

# DHEA

A Credible Review  
With Exhaustive  
References

*Article presented by  
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## The DHEA Debate

March 2004

### COVER STORY

A critical review of clinical and experimental data

One of the most confusing issues in health care today is the role of DHEA in anti-aging. While some promoters claim that it is a magic bullet that will confer health and longevity, others state emphatically that it has no value or is actually dangerous. Consumers are left in a quandary. Concluding that it is better to be safe than sorry, millions of Americans ignore what may be one of the most important anti-aging, health-sustaining substances available today.

Stephen Cherniske, MS, is a biochemist with more than 30 years of academic, clinical, and research experience. He was an adviser to members of the US Olympic team, served on the faculty of the American College of Sports Medicine, and taught clinical nutrition at the university level for over a decade. His 1996 book, *The DHEA Breakthrough* (Random House), was an international best-seller that helped launch the anti-aging movement worldwide.

In 1998, he was chosen to direct the Bioregenics Project, an international research effort to explore the physiology of aging. In 2001, the project was completed with an independent, double-blind, placebo-controlled human clinical trial demonstrating that the underlying causes of aging can be modified by nutrition, diet, and lifestyle.

This remarkable three-year research project forms the basis for his latest book, *The Metabolic Plan* (Random House, 2003). Between 1996 and 2003, Cherniske conducted hundreds of interviews and presented more than 1,000 hours of lectures to professional and lay audiences. In these interviews and scientific conferences, he encountered tremendous resistance to the use of DHEA. At the same time, more than 3,000 scientific studies on DHEA were published, leading to a clear understanding of the chemistry, function, and clinical value of this important hormone.

The DHEA controversy continues to rage, fueled more by opinion than facts. The following interview of Stephen Cherniske by an imaginary “naysayer” was designed to explore all of the objections that have been raised to the prudent use of DHEA. Importantly, Cherniske provides meticulous documentation for his views, with more than 160 references to current biomedical literature. It is our fervent hope that this level of scientific support will clear up the DHEA controversy once and for all. Failing that, it should at least force the naysayers to back up their claims with reasonable evidence.

#### Opening statements

**Naysayer:** DHEA, once touted as the cure-all for aging, has been a bust. It does not enhance sports performance, eliminate wrinkles, restore energy levels, or confer any significant anti-aging benefit. In fact, since it is converted to testosterone and estrogen, DHEA can promote cancer.

**Stephen Cherniske:** In science, you only find what you’re looking for. Naysayers invariably are looking for short-term benefits, when aging is a complex, lifelong process. It’s like the farmer who plants an apple orchard and concludes that his efforts were wasted because after six months, he has no fruit. When DHEA supplementation does not produce remarkable results (for example, weight loss) in 28 days, naysayers conclude that “it doesn’t work.”<sup>1</sup>

In reality, DHEA is an effective tool in weight management, but you have to break out of the diet-drug, instant-results mentality. In fact, you have to stop thinking about weight loss and

remember that the goal is fat loss, in which case the long-term solution is one that improves insulin sensitivity and promotes muscle mass. In human clinical trials, DHEA has been shown to do both.<sup>2-5</sup> Research shows that obese women have lower DHEA levels than lean controls.<sup>6</sup> New research is also showing that declining DHEA levels are associated (in animals and humans) with a subsequent decline in carnitine-driven fatty acid oxidation. Thus, restoring optimal DHEA levels may have a profound effect on long-term weight management. Remember that fat burning produces energy but also requires energy to get started. Thus the accumulation of fat with advancing age may be related as much to decreased energy production as it is to a sedentary lifestyle. Researchers at the University of California, San Francisco, conclude that reduced carnitine availability correlates with the age-related decline of DHEA.<sup>7</sup> Here is a quote from a study that investigated the role of DHEA and fat loss:

**“Regarding the action of DHEA as a fat-reducing hormone, it is possible that this hormone reduces the peripheral requirement for insulin by increasing glucose disposal, and that lower insulin levels are associated with a higher plasma ratio between lipolytic hormones and insulin, and a higher efficiency of lipolysis and loss of body fat.”<sup>8</sup>**

Another area where the instant-results mentality causes confusion is in the area of mood and feelings of vitality or well being. We know that DHEA is positively associated with feelings of well being, and that low levels of DHEA are associated with depression.<sup>9-11</sup>

Naysayer: Wait a minute. There are good studies showing that DHEA does not enhance feelings of well-being.<sup>12,13</sup>

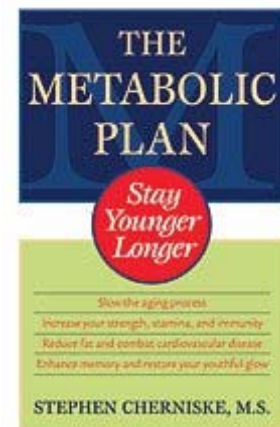
Stephen Cherniske: Both of those are two-week studies, which is a flawed design for the evaluation of changes in mood, memory, and cognition. What concerns me is that naysayers use this two-week (too weak) data, even when they are aware of longer studies (of up to one year) that demonstrate remarkable effects of DHEA on mood, libido, immunity, memory, and overall well-being.<sup>14-20</sup>

One study in particular shows a beneficial effect of DHEA on midlife dysthymia, otherwise known as the “blahs.” I include the abstract from this study in the sidebar on the next page because it demonstrates improvements in “anhedonia (lack of joy/pleasure), fatigue, lack of motivation, emotional ‘numbness,’ sadness, inability to cope, and worry.”<sup>21</sup>

Interestingly, these effects were experienced in as little as three weeks, but I maintain that the range of health and anti-aging benefits from DHEA unfold gradually over the course of years. Weight loss is gradual and requires regular exercise. The important difference is that DHEA can help restore the metabolic state in which exercise becomes easier, more enjoyable, and productive.

Naysayer: So you have demonstrated that DHEA supplementation can reverse certain psychological aspects of aging, but what about your claims that DHEA exerts anti-aging physical benefits?

Stephen Cherniske: One of the most consistent and devastating aspects of aging is the emergence of the metabolic syndrome, which is also termed Syndrome X. Decreased insulin sensitivity, free testosterone, and HDL, along with increased LDL, total cholesterol, and triglyceride levels, characterize the metabolic syndrome. The decline in DHEA secretion contributes to the metabolic syndrome and its related diseases such as heart attack, stroke, and type II diabetes.



