The Case for DHEA

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Background

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

The Author

Stephen Cherniske is a biochemist with more than 50 years of academic, clinical and research experience. He taught university clinical nutrition, directed the nation's first FDA-licensed clinical lab specializing in nutrition and immunology, and served on the faculty of the American College of Sports Medicine. His book, *The DHEA Breakthrough* (Random House 1996) was an international best-seller which helped to launch the anti-aging movement worldwide. Cherniske is considered to be the chief architect of the metabolic model of aging – now the predominant model used in research protocols throughout the world.

In 1998, he was chosen to direct the Bioregenics Project, an international research effort to explore the physiology of aging. In 2002, the project was completed with irrefutable evidence showing that the underlying causes of aging can be modified by nutrition, diet and lifestyle. Specifically, more than 150 repair functions - in virtually all tissues of the body and brain - were found to be driven by DHEA.

This remarkable four year research project formed the basis for his next book, *The Metabolic Plan* (Random House, 2003) and his latest work, written with his wife, Dr Natalie Kather, entitled,*The Metabolic Makeover* (Altea Media, 2014). Between 1996 and 2016, Cherniske conducted hundreds of interviews and presented more than 4,000 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 7,000 additional studies on DHEA were published, leading to a clear understanding of the chemistry, function and clinical value of this important hormone.

As we near the end of 2019, however, the DHEA controversy continues to rage, fueled more by opinion than facts. The following interview between Stephen Cherniske and 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 200 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 doesn't enhance sports performance, restore energy levels or confer any significant anti-aging benefit. In fact, since some is converted to testosterone and estrogen, DHEA can promote cancer.

SC: Let's first debunk the DHEA cancer canard. While it is true that a portion of DHEA (produced by the body or ingested) can be converted to testosterone and then to estrogens, this conversion occurs in peripheral tissues where and when these tissues need repair. Of course, neither testosterone nor estrogen cause cancer. If they did, cancer rates would be highest in 20 year-olds, when in fact cancer is primarily a disease of aging. Likewise, there is no evidence that a physiologic dose of DHEA (the amount produced by a healthy 30 year-old) increases cancer risk. In fact, as we will see in the following pages, there are clear indications that DHEA plays an important role in cancer *prevention*.

Kelloff et al have identified important ways in which DHEA provides protection at all three stages of cancer. [1]

1. **Initiation**: by inhibiting oncogene activity
2. **Progression**: by inducing apoptosisL
3. **Metastasis**: by inhibiting G6DP, an enzyme required for tumors to proliferate

New research published in *Endocrine-Related Cancer* shows that DHEA acts as a tumor "kill switch," and strongly suggests that the increased incidence of cancer with advancing age results in great part to declining levels of DHEA.[2]

Regarding the statement that DHEA research has been a bust; I'll just point out that you only find what you're looking for. Naysayers invariably are looking for dramatic short-term benefits, when aging is a complex, life-long process. It's like the farmer who plants an apple tree and concludes that his efforts were wasted because after 6 months, he has no fruit. When DHEA supplementation does not produce remarkable results (eg weight loss) in 28 days, naysayers conclude "it doesn't work."[3]

The Weight of Evidence

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.[4],[5],[6],[7]

Research also shows that declining DHEA levels are associated (in animals and humans) with a subsequent decline in carnitine-driven fatty acid oxidation. In fact, the effect of DHEA on adipose tissue is a hot research topic. New research shows that this hormone regulates adipose tissue metabolism by controlling the production of leptin, adiponectin, and resistin.[8]

Everyone knows that burning fat becomes more difficult the older you get, and now we know why. 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: "Reduced carnitine availability correlates with the age-related decline of DHEA levels. These results are consistent with the hypothesis that decreased energy metabolism with age relates to DHEA levels and carnitine availability."[9]

> "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."
>
> Pergola GD. Adipose tissue metabolism: role of testosterone and DHEA. Int J Obesity 2000; 24: Suppl 2. S59-S-63

Now, let's connect the dots by looking at the gene (transcription) pathways through which DHEA acts as an anti-obesity agent. I'll include this abstract for a deeper dive.

Steroids. 2012 Nov;77(13):1359-65. Fat-reducing effects of DHEA involve upregulation of ATGL and HSL expression, and stimulation of lipolysis in adipose tissue. Karbowska J, Kochan Z.
Abstract:
DHEA reduces body fat in rodents and humans, and increases glycerol release from human visceral adipose tissue explants. This suggests that DHEA stimulates triglyceride hydrolysis in adipose tissue. We examined the effects of DHEA on the expression of adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), the key enzymes of lipolysis. Rats that received DHEA gained less weight and had 23% lower fat mass and 31% higher serum FFA levels than controls. Cultured explants of adipose tissue from DHEA-treated rats released 81% more glycerol than those from control rats. DHEA administration upregulated ATGL mRNA and protein expression as well as augmented HSL mRNA levels. PPARγ2 and FAT mRNA levels were also increased in DHEA-treated rats. Moreover, ATGL, HSL, and FAT mRNA levels were positively correlated with PPARγ2 expression. This study demonstrates that DHEA promotes lipid mobilization in adipose tissue by increasing the expression and activity of ATGL and HSL. The effects of DHEA appear to be mediated, at least in part, via PPARγ2 activation, which in turn upregulates ATGL and HSL gene expression.

