reflect a causal relationship, or simply some statistical association. From a practical standpoint, could an increase in DHEA prevent or minimize the development of arteriosclerosis, cancer, and other manifestations of the aging process? Some animal

(Continued on page 2)

ALSO INCLUDED IN THIS ISSUE

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Editor-in-Chief

(Continued from page 1)

studies strongly support such capabilities, but how can they be explained in view of what is known about the varied etiologies of these diverse disorders? Similar anti-aging effects have been attributed to antioxidant Vitamins D, E, and beta carotene, presumably because of their ability to block free radical activities. Free radicals appear to be a common cause for most stigmata of aging, but there is no evidence that DHEA has any antioxidant effects. There are several strong links between stress, cancer and aging, as discussed in prior Newsletters. These most likely result from increased glucocorticoid secretion, and in rodent studies, DHEA seems to oppose these. DHEA also inhibits glucose-6-dehydrogenase activity, which is involved in immune system-cancer activities, and there are significant influences on other important enzyme systems such as glutamate and gamma-aminobutyricacid (GABA), which may be relevant.

In addition to improving immune system function, DHEA has been reported to lower cholesterol and triglycerides, prevent the development of obesity and diabetes, and to enhance memory. As a result, clinical trials are now in progress to evaluate its benefits in disorders ranging from obesity, diabetes, and coronary heart disease, to lupus, various malignancies, and AIDS. In one study, two weeks of DHEA replacement therapy in 40 to 70 year old men and women restored levels to those seen in young adults. This was associated with evidence of enhanced immune system function and improvement in joint pain, mobility, sleep, and other indices of physical and mental well being. However, there is no evidence that supplementation enhances sexual desire or performance.

As a result of all the media hype, health food stores have had difficulty in replenishing their stocks of DHEA supplements. Most consumers are apt to be disappointed, since the dosages usually available are minuscule, and would be more appropriate for a small mouse. There could also be disturbing side effects. One trial to determine appetite suppressant effects was halted prematurely, when female participants started to develop disturbing signs of masculinization. High doses have been shown to cause changes in the liver that might predispose to malignancy. Furthermore, administering synthetic DHEA in large amounts, or for extended periods, would very likely suppress the body's ability to manufacture the natural product. This could have a variety of adverse long term consequences similar to those seen with protracted cortisone therapy.

One novel and exciting approach to this problem was reported on at our last International Montreux Congress on Stress by Dr. Norman Shealy. He had previously demonstrated that depressed patients have low levels of serotonin and DHEA. Daily treatment with the Liss Cranial Electrical Stimulator often restored serotonin to normal within two or three weeks, along with evidence of marked clinical improvement, but without any concomitant rise in DHEA. He subsequently discovered that this same electrical stimulation, when applied to specific acupuncture sites in the body, rather than transcranially, resulted in a significant increase in DHEA. Both DHEA and progesterone are derived from pregnenolone, and there is some evidence that progesterone can be converted into DHEA. Preliminary studies showed that the application of a 3% progesterone cream twice daily resulted in increased DHEA levels. Combined administration of progesterone cream and electrical stimulation resulted in an additive and synergistic effect. It is not clear

(Continued on page 3)

(Continued from page 2)

whether the magnitude of these responses are dose dependent, since this does not occur with cranioelectrical stimulation.

To examine this, experiments were conducted in a half dozen individuals with a GigaTENS™ electrical stimulator, which emits less than one millivolt at 50 -70 billion cycles per second. This device has been used extensively in Russia and has an excellent safety record. Application for three minutes to the acupuncture sites previously noted produced even greater DHEA elevations, approaching tenfold in one patient. Along with this was an improved sense of well being, and in contrast to the experience with DHEA supplementation, one older individual reported a rather remarkable increase in libido and potency. These very preliminary findings have important clinical implications if confirmed by others. A larger study is now under way, and will hopefully be reported on at our Eighth International Montreux Congress on Stress, February 18-23, 1996.

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

More On Stress And Low Back Pain

Low back pain is one of the ten leading diagnoses made by primary care physicians, and the second most common reason for surgery in the United States. Associated direct medical expenses are estimated to be in excess of $25 billion annually. The total price tag is much higher, when one considers the additional costs of insurance claims, workers compensation awards, and lost productivity. According to a recent article, these expenditures could be significantly reduced by dispelling the following three common myths.

1. **Bed rest helps**. While this used to be the standard treatment, along with traction, prolonged bed rest is of little value, except perhaps in some cases of severe sciatica due to a free floating herniated disc.