DHEA-mediated reduction of cardiovascular risk is a gradual process, resulting from decreased platelet aggregation, reduction of serum lipids, and improvements in insulin sensitivity and endothelial function.<sup>3,22</sup> A study on DHEA and heart disease uncovered the following: **“A 100 micrograms per deciliter increase in DHEA sulfate concentration corresponded with a 48% reduction in mortality due to cardiovascular disease and a 36% reduction in mortality for any reason. The natural level of DHEA sulfate was measured and those individuals with higher DHEA sulfate levels lived longer and had a much lower risk of heart disease.”**<sup>23</sup>

Seeking to explain these remarkable benefits, researchers found that DHEA sulfate levels are positively associated with HDL and negatively correlated with LDL and total cholesterol.<sup>24</sup> A human study in the Journal of Epidemiology concluded:

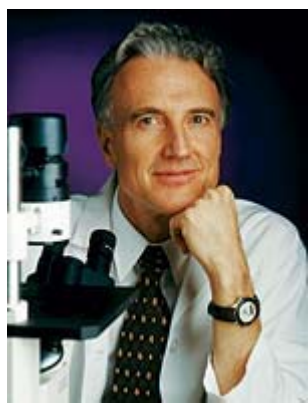
**“The mean Atherogenic index was significantly inversely correlated with the rise of tertiles in DHEAS levels, both before and after adjustment for age, total cholesterol HDL, and triglyceride. These results suggest that DHEAS may have an important role in the etiology and prevention of atherosclerosis.”**<sup>25</sup>

Recently, scientists found a strong correlation between low DHEA levels and hypothyroidism.<sup>26</sup> But instead of looking at the long-term benefits of DHEA therapy, naysayers pointed to the failure of DHEA to restore thyroid function in short-term studies. They missed the point entirely.

Naysayer: And the point is?

Stephen Cherniske: That restoring DHEA levels is very likely to have a beneficial effect on the entire endocrine system, including the thyroid, but this effect will be gradual. In fact, most pathology is cumulative, but conventional medicine acts only when problems become acute. In other words, a person does not become thyroid deficient overnight. In most cases, years of degeneration precede the metabolic disease state. Unfortunately, this degeneration goes unnoticed and a pharmaceutical “fix” known as thyroxine is used for the end-stage disease.

Naysayer: What’s wrong with thyroxine?



Stephen Cherniske,  
MS

Stephen Cherniske: Nothing. It is a useful drug to treat hypothyroidism; but there is something wrong with a health care system that does nothing to prevent a disease, and only springs to action when the problem becomes acute. The data strongly suggest that hypothyroidism develops in part due to declining levels of DHEA, and there is good evidence that people with optimal levels of DHEA are at decreased risk for thyroid disease.<sup>27-29</sup> Moreover, hypothyroidism is often caused by an autoimmune reaction, and high levels of antithyroid antibodies have been correlated with low levels of DHEA.<sup>30</sup>

Bottom line, we think the problem is our thyroid, or our blood pressure, cholesterol, blood sugar, expanding waistline, or failing memory. But these are not the problem, they are the symptoms of one problem known as aging. Until we address the underlying cause of aging, we will simply be chasing after each of the symptoms as they inevitably arise.

Naysayer: But you said that aging was a complex process. Now you’re saying that it has a simple underlying cause that can be easily altered.

Stephen Cherniske: No, declining production of DHEA is not the single cause of aging. The underlying cause of aging is the loss of regenerative capacity and the accumulation of cellular damage. The Metabolic Model of Aging describes this as a seesaw between damage and

repair, and the model holds true on every level, from the sub-microscopic realm of DNA to the cell, organs, and the entire organism.

With this understanding, DHEA plays a critical role because it is the most comprehensive anabolic (repair) signal in the human body. It can therefore help to tip the see-saw in your favor by supporting repair functions throughout the body and brain. Moreover, DHEA has been shown to reduce cellular damage via its antioxidant and immune-stimulating activity.

Another long-term factor contributing to “the DHEA advantage” arises from a reduction in stress hormone-related catabolic damage. Elevated stress hormones and low DHEA are strongly associated with immune suppression, depression, brain degeneration, and even dementia.<sup>31,32</sup> Conversely, DHEA supplementation has been shown to effectively reduce this type of degeneration.<sup>33</sup>

Naysayer: Still, the only intervention that has been proven to slow or reverse the aging process is calorie restriction.

Stephen Cherniske: You’re right that calorie restriction can prevent disease, maintain health and youth in animals at advanced ages, and even extend maximal life span to the human equivalent of 140 years.

But one of the most remarkable observations seen in calorie-restricted animals, including primates, is that the treatment raises DHEA levels.<sup>34</sup> In fact, some leading endocrinologists believe that the improvements in health and longevity from calorie restriction stem in great part from the life-long maintenance of DHEA.<sup>35-37</sup> Again, these are long-term influences on immunity, glucose tolerance, body composition, and cardiovascular risk factors that would be missed in short-term studies.

#### DHEA AND WELL BEING: STUDY ABSTRACT

“This study evaluated the efficacy of the adrenal androgen, dehydroepiandrosterone, in the treatment of midlife-onset dysthymia. A double-blind, randomized crossover treatment study was performed as follows: 3 weeks on 90 mg dehydroepiandrosterone, 3 weeks on 450 mg dehydroepiandrosterone, and 6 weeks on placebo. Outcome measures consisted of the following. Cross-sectional self-ratings included the Beck Depression Inventory and visual analogue symptom scales. Cross-sectional objective ratings included the Hamilton Depression Rating Scale, the Cornell Dysthymia Scale and a cognitive test battery. Seventeen men and women aged 45 to 63 years with midlife-onset dysthymia participated in this study. Response to dehydroepiandrosterone or placebo was defined as a 50% reduction from baseline in either the Hamilton Depression Rating Scale or the Beck Depression Inventory.

**RESULTS:** In 15 patients who completed the study, a robust effect of dehydroepiandrosterone on mood was observed compared with placebo. Sixty percent of the patients responded to dehydroepiandrosterone at the end of the 6-week treatment period compared with 20% on placebo. A significant response was seen after 3 weeks of treatment on 90 mg per day. The symptoms that improved most significantly were anhedonia, loss of energy, lack of motivation, emotional “numbness,” sadness, inability to cope, and worry.