Well Being

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.[10],[11],[12]

Naysayer: Wait a minute. There are two studies showing that DHEA does not enhance feelings of well-being.[13],[14]

SC: Both of those are two week studies, which is an absurd 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 (up to one year) that demonstrate remarkable effects of DHEA on mood, libido, immunity, memory and overall well-being.[15],[16],[17],[18],[19],[20]

> "It is important to know that significant improvements in mood and health-related quality of life may occur only after 3 or 4 months of DHEA treatment, possibly as a result of gradual adjustment of the neuro-steroidal equilibrium."
> DHEA Supplementation: The Claims in Perspective. Cleveland Clinic Journal of Medicine, Volume 72, Number 11 November 2005

Picture this: According to the IMS Institute for Healthcare Informatics, antidepressants are the second most widely prescribed class of drugs in the world, with more than 300 million prescriptions filled in 2016. You would think that anything that could dramatically improve patient outcome would be welcomed by medical review boards, right?

Well, numerous studies have shown that patients treated with antidepressants who have higher levels of serum DHEA are nearly twice as likely to experience remission compared to those with low DHEA levels.[21], [22] DHEA supplements are inexpensive and widely available. Are you aware of any directive, by any medical board to recommend co-prescribing DHEA along with antidepressants?

Naysayer: Of course not. That would require evidence that DHEA *administration* can be useful in treating depression.

SC: Fair enough. Here's a double-blind, randomized, placebo-controlled, crossover treatment study conducted at The National Institute of Mental Health. Will that do? The conclusion is pretty straightforward:

> "We find DHEA to be an effective treatment for midlife-onset major and minor depression."
> Arch Gen Psychiatry 2005; 62: 154-162. DHEA Monotherapy in Midlife-onset Major and Minor Depression. Schmidt PJ, Daly RC, et al.

Another clinical trial evaluated the beneficial effects of DHEA on midlife depression. I include the abstract because it demonstrates improvements in "anhedonia (lack of joy / pleasure), fatigue, lack of motivation, emotional "numbness," sadness, inability to cope, and worry."

> Bloch M, Schmidt PJ, Danaceau MA, Adams LF, Rubinow DR. Dehydroepiandrosterone treatment of midlife dysthymia. Biological Psychiatry 1999 Jun 15;45(12):1533-41
> BACKGROUND: This study evaluated the efficacy of the adrenal androgen, DHEA, in the treatment of midlife-onset dysthymia. METHODS: A double-blind, randomized crossover treatment study was performed as follows: 3 weeks on 90 mg DHEA, 3 weeks on 450 mg DHEA, and 6 weeks on placebo. Response to DHEA or placebo was defined as a 50% reduction from baseline in either the Hamilton Depression Rating Scale or the Beck Depression Inventory.
> **RESULTS: In patients who completed the study, a robust effect of DHEA on mood was observed compared with placebo. Sixty percent of the patients responded to DHEA at the end of the 6-week treatment period compared with 20% on placebo.**

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.

The Heart of the Matter

Research shows that DHEA supplementation reduces risk for cardiovascular disease - also in a gradual fashion – by normalizing platelet aggregation, lowering serum lipids (especially LDL), and improving insulin sensitivity and endothelial function.[23],[24] Human clinical trials have shown a beneficial effect of DHEA supplements on angiographic evidence of atherosclerosis,[25] arterial stiffness[26] and improvement of vascular function.[27],[28] Animal studies clearly demonstrate the inhibitory effect of orally administered DHEA on atherosclerosis and plaque progression.[29],[30]

One of the most reliable ways to identify a true biological effect is by measuring baseline levels of a single biomarker, then tracking a particular disease over a period of years. A landmark prospective study published in the *New England Journal of Medicine* found:

> "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."[31]

Seeking to explain these remarkable benefits, other researchers found that DHEA sulfate levels are positively associated with HDL(so-called good cholesterol) and negatively correlated with LDL (bad cholesterol) and total cholesterol.[32] A human study in the *Journal of Epidemiology* concluded:

> "The mean atherogenic index (AI) 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."[33]

Thyroid Function

Scientists have also found a strong correlation between low DHEA levels and hypothyroidism.[34] 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?

SC: 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 hypothyroid 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?

SC: 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 suggests 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.[35],[36],[37] Moreover, hypothyroidism is often caused by an autoimmune reaction and anti-thyroid antibodies have been found to be inversely related to DHEA levels.[38]

The Big Picture

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 suggesting that there is a simple underlying cause that can be easily altered.

SC: 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 see-saw between damage and repair, and the model holds true on every level, from the sub-microscopic realm of DNA, to the cell, the organs and the entire organism.
With this understanding, DHEA plays a critical role because it is the most comprehensive anabolic (repair) signal in mammalian physiology. It can therefore help to tip the see-saw in your favor by supporting repair functions throughout the body and brain. Moreover, DHEA has also been shown to reduce cellular and tissue damage, via its antioxidant, anti-inflammatory 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 (eg cortisol) and low DHEA are strongly associated with immune suppression, depression, brain degeneration and dementia.[39] [40]
Conversely, DHEA supplementation has been shown to effectively reduce this type of degeneration.[41]

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

SC: You're right that calorie restriction (CR) 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.[42] In fact, some leading endocrinologists believe that the improvements in health and longevity from CR stem in great part from the life-long maintenance of DHEA.[43],[44],[45] Again, these are long-term influences on immunity, glucose tolerance, body composition and cardiovascular risk factors that would be missed in short-term studies.