2. **An MRI study will provide the correct diagnosis**. In most cases, it will not only fail to do so, but may provide misleading information. The procedure is expensive, and frequently shows abnormalities in patients who have never had any back pain. The same is true for CTT scans.

3. **A correct diagnosis of the problem can always be made.** Surprisingly enough, an NIH consensus panel concluded that a precise diagnosis can't be made in about 85% of all cases of back pain!

Fortunately, serious causes of back pain, such as metastatic cancer, spinal osteomyelitis and epidural abscess, only occur in 1% of patients. These can usually be detected by other means. Four out of five patients with an underlying malignancy will be over the age of 50. Most have some other systemic signs, such as unexplained weight loss, lymph node enlargement, or hematuria. If a sedimentation rate and routine X-ray are normal, malignancy is most unlikely. The most common reasons for surgery are persistent neurological deficits due to a herniated disc, or spinal stenosis in older patients who fail to improve on conservative therapy. Not infrequently, surgery is recommended without an adequate trial on anti-inflammatory or muscle relaxation medications, and an appropriate exercise regimen. Antidepressants and stress reduction strategies can also provide important benefits that are often overlooked.

As reported in prior Newsletters, emotional stress may significantly aggravate low back pain symptoms because of associated increased muscle spasm. Other stress related influences include anxiety, depression, and substance abuse. Whether workers' compensation benefits are being sought is another important factor. With respect to delaying recovery, "this probably tops the list. If it's involved, there are all kinds of incentives not to get better." Psychological factors should be particularly suspected in patients who complain of numbness throughout the entire leg, describe their pain as constant, continuous, and not relieved by anything, or whose leg keeps giving way when attempting to stand. Recognizing and treating psychological and stress related contributors to low back pain can appreciably shorten convalescence and avoid the need for surgery in many patients.

ACP Observer-May, 1995

Stress And Premature Birth

Old wives' tales abound with suggestions that severe emotional stress can precipitate premature labor, and a recent study seems to support this. Australian researchers report that increased levels of stress related corticotrophin releasing hormone (CRH) have a high correlation with premature delivery, based on a study of almost 500 mothers. They found that those who delivered prematurely, had higher levels of CRH earlier in their pregnancies, compared to others who delivered on or after their due date. Whether this is an associated or causative phenomenon is not clear. However, if confirmed by others, a simple blood test might eventually help to predict whether delivery will occur earlier than expected. It could also conceivably lead to ways to prevent this, which has important implications.

More than 10% of U.S. babies are born prematurely. They are therefore at increased risk for lung disease, mental retardation, and other potential problems. The response to stress involves a cascade of events involving the hypothalamic-pituitary-adrenal cortex axis. Hypothalamic CRH stimulates the release of ACTH from the pituitary, resulting in increased secretion of adrenal cortical hormones. If increased CRH is at the root of premature labor, then blocking its subsequent chain reaction might prevent this problem.

USA Today-5/1/95
Nature Medicine-May, 1995

Evidence Of Chronic Stress In Women With PTSD Due To Sexual Abuse

PTSD (Post Traumatic Stress Disorder) has only been formally recognized as a diagnostic entity since 1980. Most of the early reports dealt with male combat veterans, who exhibited extreme emotional upsets as a result of flashbacks to extremely stressful war experiences. In recent years, PTSD has been increasingly recognized in various traumatized groups, particularly, civilian war victims, and others subjected to severe natural disasters, accidents, and violent crimes, such as rape and sexual abuse.

The incidence of PTSD in adult survivors of childhood sexual abuse has been estimated to range from 25-62%. However, the criteria for establishing this diagnosis is more difficult because of greater time delays in onset of symptoms, and difficulties in verifying and evaluating the precipitating traumatic incident. Soldiers with PTSD exhibit certain hormonal changes that distinguished them from patients with other psychiatric disorders, such as severe depression, bipolar disorder, and schizophrenia. These were characterized by high levels of adrenaline, but low levels of cortisol excretion. A prior study of sexually abused girls aged 8-15 had also reported persistently higher levels of catecholamines and mood disturbances. Therefore, the diagnosis of PTSD resulting from sexual abuse in older individuals might be supported by demonstrating that such individuals showed similar endocrine patterns. To evaluate this, 3 groups of women were studied.

1. Those who had been traumatized by childhood sexual abuse, and qualified for the diagnosis of PTSD.

2. Women who experienced childhood sexual abuse but did not appear to suffer adverse long time consequences.

3. Age comparable controls who had not experienced any childhood sexual abuse, and had no history of any other psychiatric problems.