**CONCLUSIONS:** This pilot study suggests that dehydroepiandrosterone is an effective treatment for midlife-onset dysthymia.”<sup>21</sup>

21. Bloch M, Schmidt PJ, Danaceau MA, Adams LF, Rubinow DR. Dehydroepiandrosterone treatment of midlife dysthymia. *Biological Psychiatry*. 1999 Jun 15;45(12):1533-41

Naysayer: That’s just it. There doesn’t seem to be any long-term studies to back up the anti-aging claims for DHEA.

Stephen Cherniske: You just haven't looked. When the National Institutes on Aging analyzed data from the Baltimore Longitudinal Study of Aging, they found a profound relationship between DHEA levels and survival.<sup>38</sup>

**“Consistent with the beneficial effects of calorie restriction on aging and life span in other animals, men with lower temperature and insulin and those maintaining higher DHEA levels have greater survival than their respective counterparts.”<sup>39</sup>**

Likewise, studies of people aged 90 to 106 demonstrate that those who reach this remarkable milestone have higher-than-average DHEA levels. As you would expect, this was associated with a higher muscle-to-fat ratio and greater functional ability.<sup>40,41</sup>

The average adult replaces more than 300 billion cells each day. Anti-aging is accomplished in three ways: by providing optimal raw materials for this repair activity, reducing the damage that these cells are exposed to, and restoring and maintaining anabolic (repair) metabolism. As I mentioned, DHEA is the most comprehensive repair signal in human biochemistry, and it is time that we fully appreciate the influence it has on one's rate of aging. I am not the only scientist who believes that anti-aging is virtually impossible without paying careful attention to one's DHEA level. Here are the findings from a study on hormones and aging:

**“The maintenance of a good physical functional ability and quality of life is related to serum testosterone, estrogen, and DHEA(S) concentrations.”<sup>42</sup>**

Naysayer: But isn't that the problem—that DHEA, because it is a cell proliferator, might accelerate nascent tumors?

Stephen Cherniske: Wrong! DHEA is a cell regulator. It induces apoptosis (cell death) in malignant and malfunctioning cells,<sup>43-45</sup> and controls hyperplasia (abnormal cell growth) in the smooth muscle of the lungs.<sup>46</sup> In numerous animal models, it has been shown to mimic the cell-regulating, anticancer benefits of calorie restriction.<sup>36,47</sup>

In thousands of animal studies, DHEA has been shown to prevent diabetes, obesity, infection, liver disease, and many types of cancer.<sup>48</sup> In humans, DHEA levels predict mortality in a number of disease states, including AIDS, sepsis, cancer, and heart disease.<sup>49-52</sup> And supplementation with DHEA has been shown—in controlled human studies—to increase muscle mass, improve bone density, combat stress and depression, enhance quality of life, restore immunity, protect the brain, improve memory, reduce the symptoms of systemic lupus erythematosus, and reduce risk for diabetes and cardiovascular disease.<sup>3,4,22,53-61</sup>

Naysayer: How can you be sure that DHEA won't cause cancer?

Stephen Cherniske: There are no data to suggest that. In fact, all the evidence is to the contrary. Dr. Marian Laderoute, a pathologist at the Canadian Bureau of Infectious Diseases, reminds us that cancer is associated with low DHEA levels. She and others point out that the specific mutations required for carcinogenesis can be traced to a failure of immunity and cell regulation that takes place as a consequence of falling levels of DHEA.<sup>62</sup>

Clearly, cancer does not take place due to high levels of DHEA. If that were the case, young people would get cancer, when in fact it is remarkably rare in the young. Declining immunity must be a factor, but we also do not see an increased incidence of cancer among young patients on immunosuppressive therapy (for example, organ transplant recipients). Cancer incidence, it turns out, is tied to numerous aspects of aging, including impaired apoptosis, decreased immune surveillance and decreased number and activity of NK (natural killer) cells. DHEA has been shown to improve every one of these factors.<sup>45,55,63,64</sup>

Current research also shows that DHEA, like calorie restriction, reduces the inducible generation of nitric oxide, which is yet another way of reducing cancer risk.<sup>65</sup> On the gene level, DHEA's anticancer activity includes a reduction in levels of the mutant gene p53.<sup>66</sup> Moreover, aging and cancer are associated with the dysregulation of cytokine production in which IL-6 predominates over IL-2. It is known that IL-2 has powerful anticancer activity, and IL-2 injection is presently used in Europe with various stages of cancer. Since optimizing DHEA has been shown to significantly increase IL-2 and normalize cytokine balance, maintaining optimal levels of DHEA appears to be an effective cancer-preventive strategy.

Indeed, animal studies have supported this idea for over 25 years, where DHEA administration has reduced the risk of cancer of the liver, adrenals, pancreas, breast, lung, thyroid, colon, skin, and lymphatic tissue.<sup>67-75</sup>

In all, there is compelling genomic, biochemical, and biological evidence supporting the ability of DHEA to reduce cancer risk. But perhaps you have data from human trials showing that DHEA somehow stimulates cancer growth.

Naysayer: DHEA has been shown to cause liver cancer in mice.

Stephen Cherniske: Yes, there is a study in which mice were given a massive dose of DHEA—the human equivalent of 10,000 mg per day. And even then, this dose had to be administered continuously for at least 18 months (the human equivalent of 76 years) before they could induce cancer in these poor animals.<sup>76</sup>

Do you really think that this is relevant, considering that studies using a lower dose (the human equivalent of 2,000 mg per day) did not produce cancer,<sup>77</sup> and more than 50 rodent studies show that DHEA reduces cancer risk? Importantly, DHEA administration has reduced cancer risk in every conceivable model, whether the cancers were spontaneous or induced by a virus or carcinogenic chemical.<sup>78</sup>

Naysayer: Well, there are other studies . . .