> "Consistent with the beneficial effects of calorie restriction on aging and life span in other animals...those maintaining higher DHEA levels have greater survival than respective counterparts."
> Roth GS, Lane MA, Ingram DK, Mattison JA, Elahi D, Tobin JD, Muller D, Metter EJ. Biomarkers of calorie restriction may predict longevity in humans. Science 2002; 297:811.

Naysayer: Still, there doesn't seem to be any longitudinal studies to back up the anti-aging claims for DHEA.

SC: 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.[46]

Likewise, studies with people ages 90 to 106 demonstrate that people 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. [47],[48]

In the Metabolic Model, we recognize that the average adult replaces more than 300 billion cells each day. Anti-aging is accomplished in three ways. By providing optimal raw materials for repair, reducing the damage that these cells are exposed to, and by restoring and maintaining anabolic (repair) metabolism.

Again, DHEA is the most comprehensive repair signal in human physiology, 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.

> "The maintenance of a good physical functional ability and quality of life is related to serum T, E2, and DHEA(S) concentrations."
> van den Beld AW, Lamberts SW. The male climacterium: clinical signs and symptoms of a changing endocrine environment. Prostate. Suppl 2000;10:2-8

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

SC: Wrong! DHEA is a cell *regulator*. It induces apoptosis (cell death) in malignant and malfunctioning cells,[49],[50],[51] controls hyperplasia (abnormal cell growth) in the smooth muscle of the lungs,[52] and in numerous animal models, DHEA has been shown to mimic the cell-regulating, anti-cancer benefits of calorie restriction.[53],[54]

In hundreds of animal studies, DHEA has been shown to prevent diabetes, obesity, infection, liver disease and many types of cancer.[55],[56],[57] In humans, DHEA levels predict mortality in a number of disease states including AIDS, sepsis, cancer and heart disease.[58],[59],[60],[61] 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 rheumatoid arthritis and lupus. and reduce risk for diabetes, cancer and cardiovascular disease.[62],[63],[64],[65],[66],[67],[68],[69],[70],[71],[72],[73]

Naysayer: But how can you be sure that DHEA won't increase risk for cancer?

SC: There is no data to suggest that. In fact, there is plenty of evidence 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.[74]

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 increased incidence of cancer among young patients on immunosuppressive therapy (eg 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 cells. DHEA has been shown to improve every one of these factors.[75],[76],[77],[78]

Let's go even further. At the cell level, P53 is the most critical quality control gene. A mutation of P53 dramatically increases risk for virtually all types of cancer. We now know that DHEA acts as a chemopreventive agent by reducing levels of mutant p53.[79] What's more, new research shows that DHEA acts as a tumor "kill switch" in cells where P53 has been inactivated.[80]

Aging and cancer are also associated with the dysregulation of cytokine production in which IL-6 predominates over IL-2. It is known that IL-2 has powerful anti-cancer 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 optimum levels of DHEA should be considered as a sensible and effective cancer-preventive strategy.

Indeed, animal studies have supported this idea for over 30 years, where DHEA administration has reduced risk for cancer of the liver, adrenals, pancreas, breast, lung, thyroid, colon, skin and lymphatic tissue.[81],[82],[83],[84],[85],[86],[87],[88],[89],[90]

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 was shown to cause liver cancer in mice.

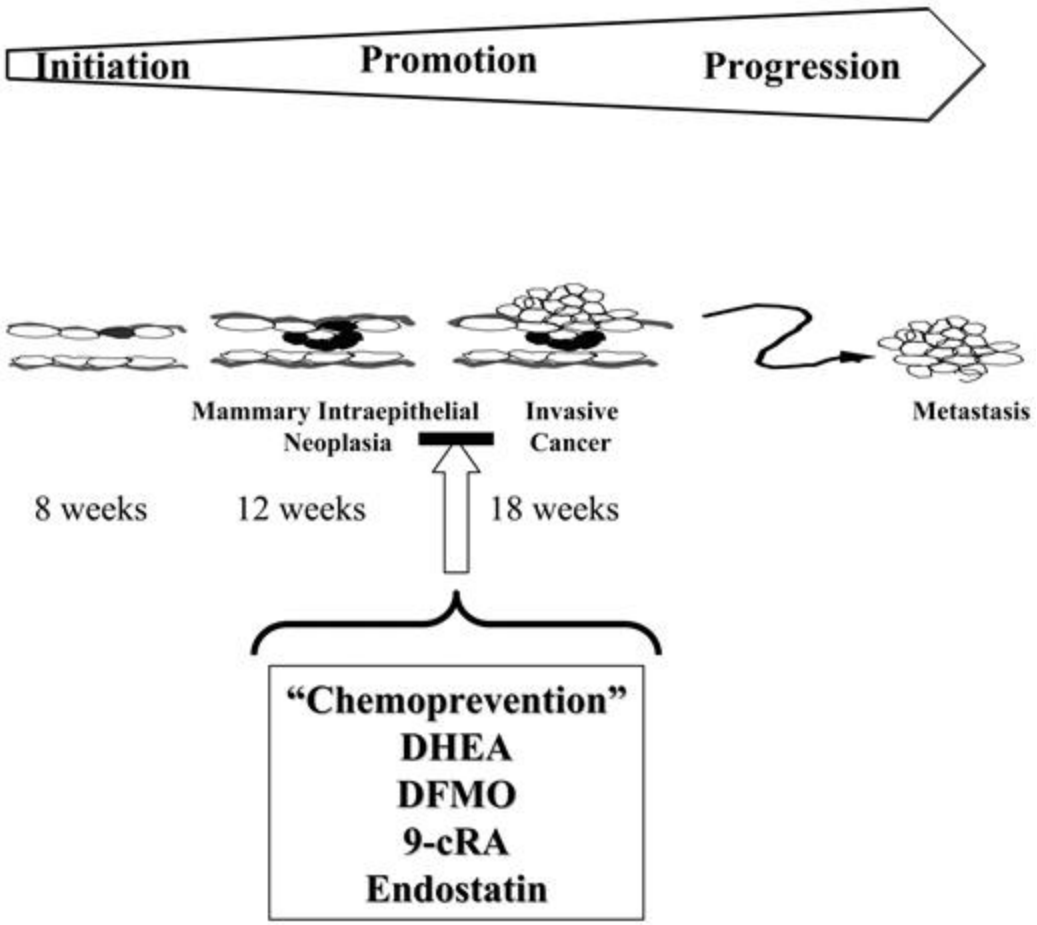
SC: Yes, there is a study in which mice were given a massive dose of DHEA – the human equivalent of 10,000 mg per day... and even then, this dose had to be administered continuously for at least 18 months (the human equivalent of 76 years) before they could induce cancer in these unfortunate animals.[91]