The 3 groups did not differ statistically with respect to income level, marital status, or age, which ranged from 26-52 years. All were evaluated for behavioral complaints, particularly with respect to premenstrual symptomatology. Both of the groups who had experienced childhood sexual abuse scored significantly higher on PMS symptoms such as physical discomfort, fluid retention, fatigue, impaired social functioning, low mood, anxiety, impulsiveness, atypical depression, and social withdrawal. However, those classified as having PTSD scored slightly higher in each of these categories. The PTSD sufferers had the highest excretion of

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(Continued from page 4)

adrenaline and other catecholamines, whereas the sexual abuse non-PTSD differed little from controls. The severity of PTSD symptoms also showed a significant correlation with catecholamine levels, as has been reported in victims of traumatic battle and natural disaster experiences. However, unlike soldiers suffering from PTSD, the women in this study had elevated, rather than reduced cortisol levels. The reason for this is not clear but may be gender related. This group also had a higher incidence of obesity, which could be related to their chronic increased cortisol secretion.

Psychosomatic Medicine-March/April, 1995
Am Acad Child Adolesc Psychiatry-Mar-April/1994

Diet, Stress, And Aging

Will you live longer if your weight is above, below or just in accord with normal values based on your height and body build? Thin people live longer by far than those who are overweight or even within the normal range based on body build. Rodent research also clearly demonstrates that marked caloric restriction is associated with a longer lifespan, lower blood pressure, and reduced levels of blood sugar and cholesterol. Similar findings have been reported in monkeys. Presumably, this is because less caloric intake reduces metabolism and the production of free radicals, which are responsible for most age related damage.

The recent experience of participants isolated in Biosphere 2 now suggest the same may be true for humans. On an 1800 calorie/day diet, cholesterol levels dropped 35% in six months, and weight loss averaged 26 lbs. in men and 15 in women. Blood pressure and blood sugar also fell, and white blood cell changes were consistent with an increase in immune system resistance.

In addition to decreasing free radical production, other antiaging mechanisms, such as the production of stress proteins, which are vital to the repair or regeneration of damaged cells, may also be involved. These are also known as heat shock proteins, since when cells from older animals are exposed to heat, they die much more rapidly because of a decreased ability to manufacture these important protective agents. However, when older animals are placed on a low calorie diet, their ability to make stress proteins reverts to that seen when they were young, and they regain their resistance to damage from heat, free radicals and other toxins.

The ability to manufacture stress related glucocorticoid hormones may be another important factor. Cushing's Disease is due to an increased production of glucocorticoids, and is characterized by osteoporosis and other signs of premature aging. High levels of glucocorticoids also destroy neurons in the hippocampus, an important memory processing center of the brain. Memory loss is one of the early signs of aging and Alzheimer's disease. But, glucocorticoids, also reduce inflammation and many of the other adverse effects of stress. It is now believed that either too much or too little may be damaging, but that just the right amount is protective. Diet restricted animals seem to have an improved ability to achieve this happy medium.

Longevity-May, 1995

One should eat to live, not live to eat.

Moliere

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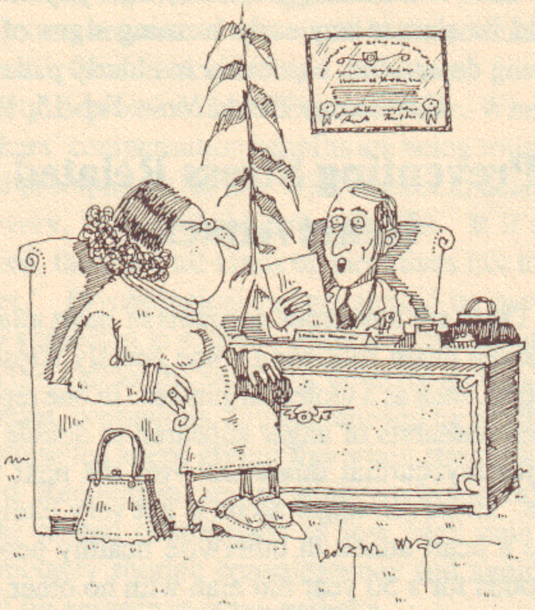
To know how to grow old is the masterwork of wisdom, and one of the most difficult chapters in the great art of living.

Henri-Frederic Amiel



It's partly glandular and partly 15,000 calories per day."