Stephen Cherniske: Yes, the study at the University of Oregon where DHEA was fed to trout—an organism that does not even produce DHEA naturally.<sup>79</sup> Such data would be useful only if there were indications that the same thing might occur in humans. But in a review of more than 5,500 studies published on DHEA, not one has shown that DHEA stimulates cancer growth. In fact, DHEA has been used successfully in the treatment of cancer.<sup>80</sup>

Look at the recent research conducted by the National Cancer Institute. They created a reliable animal model for the study of breast cancer and found that DHEA administration significantly reduced both the incidence and multiplicity of tumors.<sup>81</sup> Here's the quote that appeared in the *Journal of Nutrition* (p. 2408S):

**“Whenever it has been tested in a model of carcinogenesis and tumor induction, DHEA has preventative effects.”<sup>82</sup>**

Another animal study from 2001, also conducted by the National Cancer Institute, showed that DHEA administration reduced breast cancer incidence by 30% and multiplicity by 50%.<sup>83</sup> The following year, NCI published a mode-of-action study explaining how DHEA helps to limit cancer growth.<sup>84</sup>

DHEA has even shown powerful anti-cancer activity in mice selectively bred to be highly susceptible to cancer.<sup>85</sup> Researchers have also found the specific genes that confer this advantage (including p53, DHEA ST, and p21) are upregulated by oral administration of DHEA.<sup>86,87</sup>

DHEA may also be effective in reducing risk for colon cancer. Scientists in Japan exposed mice to a chemical that induces abnormal cellular proliferation in the colon. After this exposure, some

of the mice were fed DHEA. At the end of the experiment, the DHEA-supplemented mice had a significant decrease in precancerous lesions compared to controls.<sup>88</sup>

In another animal study, small doses of DHEA were shown to significantly prevent breast cancer. DHEA treatment resulted in a marked reduction in tumor incidence and a whopping 92% reduction in tumor size compared to controls.<sup>89</sup>

Naysayer: But these are animal studies. They don't prove that DHEA prevents breast cancer in human beings.

Stephen Cherniske: Agreed. But they certainly disprove your "sky-is-falling" diatribe that DHEA might cause breast cancer. There isn't any evidence whatsoever that DHEA increases risk for breast cancer. In fact, a study published in the prestigious journal *The Lancet* showed a remarkable correlation between breast cancer and low DHEA levels.

In this longitudinal study, researchers measured DHEA metabolites in 5,000 women, and then followed these subjects for nine years for breast cancer. DHEA levels were significantly lower in cases (women who were subsequently diagnosed with breast cancer) compared to matched controls, leading the researchers to conclude that women with low DHEA levels are at increased risk for breast cancer.<sup>90</sup>

So the breast cancer scare is a red herring. You also claim that DHEA might cause prostate cancer, when all the evidence is to the contrary.

Naysayer: I disagree. DHEA can be converted to testosterone.

Stephen Cherniske: So? Human studies show that there is no correlation between DHEA or testosterone and prostate cancer.<sup>91-95</sup> In- vitro studies show that DHEA actually inhibits prostate cancer,<sup>96</sup> and even giving massive amounts of DHEA to animals does not induce abnormal growth in the prostate. A study published in the journal *Cancer Research* states: **"No effect on the development of prostate cancer precursor lesions was observed when mice were treated with DHEA."**<sup>83</sup>

Naysayer: But I've read in dozens of articles that DHEA might cause prostate cancer. All of those articles can't be wrong.

Stephen Cherniske: Sure they can. Journalists are not scientists. If they believe their source to be accurate, they print the information without checking the medical literature. Then the story is repeated and, as you know, if an error is repeated enough, it appears to be true. If journalists were willing or able to carefully research this topic, they'd find an animal study reported in the *European Journal of Urology* that concludes:

**"DHEA and 9-cis-retinoic acid are the most active [cancer-preventive] agents identified to date. DHEA inhibits prostate cancer induction both when chronic administration is begun prior to carcinogen exposure, and when administration is delayed until preneoplastic prostate lesions are present."**<sup>97</sup>

Notice that DHEA administration inhibited prostate cancer when given prior to carcinogen exposure, and was effective even after the initial stages of prostate cancer.

Naysayer: But again, that's an animal study.

Stephen Cherniske: And animal studies are routinely used to establish safety and efficacy, especially when there is no evidence that DHEA might cause or accelerate abnormal prostate growth in humans.

Naysayer: There must be evidence.



Stephen Cherniske: No, there's only inference, speculation. Look, if DHEA caused abnormal prostate growth, high levels of DHEA would be associated with high PSA scores. In fact, low DHEA levels are associated with elevated PSA in men, and the converse is also true: men with higher DHEA levels have lower PSA scores.<sup>98</sup>

Naysayer: Still, DHEA supplements might raise PSA levels.

Stephen Cherniske: That does not occur. In study after study, supplementation with DHEA—even at high doses—has been shown to have no negative effect on PSA levels.<sup>99,100</sup> In private communication, many clinicians have told me that they have observed a gradual decline in PSA levels in patients taking DHEA. Consistent with this are recent findings that prostate cancer patients have higher serum levels of immunosuppressive glucocorticoids<sup>95</sup> (DHEA counters that) and that DHEA metabolites can inhibit PSA expression by interrupting androgen binding to the prostate androgen receptor.<sup>101</sup> These provide yet more evidence that DHEA may actually reduce prostate cancer risk.

Naysayer: Well, if there is no danger, and DHEA might even help prevent prostate disease, why are there no human trials with DHEA and prostate health?

Stephen Cherniske: Actually, the Division of Cancer Prevention at the National Cancer Institute is planning to study DHEA supplementation as a way to prevent prostate cancer in men.<sup>102</sup> DHEA has already been used successfully in the treatment of erectile dysfunction.<sup>103,104</sup> Here are the findings from a study that reviewed the effects of DHEA on common age-related ailments:

**“Low concentrations of DHEA are associated with immunosenescence, physical frailty, decline in muscle mass, increased mortality, loss of sleep, diminished feelings of well-being and impaired ability to cope, and occur in several common diseases (including cancer, atherosclerosis, hypertension, diabetes, osteoporosis and Alzheimer’s disease.”<sup>105</sup>**

Naysayer: Still, DHEA stimulates IGF-1, and that promotes cancer.