Do you really think that this is relevant, considering that studies using a lower dose (the human equivalent of 2,000 mg per day) do not produce cancer,[92] and there are more then 50 rodent studies showing 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.[93]

Naysayer: Well, there are other studies...

SC: Yes, a study at the University of Oregon, where DHEA was fed to trout; an organism that does not even produce DHEA.[94] 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 9,000 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.[95]

Look at the 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.[96] Here's the chart that appeared in the *Journal of Nutrition* (pg 2408S).



Dr. William Regelson, a specialist in medical oncology at the Medical College of Virginia, stated: "Whenever it has been tested in a model of carcinogenesis and tumor induction, DHEA has preventative effects."[97]

Another animal study from 2001 showed that DHEA administration *reduced* breast cancer incidence by 30% and multiplicity by 50%.[98] The following year, the National Cancer Institute published yet another mode of action study describing how DHEA helps to limit cancer growth.[99]

DHEA has even shown powerful anti-cancer activity in mice selectively bred to be highly susceptible to cancer.[100] In addition, researchers have found the specific genes that confer this advantage (including p53, DHEA ST and p21) and we now know how these genes are upregulated by oral administration of DHEA.[101],[102]

> "Long-term oral treatment with DHEA, an adrenal steroid found in subnormal plasma concentrations in women predisposed to develop breast cancer, inhibits the formation of spontaneous mammary cancer in female mice."
> Cancer Res. 1979 Mar;39(3):1129-32. Inhibition of spontaneous breast cancer formation in female C3H(Avy/a) mice by long-term treatment with dehydroepiandrosterone. Schwartz AG.

DHEA may also be effective in reducing risk for colon cancer. Scientists in Japan exposed mice to a chemical that induces abnormal cell 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.[103]

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.[104]

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

SC: Agreed. But they certainly disprove your "sky-is-falling" diatribe that DHEA might cause breast cancer. There isn't any evidence that DHEA increases risk for breast cancer. In fact, a study published in the prestigious journal 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.[105] So the breast cancer scare is a red herring. You also claim that DHEA might cause prostate cancer, when once again, all the evidence is to the contrary.

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

SC: So? Human studies show that there is no correlation between DHEA or testosterone and prostate cancer.[106],[107],[108],[109] In vitro studies show that DHEA actually *inhibits* prostate cancer,[110] 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."[111]

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

SC: 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 starts to appear accurate. 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 pre-neoplastic prostate lesions are present."[112]

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.

SC: 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.

SC: No, there's only inference and 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 tend to have lower PSA scores.[113]

Naysayer: Still, DHEA supplements might raise PSA levels.

SC: Listen to what you are saying. Speculation without evidence is a breach of scientific ethics. In study after study, supplementation with DHEA — even at high doses — has been shown to have no negative effect on PSA levels.[114], [115],[116] In private communication, many clinicians have told me that they have observed a gradual *decline* in PSA levels in men taking DHEA. Consistent with this are recent findings that prostate cancer patients have higher serum levels of immunosuppressive glucocorticoids.[117] DHEA counters that, and research has also shown that DHEA metabolites can inhibit PSA expression by interrupting androgen binding to the prostate androgen receptor.[118] These provide yet more evidence that DHEA *reduces* prostate cancer risk.

Think about this. Epidemiological studies clearly show an inverse relationship between serum DHEAS and the incidence of erectile dysfunction.[119] And DHEA has been used successfully in the *treatment* of erectile dysfunction.[120],[121],[122] So how many men have been told *by their doctors* to avoid a safe, effective and inexpensive remedy simply because the doctor read a misleading article written by an uninformed naysayer? I would guess millions.

> "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 [low DHEA] is found in several common diseases, including cancer, atherosclerosis, hypertension, diabetes, osteoporosis and Alzheimer's disease."
> Steel N. Dehydroepiandrosterone and Aging. Age and Ageing 1999; 28:89-91

Naysayer: But DHEA is converted to testosterone and estrogens.