Depression Can Really Break Your Heart

A variety of stressful emotions and behaviors have been linked with heart attacks, including hostility, anger, aggressiveness, and other Type A traits. However, an increase in depressive symptoms can literally lead to a broken heart, even when they do not seem severe. This was recently confirmed in a five year study of almost 5000 men and women over the age of 60 being followed for elevated systolic blood pressure. Periodic evaluation of emotional status revealed that those with a worsening of depressive symptoms over this time period were significantly more likely to suffer heart attacks, than those remained stable. They also had significantly higher mortality rates from stroke and cancer.

It should be emphasized that only a third of these individuals would have been considered to be clinically depressed. The vast majority simply scored higher than average on depression rating scales. The correlation was seen only when ratings began to worsen, and there was no connection between baseline levels of depression and subsequent cardiovascular disease. Studies currently in progress may determine whether prompt recognition and treatment can reduce future cardiac damage. However, family, friends, and physicians should be alert to any early warning signs of increasing depression, especially in elderly patients.

Cardiology World News-Feb.15, 1995

Preventing Stress Related Heart Attacks

There are numerous accounts of heart attacks or sudden death following some acutely stressful situation, such as a violent argument. In one report, sudden outbursts of anger appeared to double the risk for myocardial infarction over the next two hours. However, anger alone is not very likely to cause a heart attack in otherwise healthy people. The odds for a 50 year old man with no other risk factors is about one in a million, so that doubling this to two in one million would still be negligible.

However, anger outbursts might be more perilous for those at greater risk, based on interviews with 1600 heart attack victims. About 2.5% reported experiencing moderate to great anger in the two hours preceding the event, and this was more common in women. Strenuous physical exertion is another significant trigger for heart attacks, and similar mechanisms may be involved. Both anger and heavy physical activities are associated with the release of adrenaline and other stress related hormones. These elevate blood pressure and heart rate, thus promoting the disruption of atherosclerotic plaque, and also increase platelet clumping and clot formation, which also causes arterial blockage and obstruction.

Patients who took an aspirin tablet daily were much less likely to suffer a heart attack following an outburst of anger, compared to those not taking aspirin. Large scale studies have shown that taking aspirin daily reduces the incidence of heart attacks, probably by inhibiting the platelet aggregation and clumping that contributes to clot formation. Beta blockers like Inderal also reduce heart attack rates by blunting rises in heart rate and blood pressure during stress that physically cause plaque disruption and obstructive arterial thrombi. It would seem likely that taking both types of medication might provide superior protection from the harmful effects of stress, by influencing both of these different mechanisms.

Cardiology World News-March 15, 1995

"I don't care for people who try and catch my eye."

Reducing Job Stress Lowers Cholesterol

Numerous studies confirm that acute stress can cause a marked rise in blood cholesterol. In addition, this is far greater than that produced by increased intake of dietary fat. This was vividly demonstrated in medical students, where levels shot up on the day preceding final examinations, fell towards normal after it had been completed, but spiked again in those students who were erroneously notified that they had failed. Chronic stress also raises blood fats, as seen in tax accountants who show a progressive rise as April 15 approaches, but a return to normal over subsequent weeks, despite any significant change in diet or eating habits. Since job stress is the most common cause of stress in adults, one might suspect that lipid levels would be higher in those with greater occupational pressures, but this would be difficult to prove because of marked individual variation. However, a recent Swedish study, using workers as their own controls, has now shown that an effective stress reduction program can also lower those lipid profiles considered to be an important risk factor for heart attacks.

The research was conducted in Sweden's occupational health care centers, where civil servants participated in an 8 month stress reduction program. Periodical monitoring was made of various lipid parameters including the ratio between high density lipoproteins (HDL or "good" cholesterol) and low density lipoproteins (LDL or "bad" cholesterol), a calculation commonly considered the best cholesterol indicator of cardiovascular risk. The program was designed to give participants an increased sense of control over their work, as well as greater support from colleagues and supervisors, and involved 97 female and 35 males in four different worksite intervention groups, and a control group.

Those in the treatment groups received a two day course in the physiological and psychological aspects of stress and methods of coping. Personal lifestyle habits with respect to eating, smoking and exercise were reviewed. They were given instruction in relaxation training and meditation techniques, and encouraged to practice these regularly. They were also asked to identify their sources of worksite stress, as well as aspects of their jobs they found particularly satisfying and enjoyable, and to suggest ways that both could be improved. Particular efforts were directed to how the physical work environment might be enhanced, and who should be responsible for implementing any changes and evaluating their results. These issues were brought up at coffee breaks and after work, and many employers also allocated work time to foster such discussions.