Stephen Cherniske: First of all, the widely cited association between IGF-1 and prostate cancer has been debunked.<sup>106,107</sup> That said, the concern for tumor acceleration does make sense because IGF has angiogenic activity that would favor tumor growth. But IGF-1 has only been shown to accelerate tumor growth in test tubes. Test tubes and petri dishes do not have immune systems, which are upregulated by IGF-1. In fact, the preponderance of the evidence shows that IGF-1 does not promote cancer in any living organism, whether animal or human. Even direct injection of IGF-1 does not promote tumor growth in animals.<sup>108</sup> In Europe, IGF-1 is routinely given to cancer patients to help them gain weight.

Aside from this, it is important to note that increases in IGF-1 after DHEA supplementation are significant but modest, and there are no published studies in which DHEA administration caused IGF-1 to rise above the normal range. Moreover, scores of published studies demonstrate the essential role that IGF-1 plays in the repair and regeneration of the brain, skeleton, and cardiovascular and immune systems.<sup>109-112</sup> Conversely, low IGF-1 levels have been associated with dementia, atherosclerosis, osteoporosis, and sarcopenia,<sup>54,113</sup> and a study in the journal *Gerontology* shows that men who maintain youthful levels of IGF-1 do not experience the decline in testosterone or muscle mass, or the accumulation of fat, that has been considered an inevitable consequence of aging.<sup>114</sup>

Naysayer: But DHEA is converted to testosterone and estrogen . . .

Stephen Cherniske: Some DHEA is converted to testosterone and estrogens. But there are enzymes in every tissue of the human body and brain that metabolize DHEA itself. The idea that DHEA is merely a reservoir for sex steroids was debunked decades ago. A recent study in the journal *Steroids* documents the anticancer effects of DHEA and all of its major metabolites.<sup>115</sup> Likewise, the ability of DHEA to reduce risk for cardiovascular disease is independent of its conversion to sex steroids.<sup>116</sup> A study with 375 men with a mean age of 60 found that sexual activity and satisfaction was far more closely associated with DHEA levels than testosterone.<sup>98</sup>

Naysayer: But it is converted to testosterone and estrogen . . .

Stephen Cherniske: Yes it is, but are you saying that is inherently unsafe?

Naysayer: Well, look at the disaster that we just saw with hormone replacement therapy (HRT).

Stephen Cherniske: That was caused by conventional HRT using large doses of synthetic hormones. Yes, that was a disaster, given to more than 80 million women, which actually increased risk for breast cancer, stroke, and pulmonary embolism.<sup>117</sup> So, because large amounts of synthetic hormones increased disease risk, you believe that small amounts of a natural hormone will do the same thing, even though we've been over this already and you've seen that there is no evidence that DHEA promotes abnormal growth of any tissue in the human body. Even though studies with human volunteers show that a 50-mg daily dose of DHEA does not elevate systemic or blood levels of estradiol.<sup>19</sup> Heck, human studies with 200 mg of DHEA per day have shown no systemic elevation of estradiol.<sup>118</sup> On the contrary, conversion of DHEA to sex steroids appears to take place on an as-needed basis, through an inherent self-regulating activity.

The dangers of HRT stem not only from the systemic elevation of estradiol. We now know that HRT lowers DHEA levels.<sup>119</sup> Importantly, DHEA supplementation does not raise sex steroid levels above normal. Most of the repair and regenerative benefits of DHEA come from local (or peripheral) anabolic activity such as was recently demonstrated in *Mechanisms of Ageing and Development*. This important study utilizing genomic technology revealed that DHEA improves bone density, not by raising systemic levels of estradiol but through local conversion to estrone by osteoblasts.<sup>120</sup> In other words, DHEA is converted by repair cells in the bone to estrone, which does not promote cancer, while leaving estradiol levels in the breast and uterus unchanged.

In fact, a growing number of endocrinologists are realizing that the solution to maintaining bone density in postmenopausal women was staring us in the face for more than 40 years, but the pharmaceutical-based health care system ignored this natural, safe, and effective treatment in favor of prescription drugs, even though those drugs have been known to be unsafe for at least the last 15 years.

Research shows conclusively that DHEA deficiency contributes significantly to age-related bone loss in men and women.<sup>42</sup> And a recent study with postmenopausal women demonstrates the significant anabolic benefits that can be obtained from DHEA supplementation. Women in the treatment group experienced improvements in virtually all anabolic (repair) hormones, including DHEA, estrone, estradiol, androstenedione, and testosterone. Importantly, none of these steroids rose to levels that would be considered unsafe. What's more, increases in osteocalcin and IGF-1 indicate that 50 mg of DHEA might be more effective in maintaining bone density

than high doses of synthetic estrogen and progestins (conventional HRT). The researchers conclude:

**“Our data support the hypothesis that DHEA treatment acts similarly to estrogen-progestin replacement therapy on the GHRH-GH-IGF-1 axis. This suggests that DHEA is more than a simple ‘antiaging product’; rather it should be considered an effective hormonal replacement treatment.”**<sup>121</sup>

One final note on women’s health is the ability of DHEA supplements to help balance estrogen and progesterone.

Naysayer: How can that be? DHEA is not converted to progesterone.

Stephen Cherniske: Not directly, but DHEA can raise progesterone levels by inhibiting conversion of pregnenolone to cortisol (via 17-hydroxyprogesterone).<sup>122</sup> Thus, by any measure, DHEA appears to be a valuable and safe hormone supplement for women and men.

Naysayer: Men don’t need progesterone.

Stephen Cherniske: Of course they do. And a study just published with men suffering from fatigue and depression suggests that improvements in mood, energy, and libido derived from 25 to 50 mg of DHEA resulted from increased progesterone levels, not testosterone.<sup>18</sup>

Naysayer: There’s still no proof that DHEA is safe.

Stephen Cherniske: Yes, there is. You’ve been trying to persuade the public that safety data do not exist, when there are adequate human clinical trials, including year-long studies with as many as 300 volunteers. Listen to the conclusion of one of these studies published in the Journal of Clinical Endocrinology and Metabolism. This is a human study with a 25-mg/day group and a 50-mg/day group:

**“No accumulation of steroids was observed. No worrying transformation to androgen and estrogen was recorded; indeed, the limited increased estradiol in aged women could be predicted to be beneficial. These results suggested that daily oral administration of DHEA (25/50 mg) is safe in elderly subjects. The 50-mg dose was chosen for a 1 yr, double blind, placebo-controlled trial of daily oral administration of DHEA in 60- to 80-yr-old individuals.”**<sup>123</sup>

This was followed by an even larger, year-long evaluation. This landmark project, known as the DHEAge study, was published in the Proceedings of the National Academy of Science. The conclusion:

**“No potentially harmful accumulation of DHEAS and active steroids was recorded . . . A number of biological indices confirmed the lack of harmful consequences of this 50 mg/day DHEA administration over one year, also indicating that this kind of replacement therapy normalized some effects of aging.”**<sup>124</sup>

Naysayer: Well, what about the well-known side effects that DHEA produces in women?