SC: A small amount of DHEA is converted to testosterone and estrogens, which certainly contributes to myriad beneficial effects. 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. Anti-cancer effects have been identified for DHEA and all of its metabolites.[123] Likewise, the ability of DHEA to reduce risk for cardiovascular disease is independent of its conversion to sex steroids.[124] 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.[125]

Naysayer: But testosterone and estrogen promote cancer.

[long pause]

No they don't. If that was true, young people would have high rates of breast and prostate cancer, when in fact, these cancers occur primarily when these hormones are declining later in life.

Naysayer: Still, women with breast cancer usually receive an anti-estrogen drug like Tamoxifen and the treatment of prostate cancer almost always includes suppressing testosterone. So there is a connection.

SC: That's right, so let's look at that connection; which requires that we look at the wide scope of sex steroid activity. First, we have to eliminate the common misconception that testosterone is a "male hormone" and estrogens (estrone, estriol and estradiol) are "female hormones." Both are required by both sexes for optimum health; only in differing amounts. Both have growth and repair signaling activity throughout the human lifespan.

Now, with breast or prostate cancer, conventional treatment includes suppressing all growth signals in order to slow tumor growth. While that makes sense, it also highlights the limitations of conventional therapy, in that these cancers were not caused by excess testosterone or estrogen. What's more, Tamoxifen may reduce breast cancer recurrence, but it dramatically increases a woman's risk for endometrial and uterine cancer.[126] The complex interplay of hormone suppression and tumor growth is still unfolding.

In thousands of published studies dealing with these cancers, there is still one glaring omission: what about DHEA? Given what we now know about DHEA's ability to act as a tumor "kill switch,"[127] it may very well be that the age-related increased risk for breast and prostate cancer is due primarily to falling levels of DHEA.

Naysayer: What about the disaster that we saw with Hormone Replacement Therapy (HRT)?

SC: That was caused by conventional HRT using large doses of synthetic hormones, which increased risk for of breast cancer, stroke and pulmonary embolism.[128] 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.[129] Heck, human studies with 200 mg of DHEA per day have shown no systemic elevation of estradiol.[130] We now know that conversion of DHEA to sex steroids takes place on an as-needed basis, through an inherent self-regulating activity. We have also learned that conventional HRT lowers DHEA levels! [131]

Importantly, DHEA supplementation does not raise any sex steroid levels above normal. Most of the repair and regenerate benefits of DHEA come from local (or peripheral) anabolic activity such as was recently demonstrated in *Mechanisms of Ageing and Development*. This important study utilized genomic technology to reveal that DHEA improves bone density, not by raising systemic levels of estradiol, but through local conversion to estrone by osteoblasts.[132] 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 pharmceutical-based health care system ignored this natural, safe and effective treatment in favor of prescription drugs; even though those drugs were known to be unsafe for at least 15 years.

Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: contribution of the DHEAge Study to a sociobiomedical issue. Proc Natl Acad Sci U S A. 2000 Apr 11;97(8):4279-84. Baulieu EE, Thomas G, Legrain Set al.
The secretion and the blood levels of DHEA and its sulfate ester (DHEAS) decrease profoundly with age, and the question is posed whether administration of the steroid to compensate for the decline counteracts defects associated with aging. Two hundred and eighty healthy individuals (women and men 60-79 years old) were given DHEA, 50 mg, or placebo, orally, daily for a year in a double-blind, placebo-controlled study.
No potentially harmful accumulation of DHEAS and active steroids was recorded. Besides the reestablishment of a "young" concentration of DHEAS, a small increase of testosterone and estradiol was noted, particularly in women, and may be involved in the significantly demonstrated physiological-clinical manifestations here reported. Bone turnover improved in women >70 years old, as assessed by DEXA, and the decrease of osteoclastic activity. A significant increase in most libido parameters was also found in these women. Improvement of the skin status was observed, particularly in women, in terms of hydration, epidermal thickness, sebum production, and pigmentation. 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.

Research shows conclusively that DHEA deficiency contributes significantly to age-related bone loss in men and women.[133],[134] 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."*
> Genazzani AD, Stomati M, Strucchi C, Puccetti S, Luisi S, Genazzani AR.
> **Oral dehydroepiandrosterone supplementation modulates spontaneous and growth hormone-releasing hormone-induced growth hormone and insulin-like growth factor-1 secretion in early and late postmenopausal women.**
> Fertil Steril. 2001 Aug;76(2):241-8.

Again, we now know the precise mechanism by which DHEA strengthens bones. It is NOT by elevating systemic levels of sex steroids, but by peripheral effect on osteoblastic (bone-building) cells.[135]

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

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

SC: Not directly, but DHEA can raise progesterone levels by inhibiting conversion of pregnenolone to cortisol (via 17μOH PREG).[136] Thus by any measure, DHEA appears to be a valuable and safe hormone supplement for women and men.

Naysayer: Men don't need progesterone.

SC: 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. [137]

Naysayer: I'm still waiting for long-term safety studies. How do we know that years down the road, DHEA won't turn out to be dangerous?

SC: First of all, There are numerous safety studies with men, women and non-human primates, some using large doses for over two years. But there is also something called the risk / reward ratio. If there is no science suggesting a long term risk, why would you ignore the proven benefits out of some irrational fear? Naysayers have been trying to persuade the public that safety data doesn't exist, when there are more than adequate human clinical trials including multi-year studies with hundreds of 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."*
>
> Legrain S, Massien C, Lahlou N, Roger M, Debuire B, Diquet B, Chatellier G, Azizi M, Faucounau V, Porchet H, Forette F, Baulieu EE. Dehydroepiandrosterone replacement administration: pharmacokinetic and pharmacodynamic studies in healthy elderly subjects. J Clin Endocrinol Metab 2000 Sep;85(9):3208-17.