After eight months, those in the intervention groups reported a much higher sense of stimulation and autonomy at work, as well as a greater sense of support from their superiors. No such responses were mentioned by the controls. No significant change occurred in lifestyle habits, including smoking, drinking alcohol consumption, diet, weight, exercise. There was no change in total cholesterol or triglycerides in any of the participants. However, the intervention group did show a rise in HDL and a change in HDL/LDL ratios, similar in magnitude to those seen with cholesterol lowering drugs that are thought to reduce the risk of heart attacks.

The mechanisms responsible for these findings are not clear. However, they are different from those causing elevation of cholesterol during acute stress, which involve increased secretion of stress related hormones that break down fat stores. There is evidence that loss of control and associated feelings of helplessness and depression may increase cortisol levels, to which the hypothalamus responds by increasing insulin resistance. This, in turn, would cause low density lipoproteins to rise and HDL to fall. Providing workers with a better sense of control and autonomy at work may reverse this process. It might also lessen the higher incidence of hypertension and coronary heart disease known to be associated with increased levels of job stress.

Mental Medicine Update-Vol. III, No.3, 1994
International Journal of Behavioral Medicine-13:204-214, 1994

Book Reviews • Meetings and Items of Interest

Book Review

Psychological Factors Affecting Medical Conditions, Stoudemire, A., M.D., ed., American Psychiatric Press, Washington, D.C., 1995, 201 pgs., $29.00

Clinical interest in psychosomatic medicine and mind/body relationships have tended to be in a state of limbo. Psychiatrists are generally more concerned with the study of major or specific psychiatric disorders. On the other hand, primary care physicians, while acknowledging that such links exist and may be significant, point out that most of our information comes from anecdotal observations rather than hard science. In addition, most therapeutic interventions would be time consuming, and not cost effective. However, over the past few decades, advances in psychoanalysis, psychophysiology, and psychobiology may change such attitudes. They have steadily confirmed the important significance of psychological factors in many disorders, as well as the benefits of behavioral modification and the development of coping strategies in their management. The DSM-IV now defines a variety of diagnostic criteria for psychological factors that can affect medical conditions, as indicated in this volume.

Chapters devoted to cardiovascular aspects deal with coronary artery disease, Type A behavior and its various components, the role of depression and anxiety, ventricular arrhythmias and sudden death, sociocultural and interpersonal factors, and differences in personality and coping styles in patients with hypertension. Neurological disorders include stroke, multiple sclerosis, Parkinson's disease, and epilepsy with discussions of various mechanisms that may be involved. A summary of the current polemic dealing with the relationship between stress and cancer reviews such aspects as the role of psychosocial variables, coping mechanisms, stressful life events, the immune system, depression, and animal research models that may have clinical implications. The chapter on gastrointestinal conditions includes esophageal disorders, peptic ulcer disease, ulcerative colitis, Crohn's disease, and irritable bowel syndrome. The skin is the largest organ of the body and most dermatologists readily acknowledge the important role of stress in a variety of disorders ranging from pruritis and atopic dermatitis, to acne and psoriasis. A useful discussion on self induced dermatosis and the use of psychotropic agents is included. Pulmonary and rheumatologic diseases are lumped together, concluding that prospective studies will be required to shed more light on possible psychological influences on these disorders. The chapter on end stage renal disease seems somewhat out of place, since there is little evidence that psychological factors contribute to this and most of this chapter deals with the emotional consequences of patients with uremia, especially those who require chronic dialysis. The chapter on endocrine diseases includes useful discussions of the relationship between stress and diabetes, Graves' disease, and Cushing's disease, but unfortunately, there is no discussion dealing with gonadal function or important topics such as impotence and fertility. Another subject that might have been included is the role of stress and psychological factors in the development and persistence of alcoholism, and substance abuse. However, this volume is quite useful because it does provides an overview of some of the latest advances in psychosomatic medicine.

Meetings and Items of Interest

Aug. 21-25 Sixteenth Cape Cod Institute, Sound Mind, Sound Body, Speaker: K. Pelletier, call Dr. Gilbert Levin for more info at (718) 430-2307

Sept. 4-7 Healing the Healers: Physician Wellness sponsored by Lovelace Health Systems, LaFonda Hotel, Santa Fe, New Mexico, call (404) 641-9773

Sept. 10-15 International College of Psychosomatic Medicine, 13th World Congress, Holiday Inn Crowne Plaza Hotel, Jerusalem, Israel, call (972 2) 617402

Sept. 13-16 Work, Stress, and Health '95: Creating Healthier Workplaces, The Third Interdisciplinary Conference on Occupational Stress & Health, Hyatt Regency Hotel, Washington, D.C., call Lynn A. Letourneau at (202) 336-6124

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