Stephen Cherniske: Such as?

Naysayer: Oily skin, acne, and growth of facial hair.

Stephen Cherniske: Those are overdose effects, and to produce these effects, a woman would have to take an excessive dose of DHEA for months. Importantly, these effects are obvious and sequential.

In other words, if a woman takes too much DHEA, she may experience side effects from the conversion of DHEA to testosterone. The first sign is oily skin. If she ignores this and does not reduce her dose, she may develop testosterone-related acne. If she ignores the acne and continues to overdose, she may start to see hair growth on her upper lip. Importantly, these side effects are reversible and certainly not life threatening.

Naysayer: Still, such side effects are distressing.

Stephen Cherniske: But you're talking as if side effects are common, when in fact they are rare. At the clinically effective dose of 5 to 25 mg, the incidence of androgen-related side effects is less than 2%.<sup>123</sup> Compared to the known benefits, and the ease by which a safe dose can be determined, it is unreasonable and unscientific to harp on side effects that are rare and innocuous. Tremendous health benefits are obtainable from 5 to 25 mg of DHEA. It significantly reduces risk for diabetes and cardiovascular disease at 25 mg per day.<sup>3</sup> These two degenerative diseases account for more than 70% of deaths in the US and all you can do is wring your hands about an adverse effect that might occur at four or five times that dose.

Naysayer: Well, DHEA is sold in health food stores. People are naturally going to think that any dose is safe.

Stephen Cherniske: Aspirin is sold in convenience stores and gas stations. Aspirin can cause gastrointestinal bleeding and other side effects.

There is an absurd double standard being used here. You promote the sale and use of high-dose aspirin, which can have serious side effects, because you believe in the principle of informed choice. Yet when it comes to DHEA, you don't think people are capable of making an intelligent decision.

Naysayer: But women do not know how much DHEA they are presently producing.

Stephen Cherniske: Exactly. This is part of the education process that should be in high gear; but the exact opposite is taking place. Instead of encouraging women to measure their DHEA levels, many doctors are telling them that it doesn't matter. Instead of receiving guidance on a critically important aspect of health and wellness, patients are being misled. With what we know about the influence of DHEA on health and disease, this should be a top priority. Women with severe symptoms associated with menopause (known as climacteric syndrome) have DHEA levels that are roughly half those of age-matched controls,<sup>125</sup> but few physicians know this.

**FACT: For 70% of women, the gynecologist is the only doctor they see.**

Naysayer: You keep talking about DHEA supplementation, but couldn't people just exercise and get the same benefit? After all, studies show that individuals who exercise regularly have higher levels of DHEA and IGF-1.<sup>126,127</sup>

Stephen Cherniske: I agree, but let's look carefully at this correlation. In a recent study with elderly women, DHEA and IGF-1 were directly related to daily activity, physical exercise, muscle strength, and respiratory efficiency. The authors conclude that exercise must therefore have a positive effect on anabolic hormones.<sup>128</sup> I call this the Jack LaLanne effect, but it is important to understand that the converse is also true; that some people have a genetic ability to maintain higher levels of DHEA, which stimulates IGF-1, and this maintenance of anabolic drive is what enables them to remain active and to perform physical exercise. The vast majority of Americans do not have this genetic advantage. If people are on the "catabolic" side of life with poor exercise tolerance, telling them to "just exercise more" is unfair and unscientific. Better to

improve anabolic drive via DHEA supplementation, and then go to the gym. They will suffer less and achieve better results.

Naysayer: You don't know that.

Stephen Cherniske: Yes, we do. In a study funded by the National Institutes of Health, Dr. Dennis Villareal and his colleagues conducted a double-blind, placebo-controlled human clinical trial using 50 mg of DHEA per day with a group of elderly men and women. After only six months, those taking DHEA experienced improvements in muscle mass and bone density, and a reduction in body fat.<sup>2</sup>

As I explain in my book, *The Metabolic Plan*, this is one of the most important keys to living a long and healthy life. As we age, most people lose muscle and gain fat. You have to understand the profound effect this has on quality of life. Beyond the aesthetic effect, which affects our self-esteem and outlook on life, the accumulation of fat and loss of muscle causes a progressive loss of functional ability and a dramatic alteration in glucose metabolism. More than 70% of obese individuals will become diabetic, and the diabetic state is like turbo-aging, producing rapid degeneration throughout the body and brain.

Naysayer: So now you're going to tell me that DHEA prevents diabetes?

Stephen Cherniske: Well, it prevents diabetes in animals<sup>48</sup> and there is compelling evidence that it reduces the risk for diabetes in humans. We all know that aging is associated with a decreased muscle-to-fat ratio and decreased insulin sensitivity, which often lead to type II diabetes. DHEA has been shown in human clinical trials to improve insulin sensitivity and to help restore muscle mass.<sup>2,3</sup> It has long been known that diabetics have reduced serum levels of DHEA compared to age-matched controls.<sup>129,130</sup> Importantly, new research shows that even in healthy individuals, low DHEA levels are correlated with high plasma glucose, suggesting that DHEA deficiency contributes directly to the diabetic state.<sup>131</sup> Here is a quote from one of many studies on DHEA and aging:

**“Oral replacement of DHEA, which does not appear to cause important adverse effects, may prevent, or even reverse, some age-associated conditions.”<sup>105</sup>**

Naysayer: If DHEA is safe and beneficial, why are there two bills in Congress that seek to ban it? One of the bills, H.R. 207, is aimed at keeping anabolic steroids out of the hands of teenage athletes. You don't condone drug abuse in sports, do you?