A study was conducted by the mayo Clinic, designed to evaluate high dose supplementation over the course of two years, using a 50 mg/d dose for women and a whopping 75 mg/d dose for men. What did they find? No worrisome effects in the women's uterus or breast tissue, no adverse effects on the men's prostate. No adverse side effects.[138]

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

SC: Such as?

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

SC: Those are *overdose effects*, and to produce these effects, a woman will typically have to take an excessive dose of DHEA for months. Importantly, these effects are obvious, sequential and reversible.

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.

SC: But you're talking as if side effects are common, when in fact they are rare. At the clinically effective dose of 5 to 30 mg, the incidence of androgen-related side effects is less than 2%.[139] 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 reversable. Tremendous health benefits can be obtained from 5 to 30 mg/d of DHEA. It significantly reduces risk for diabetes and cardiovascular disease at 25 mg per day.[140] These two degenerative diseases account for nearly 70% of deaths in the U.S. and all you can do is wring your hands about a reversible adverse effect that *might* occur in *some* women 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.

SC: Aspirin is sold in convenience stores and gas stations. Even small doses of aspirin can cause gastrointestinal bleeding. Thousands of people in the US die each year as a result of adverse effects from aspirin. Even low-dose aspirin can harm the kidneys and increase risk for stroke in people with high blood pressure.[141]

There is an absurd double standard being used here. You promote the sale and use of aspirin, which has serious and often fatal 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 people do not know how much DHEA they are presently producing.

SC: Exactly. This is part of an education process that should be part of a routine doctor visit. But the exact opposite is taking place. Instead of encouraging patients to measure their DHEA sulfate (DHEAS) 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 roughly half of age-matched controls,[142] but few physicians know this.

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.[143],[144]

SC: I agree, but let's look carefully at this. In a recent study with elderly women, serum DHEA was 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 drive.[145] I call this the Jack LaLane effect, but it is important to understand that the converse is also true; that for people who maintain higher levels of DHEA, exercise is easier, more enjoyable and produces measurable benefits.

The vast majority of people over 50 are deficient in DHEA. If a person is 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.

SC: 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 6 months, those taking DHEA experienced improvements in strength, muscle mass and bone density, together with a reduction in body fat.[146] In a follow-up study where volunteers were asked to perform moderate exercise, that benefits were even greater.[147]

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?

SC: Well, it prevents diabetes in animals, and there is compelling evidence that it reduces risk for diabetes in humans.[148] We all know that aging is associated with 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.[149],[150],[151]

It has long been known that diabetics have reduced serum levels of DHEA compared to age-matched controls.[152],[153] Importantly, new research shows that even in healthy individuals, there is an inverse correlation between DHEA levels and plasma glucose, suggesting that DHEA deficiency contributes directly to the diabetic state.[154],[155]

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

SC: Only two possible interactions have been identified. Women taking Tamoxifen (an anti-estrogen) and men being treated with testosterone blockade. These are well-known and well-publicized caveats. On the other hand, studies show that many prescription drugs alter DHEA metabolism and / or reduce DHEA blood levels.[156] Unfortunately, no one seems to be concerned about this.

Remember that adverse interactions between prescription drugs is extremely common. Popular NSAID drugs 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 1,500 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.

SC: You've fallen for the biggest myth in all of health care; that the long-term effects of Rx 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."[157] Using your example of Viagra, there are very troubling questions regarding long term use. Viagra has been shown to trigger migraine in the majority of migraine sufferers.[158] This was unknown until 2003. The effects of the drug on 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 Viagra's first thirteen months on the market. They found 1,473 major adverse reactions reported to the FDA, including 522 deaths, 517 heart attacks, 161 cardiac arrhythmias and 119 strokes.[159] 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?

SC: DHEA does not reduce the efficacy of prednisone.[160] In fact, it appears to enhance the effectiveness of prednisone therapy by reducing the immune suppression associated with the anti-inflammatory drug.[161] 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 need for prednisone.[162]

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 TNF. Recent research shows that:

1. IL-6 levels tend to increase with advancing age.[163]
2. DHEA is a potent inhibitor of IL-6 in animals and humans.[164]
3. In every chronic inflammatory disease tested, including lupus, rheumatoid arthritis, polymyalgia rheumatica and inflammatory bowel diseases, DHEA and / or DHEAS levels in patients have been found to be lower than healthy controls.[165],[166],[167]
4. Oral administration with DHEA shows significant promise in the treatment of chronic inflammatory diseases.[168],[169],[170]

Naysayer: What about people undergoing surgery?

SC: This is a serious issue, because people supplementing with DHEA are often told to stop taking DHEA prior to surgery. I am not advising people to disregard the advice of their doctor, but instead, to help educate the medical profession. Surgical stress has been shown to seriously deplete DHEA, leaving the patient in a vulnerable state that can be easily prevented.[171],[172] The last thing you would want to do before surgery is to stop taking DHEA, and post-surgical use of DHEA is one of the most appropriate uses of this repair and regenerate signaling molecule.

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

SC: How about 25 million Americans with depression? That's over 10% of the adult population. Studies show that depressed individuals have much lower levels of DHEA compared to age-matched controls,[173] and there are a growing number of studies showing that DHEA has profound anti-depressive benefits.[174],[175],[176],[177] To take this issue even further, we now have evidence that people with major depressive disorder (MDD) who are treated with SSRI drugs are far more likely to experience complete remission if their DHEA levels are in the optimum range.[178]

> "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."
> Young AH, Gallagher P, Porter RJ. Elevation of the cortisol-dehydroepiandrosterone ratio in drug-free depressed patients. Am J Psychiatry. 2002 Jul;159(7):1237-9.

Beyond Depression: Neuroprotection

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.[179] 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 age-matched controls.[180]

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, since aging is associated with increasing stress, DHEA may well be of benefit to the normal aging brain. 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.[181]

Importantly, the area of the brain most vulnerable to age-related degeneration is the hippocampus. Hippocampal volume decreases with advancing age, and is a causative factor in decreased resilience, cognitive decline, depression and dementia. Studies with healthy elderly subjects have shown that DHEA is positively associated with hippocampal volume (HCV) and negatively associated with major depression.[182],[183] Furthermore, the *degree* of hippocampal loss correlated directly with declining DHEA levels. Those with higher levels of DHEA have less atrophy. The importance of this correlation is demonstrated by the extremely low levels of DHEA found in demented elderly.

Naysayer: Still, correlation studies are not enough to make blanket recommendations that everyone over 60 should take DHEA.

SC: Well, at least doctors and neurologists should not dissuade people from taking steps to protect their brains. Especially since animal studies show that DHEA supplementation can initiate repair of the brain, 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."[184]

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 that, "Higher DHEA levels were significantly correlated with lower symptom ratings, better performance on some measures of memory and lower ratings of Parkinsonian symptoms." Importantly, 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.[185]

New Frontiers: DHEA, Genomics, Stem Cells and Regenerative Medicine

Genomic technologies have dramatically expanded our understanding of human physiology, potentially leading to exciting new medical interventions. And while gene therapy, stem cell therapy and other gene-based treatments are still in their infancy, one thing is becoming clear. DHEA plays an important role everywhere you look.[186],[187],[188],[189],[190],[191]

Observational studies show that DHEA supplementation can increase bone density in postmenopausal women.[192],[193] We now know the gene pathways that are activated / upregulated by DHEA.[194]

> Vitam Horm. 2018;108:251-271. **Dehydroepiandrosterone and Bone.** Zhou S, Glowacki J.
> In humans, DHEA, secreted mainly from the adrenal cortex, and its sulfate ester, DHEAS, are the most abundant circulating steroids. DHEA/DHEAS possess pleiotropic effects in human aging, bone, metabolic diseases, neurologic function/neurodegenerative diseases, cancer, immune system and disorders, cardiovascular diseases, diabetes, muscle function, sexual dysfunction, and other health conditions. The age-related reduced levels of DHEA and DHEAS are associated with bone mineral density measures of osteopenia and osteoporosis. Clinical, epidemiological, and experimental studies indicate that DHEA replacement therapy may be beneficial for bone health through its inhibition of skeletal catabolic IL-6 and stimulation of osteoanabolic IGF-I-mediated mechanisms. Studies with primary cultures of human bone marrow-derived mesenchymal stem cells (hMSCs) were used to show that DHEA stimulates osteoblastogenesis. The stimulation of both osteoblastogenesis and IGF-I gene expression by DHEA in hMSCs requires IGF-I receptor, PI3K, p38 MAPK, or p42/44 MAPK signaling pathways. In summary, evidence from us and others indicates that DHEA may be useful for treating bone diseases through its inhibition of skeletal catabolic IL-6 and stimulation of anabolic IGF-I-mediated mechanisms.

To date, there is only one compound that, when added to a stem cell culture, can cause those cells to differentiate into fully-functioning neurons: DHEA[195]

> “Here, we offer that DHEA is a suitable candidate that could provide a microenvironment to stimulate neurogenesis and enhanced survival of newly formed neurons derived from hEnS cells. This provides a better insight into the maintenance of neural cells for treatment of a wide variety of neurological diseases such as Alzheimer's and Parkinson's by non-invasive autologous cell therapy."
> Med Hypotheses. 2011 Jun;76(6):843-6. **DHEA provides a microenvironment for endometrial stem cells neurogenesis**. Shoae-Hassani A, Mortazavi-Tabatabaei SA, Sharif S, Rezaei-Khaligh H, Verdi J.

"Finally we asked whether the EGF/LIF/DHEA-responsive stem cells had an increased potential for neurogenesis and found a 29% increase in neuronal production when compared to cultures grown in EGF/LIF alone. Together these data suggest that DHEA is involved in the maintenance and division of human neural stem cells. Given the wide availability of DHEA, this finding has important implications for future use."
Proc Natl Acad Sci U S A. 2004 Mar 2;101(9):3202-7. **Mitotic and neurogenic effects of dehydroepiandrosterone (DHEA) on human neural stem cell cultures.** Suzuki M, Wright LS, Marwah P, Lardy HA, Svendsen CN.

Concluding statements:

Naysayer: I have to say that all of the data that you've supplied has surprised me, especially the material relating to DHEA's potential anti-cancer role. But there's one fundamental issue that we haven't addressed, that could be called the natural law argument. DHEA levels peak late in the second 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.

SC: 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 which 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 90 million prescriptions to lower cholesterol. Diabetes is natural, but it is treated with a hormone called insulin. We are constantly messing with Mother Nature in order to prevent death and maintain quality of life.