Stephen Cherniske: Of course not, but it is absurd to put DHEA in the same category as the anabolic steroids that athletes and body-builders use. Those are synthetic testosterone analogs that produce abnormal muscle growth and have dangerous side effects. You simply cannot create abnormal muscle growth with DHEA. Because of this, there is no evidence whatsoever that athletes of any age are abusing DHEA. The USOC began testing for DHEA abuse in 1996. How many violations have they found? None. Regarding sports performance, a report in the journal *Clinical Chemistry* states:

**“Performance benefits for athletes are neither documented nor proven. DHEA is ‘guilty’ by virtue of its position in the biochemistry of gonadal hormone production.”<sup>132</sup>**

Naysayer: Well, some doctors are worried about interactions with prescription drugs.

Stephen Cherniske: Only two possible interactions have been identified. Women taking tamoxifen (an anti-estrogen) and men being treated for prostate cancer with testosterone

blockade will not want to take DHEA. These are well-known and well-publicized caveats. On the other hand, studies show that many prescription drugs alter DHEA metabolism or reduce DHEA blood levels.<sup>133</sup> Unfortunately, no one seems to be concerned about this.

Remember that adverse interactions between prescription drugs are extremely common. Popular non-steroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, have scores of adverse interactions that can be life threatening. Again, it is a matter of informed choice. You can't champion informed choice everywhere else and then call for a ban on DHEA because someone, somewhere might be harmed someday.

I come back to the double standard that is being used to evaluate DHEA. More than 600 Viagra® users have died since that drug was approved. No one has died from taking DHEA and members of Congress are trying to ban it.

Naysayer: But that's a good case in point. The effects and side effects of Viagra® are well known, whereas the long-term effects of DHEA are unknown.

Stephen Cherniske: You've fallen for the biggest myth in all of health care—that the long-term effects of prescription drugs are known. Nothing could be further from the truth. A study published in the Journal of the American Medical Association reports that "51% of approved drugs have serious adverse effects not detected prior to approval."<sup>134</sup> Using Viagra® as an example, there are very troubling questions regarding long-term use. Viagra® has been shown to trigger migraines in the vast majority of migraine sufferers.<sup>135</sup> This was unknown until 2003. How the drug affects cardiovascular health is a continuing debate. But whether or not you believe that Viagra® causes heart attacks, you can't ignore the vast number of reported adverse events associated with the drug. The Journal of the American College of Cardiology published an analysis of the first 13 months Viagra® was on the market. It found 1,473 major adverse reactions reported to the FDA, including 522 deaths, 517 heart attacks, 161 cardiac arrhythmias, and 119 strokes.<sup>136</sup> In reality, of course, this is most likely the tip of an iceberg, as only about 5% of serious adverse drug reactions are reported to the FDA.

Naysayer: Well, what about people on steroid therapy like prednisone?

Stephen Cherniske: DHEA does not reduce the efficacy of prednisone.<sup>137</sup> In fact, it appears to enhance the effectiveness of prednisone therapy by reducing the immune suppression associated with the drug.<sup>138</sup> For this reason, a growing number of researchers and clinicians are recommending that DHEA be used along with prednisone. Studies with lupus patients who are normally treated with prednisone show that supplemental DHEA can significantly reduce symptoms, and many are able to reduce or even eliminate the prednisone.<sup>139</sup>

And while we're talking about chronic inflammatory disease, please remember the Catch-22 of conventional corticosteroid therapy where the desired anti-inflammatory effect is often followed by adverse side effects, including immune suppression, osteoporosis, and the stimulation of pro-inflammatory cytokines including IL-6, nuclear factor-kappa B, and tumor necrosis factor (TNF). Recent research shows that:

1. IL-6 levels tend to increase with advancing age.<sup>140</sup>
2. DHEA is a potent inhibitor of IL-6 in animals and humans.<sup>141</sup>
3. In every chronic inflammatory disease tested, including systemic lupus erythematosus (SLE), rheumatoid arthritis, polymyalgia rheumatica, and inflammatory bowel diseases, DHEA and/or DHEAS levels in patients have been found to be lower than in healthy controls.<sup>142-144</sup>
4. Oral administration with DHEA shows significant promise in the treatment of chronic inflammatory diseases.<sup>145,146</sup>

Naysayer: What about people undergoing surgery?

Stephen Cherniske: Surgical stress has been shown to seriously deplete DHEA, leaving the patient in a more vulnerable state.<sup>147,148</sup> Post-surgical use of DHEA is one of the most appropriate uses of this repair and regenerative signaling molecule.

Naysayer: Who else would be a candidate for DHEA? Don't say, "76 million baby boomers." I want solid science.

Stephen Cherniske: How about 19 million Americans with depression?<sup>149</sup> That's nearly 10% of the adult population.

Naysayer: Studies do show that depressed individuals have much lower levels of DHEA compared to age-matched controls.<sup>10</sup> But that doesn't mean DHEA is a treatment for depression.

Stephen Cherniske: Yes, it is. Numerous studies show that DHEA has profound antidepressive benefits.<sup>17,20,150</sup> Here is one example:

**"Elevated cortisol-DHEA ratios may be a state marker of depressive illness and may contribute to the associated deficits in learning and memory. Administration of DHEA may reduce neurocognitive deficits in major depression."**<sup>151</sup>

We now know that the brain manufactures large amounts of DHEA. In fact, brain concentrations of DHEA are much higher than plasma concentrations. And just like blood levels, brain levels of DHEA fall dramatically with advancing age.<sup>152</sup> DHEA is now recognized as a critically important neurosteroid, playing an active role in neurotransmitter function, memory, and cognition. And while I am not suggesting that DHEA can treat Alzheimer's disease, it is certainly interesting to note that DHEA levels in the brains of Alzheimer's patients are far lower than in age-matched controls.<sup>153</sup> A study reported in the *Journal of Endocrinology Investigations* explores the mechanism by which DHEA may block the toxic effects of stress hormones, and concludes that because aging is associated with increasing stress, DHEA may well be of benefit to the normal aging brain.<sup>154</sup> A report in the *World Journal of Biological Psychiatry* concludes that restoring hormone balance in the brain via supplemental DHEA may significantly reduce risk for many psychiatric diseases.<sup>20</sup>

Importantly, the area of the brain most vulnerable to age-related degeneration is the hippocampus. In healthy elderly subjects, hippocampal volume has been found to correlate directly with DHEA levels,<sup>155</sup> and in animal studies, DHEA supplementation has been found not only to protect the hippocampus from stress hormone-related damage, but also to promote the anabolic repair of nerve tissue and even promote the formation of new neurons. A study just published in the *European Journal of Neuroscience* concludes:

**"These results show that DHEA, a steroid prominent in the blood and cerebral environment of humans, but which decreases markedly with age and during major depressive disorder, regulates neurogenesis in the hippocampus and modulates the inhibitory effect of increased corticoids on both the formation of new neurons and their survival."**<sup>156</sup>

In other areas of mental health, DHEA levels were found to correlate directly with better symptom scores in a group of schizophrenic patients. The authors note:

**"Higher DHEA levels were significantly correlated with lower symptom ratings, better performance on some measures of memory and lower ratings of Parkinsonian symptoms." A follow-up placebo-controlled human trial published in the *Archives of***

## **General Psychiatry reports that DHEA supplementation produced significant benefits in patients with schizophrenia.<sup>157</sup>**

Etienne-Emile Baulieu, one of the world's foremost hormone biochemists and a leading DHEA researcher, stated in the Journal of Clinical Endocrinology and Metabolism:

**“Logic pleads in favor of oral administration of DHEA at a dose that provides so called ‘young’ DHEA levels in the blood and no T/DHT and E2 concentrations superior to those of normal people of 30 to 40 years of age. Calculations based on production rates, interconversion between DHEA and DHEAS, and metabolic studies suggest that replacement doses of 25-50 mg once daily are able to fulfill this double requirement.”<sup>16</sup>**

Concluding statements

Naysayer: I have to say that all of the data that you've supplied have surprised me, especially the material relating to DHEA's potential anticancer role. But there's one fundamental issue that we haven't addressed, which could be called the natural law argument. DHEA levels peak late in the third decade of life and then progressively decline. I believe that there is probably a good reason for this, and that manipulating levels of this powerful hormone could have unforeseen consequences, perhaps much later in life. Most of the doctors I know share this feeling and therefore recommend that patients wait until long-term, conclusive studies have been performed.

Stephen Cherniske: What you call “natural law” could also be called the “do nothing” argument, or the “don't mess with Mother Nature” argument, both of which are more romantic than scientific. The doctors you refer to mess with Mother Nature every day. Mother Nature creates infections that kill people. Doctors prescribe antibiotics to keep them alive. Cholesterol is purely natural and blood levels rise with advancing age, but doctors last year wrote more than 80 million prescriptions to lower cholesterol. Diabetes is natural, but it is treated with a hormone called insulin. We are constantly messing with Mother Nature to prevent death and maintain quality of life. And by the way, a year-long review by the US Office of Technology Assessment found that only 10-20% of all procedures used in medical practice have been shown to be safe and effective by controlled clinical trials.<sup>158</sup>

In other words, health professionals are very comfortable with what is called the risk-reward ratio, or benefits versus possible side effects. This is easy to do when you're treating a life-threatening infection or a fatal disease, or surgically removing a tumor. In these critical situations, messing with Mother Nature is of no concern.

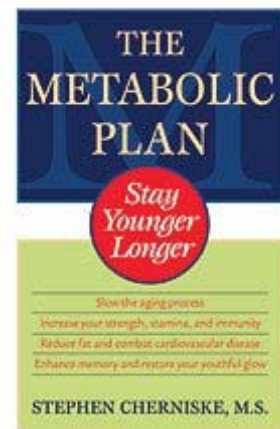
I simply want to suggest that, since aging contributes directly to virtually all disease states, it makes sense to treat aging before the signs and symptoms arise. This is not rocket science. Studies show that the hormone signal (ACTH) that produces a robust DHEA response in young people is significantly blunted in elderly men and women.<sup>152</sup> Restoring DHEA levels is not a magic bullet, but it should be an integral part of any sensible anti-aging effort. Naysayers tell us to wait for “more information” while they ignore the mountain of clinical and research data already in hand. To summarize:

1. DHEA is the most abundant circulating hormone in the human body, and influences more than 150 known anabolic (repair) functions throughout the body and brain.
2. Starting at about age 28, DHEA levels start to decline, and this loss of anabolic drive accelerates with advancing age, so that by age 70, most people are producing only 10-15% of the DHEA they were producing in their twenties.
3. High levels of DHEA are strongly associated with longevity.
4. Low levels of DHEA are associated with depression, dementia, obesity, diabetes, asthma, autoimmune disease, osteoporosis, and increased risk for cancer and cardiovascular disease.



5. Low levels of DHEA are also associated with increased mortality in a number of disease states, and one study found low DHEA to be associated with increased risk for death from all causes.<sup>23</sup>
6. One's production of DHEA can be reliably determined by measuring DHEA sulfate in serum or by measuring DHEA metabolites in a urine sample (the Anabolic/Catabolic Index, or ACI). This test has been awarded a US patent, the methodology paper was published in the Journal of Chromatography, and the age correlation study was published in the international journal Spectroscopy.159-161 The ACI test provides a snapshot view of anabolic drive and is a valid aging biomarker.
7. As opposed to what is "normal" in the aging population, leading endocrinologists believe that optimal restoration of anabolic drive (true anti-aging) will be achieved by maintaining DHEA at the level of a healthy 30-year-old.<sup>124</sup>
8. DHEA is readily absorbed from an oral dose.
9. Most human studies have used a 50 mg/day dose (the high end of the physiologic dose range), although clinically significant benefits can be achieved with doses as low as 10 mg per day.
10. There is no evidence—clinical or experimental—that associates physiologic dose DHEA supplementation with any untoward effects, save the well-known production of oily skin and acne in a small percentage of women.

My final comment relates to your assumption that declining levels of DHEA are a natural and necessary part of the aging process. This is pure speculation. Far more compelling is research showing that declining DHEA production results from progressive atherosclerosis, which reduces oxygen and glucose delivery to the area of the adrenals (the zona reticularis) where DHEA is synthesized.<sup>37</sup> We certainly understand the consequences of decreased blood supply to the heart and brain (heart attacks and stroke). Since the blood vessels leading to these organs are a great deal larger (and less convoluted) than those leading to the adrenals, it is not hard to see how age-related arterial blockage and stiffening can affect the production of DHEA. Thus, far from being a "natural" part of the aging process, declining DHEA synthesis appears to be an unrecognized aspect of cardiovascular pathology.



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