And even if you ignore these examples, you have to understand that there are thousands of men and women who have decades-long experience with DHEA supplementation. We know at least 10 pathways by which optimizing DHEA acts as a powerful anti-aging strategy.

1. Antioxidant
2. Anti-inflammatory
3. Anti-obesity
4. Balances blood sugar
5. Maintains immune competence
6. Maintains muscle mass
7. Strengthens bones
8. Activates stem cells throughout the body
9. Maintains anti-cancer enzyme activity
10. Prevents brain atrophy

> *"Both in vitro and in vivo experimental studies strongly indicate that DHEA inhibits inflammation and associated epithelial hyperplasia, carcinogenesis, and atherosclerosis, at least in part, through the inhibition of G6PDH and oxygen-free radical formation."*
> Ageing Res Rev. 2004 Apr;3(2):171-87. Dehydroepiandrosterone, glucose-6-phosphate dehydrogenase, and longevity. Schwartz AG, Pashko LL.

In other words, health professionals are very comfortable with what is called the risk / reward ratio; benefits versus possible side effects. This is easy to do when you're treating a life-threatening infection, 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 damage and degeneration become irreparable. Restoring DHEA levels is not a magic bullet, but it should be an integral part of any sensible anti-aging effort.

Let me put that another way. No anti-aging strategy; maintaining ideal weight, regular exercise, proper diet, intermittent fasting, vitamins, yoga… none of those important and valuable steps will do much if your DHEA levels are plummeting. 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 to 15% of the DHEA they were producing in their 20's.
3. High levels of DHEA are strongly associated with longevity.[196],[197],[198]

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, as well as increased risk for death from all causes.[199]

6. Conversely, higher levels of DHEA and DHEAS in the elderly are associated with greater strength, stamina, bone density and reduced risk for fracture and falls.[200]

7. One's production of DHEA can be reliably determined by measuring DHEA sulfate (DHEAS) in serum. My research group also created a test to evaluate improvements in tissue repair resulting from DHEA supplementation. This test was awarded a US patent, the methodology paper was published in *The Journal of Chromatography*, and the age correlation study was published in the journal *Spectroscopy*.[201],[202],[203]

8. As opposed to what is "normal" in the aging population, leading endocrinologists believe that optimal restoration of anabolic drive (true anti-aging) can only be achieved by maintaining DHEAS at the level of a healthy 30 year-old.[204]

Etienne-Emile Baulieu, a leading DHEA researcher and one of the world's foremost hormone biochemists, 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."[205]

9. DHEA is readily absorbed from an oral dose. Topical (transdermal) application can also be effective with the appropriate delivery compound(s).

10. Most human studies have used a 50 mg/day dose, (which is the high end of the physiologic range), although clinically significant benefits can be achieved with doses as low as 5 mg per day.

11. 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.

12. My favorite quote from recent medical literature:

> **"Conclusions.** DHEA modulates endothelial function, reduces inflammation, improves insulin sensitivity, blood flow, cellular immunity, body composition, bone metabolism, sexual function, and physical strength in frailty and provides neuroprotection, improves cognitive function, and memory enhancement. DHEA possesses pleiotropic effects and reduced levels of DHEA and DHEA-S may be associated with a host of pathologies."
> Traish AM, Kang HP, Saad F, and Guay AT. Dehydroepiandrosterone (DHEA)—A precursor steroid or an active hormone in human physiology. J Sex Med 2011;8:2960–2982.

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.[206] 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.

Closing abstract

Drugs. 2014 Jul;74(11):1195-207.

Dehydroepiandrosterone (DHEA): hypes and hopes. Rutkowski K, Sowa P, Rutkowska-Talipska J, Kuryliszyn-Moskal A, Rutkowski R.

DHEA and its sulfated form DHEAS are the most abundant circulating steroid hormones in humans. In animal studies, their low levels have been associated with age-related involuntary changes, including reduced lifespan. It has been marketed and sold in large quantities as a dietary supplement. Recent double-blind, placebo-controlled human studies provide evidence to support many of these claims. In the elderly, DHEA exerts an immunomodulatory action, increasing the number of monocytes, T cells expressing T-cell receptor gamma/delta (TCR$\gamma\delta$) and natural killer (NK) cells. It improves physical and psychological well-being, muscle strength and bone density, and reduces body fat and age-related skin atrophy stimulating collagen production. In adrenal insufficiency, DHEA restores DHEA/DHEAS and androstenedione levels, reduces total cholesterol, improves well-being, sexual satisfaction and insulin sensitivity, and prevents loss of bone mineral density. Normal levels of CD4+CD25(hi) and FoxP3 (forkhead box P3) are restored. In systemic lupus erythematosus, DHEA is steroid-sparing. In an unblinded study, it induced remission in the majority of patients with inflammatory bowel disease. DHEA modulates cardiovascular signalling pathways and exerts an anti-inflammatory, vasorelaxant and anti-remodelling effect. Its low levels correlate with increased cardiovascular disease and all-cause mortality. DHEA/DHEAS appear protective in asthma and allergy. It attenuates T helper 2 allergic inflammation, and reduces eosinophilia and airway hyperreactivity. In women, DHEA improves sexual satisfaction, fertility and age-related vaginal atrophy. A growing body of evidence supports the notion that DHEA is not just an overrated dietary supplement but a useful drug for some, but not all, human diseases.

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