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ADRENAL STRESS: Measuring and Treating

Given the types of lifestyles Americans live, the concept of stress has pervaded our social and biological view of being human. But while we are often told of stressful events (loss of family member, divorce, major life changes), what actually defines stress from a physiological perspective has been more difficult to grasp. Some have said that nearly 75% of the diseases prevalent in western society today are somehow related to the stress mechanisms of the body. Our topic is narrower here, we hope to show how stress (emotional or physical) affects the adrenal gland and how to test and support the stressed adrenal gland in a gentle but profound way.

Stress- What is it?

While it may seem obvious to most of the readers, the definition of “stress” has not been easily agreed upon by biologist over the past 75 years. Does it define the necessary changes in adapting to a stressor, or the malfunction of not adapting to these same stressors? When we think of stress, we often think of negative stress, or as some would say “distress”; but positive events (wonderful surprises, passion, athletic competition) can elicit seemingly identical responses, from a physiological perspective.

The scientist who, more than anyone, brought the concept of stress to the forefront is Hans Selye. His book *The Stress of Life* (26), written for the lay audience, popularized the notion of stress as the general response to a wide variety of insults. His research, mostly with rats, revealed a recurring set of physiological outcomes (hypertrophy of the adrenal gland, atrophy of the lymphatic organs, and ulcers in the stomach) when these rats were exposed to a variety of insults. He later formed what he called the general adaption syndrome (G.A.S.) in a three-stage format:

1. The alarm reaction, involving increased adrenocortical secretion and activation of the sympathoadrenal system.
2. The stage of resistance, involving the balancing of the adrenocortical hormones' affect on water and electrolyte balance and carbohydrate metabolism. The “true adaption” to stress.
3. The stage of exhaustion, involving the depletion or exhaustion of the adrenal glands' ability to make corticosteroids.

We recognize that Selye has simplified a very complex set of responses and his model is, at times, very limited. Some have pointed out that most of the limitations with the G.A.S., as defined, is that the animals under stress were unable to do anything to remove themselves from the stress (27). As such, this model may be best used for measuring chronic, unavoidable stressors (internal inflammations, unavoidable job stresses). Even with some of these limitations, it does give us a framework to measure stress, especially as it pertains to the hypothalamus-pituitary- adrenal axis (HPA axis) and the consequences on human health. Let us first look at the adrenal gland and the HPA axis controlling mechanisms.

The Adrenal Gland:

The adrenal glands are small (5 grams) glandular tissues lying atop each of the kidneys (See figure 1). Originally called suprarenal glands, because of their location, they were first discovered by the anatomist Bartolomaeus Eustachius, further described by Cuvier and then later by Thomas Addison. The inner portion, called the medulla, secretes epinephrine and norepinephrine and is an extension of the sympathetic nervous system. The larger outer portion, called the cortex, is responsible for secreting various steroid hormones. From every point of view, functional, structural, and developmental, the adrenal cortex and medulla can be considered as two separate glands. We will consider only the cortex in this particular paper.

Of the nearly 30 steroid hormones produced by the adrenal cortex, the principal ones include aldosterone (a mineralocorticoid), cortisol (a glucocorticoid), and various sex hormones and their precursors (DHEA, androstenedione). The mineralocorticoids play an essential role in regulating potassium and sodium levels and water balance. DHEA and its metabolites have diverse effects during the lifecycle of the individual (see side panel for DHEA discussion). Our focus here is the glucocorticoid cortisol and its easily measurable stress response.

*(continued from page 1)***Cortisol:**

The synthesis and regulation of cortisol production is shown in figure 1. Cortisol is tightly regulated by feedback mechanisms in both the hypothalamus and the pituitary glands, where the original hormonal signals trigger its production. As in other systems, the hypothalamus begins the process by secreting corticotropin-releasing factor (CRF) in response to a variety of "stressors". CRF then triggers the anterior pituitary to release adrenocorticotropic hormone (ACTH) which increases the adrenal cortex secretion of cortisol. In turn, increasing cortisol levels slow down the production of both CRF and ACTH from their respective glands. This whole circuit is referred to as the hypothalamic-pituitary-adrenal (HPA) axis or system.

Normal functioning of the HPA is known to have three attributes. First, when the system is unstressed there is a circadian rhythm of activity in the system. The rhythm consists of the highest cortisol levels shortly after awakening (7-8 a.m.) and progressively falling until they are lowest during the first several hours of sleeping (See figure 2A for normal circadian rhythm of salivary cortisol). A healthy HPA should have a circadian rhythm as well as appropriate total daily secretion of cortisol. The second function of the HPA is the various feedback loops. As mentioned previously, increasing amounts of cortisol should be able to shut down ACTH and CRF production, and hence reduce the cortisol levels eventually. Clinically appropriate challenges with corticosteroids like dexamethasone are used to test this

feedback loop. Positive tests for pituitary and adrenal cortex functions are also performed by giving patients CRF or ACTH and measuring cortisol responses.

Third, and most importantly for us, is the fact that various stressors can stimulate the HPA; and many can do so in a way that overrides both the circadian and feedback controls. It is this well-known phenomenon that allows the functional testing of the HPA system to give us a glimpse at the effects of stress (both acute and chronic) on the health of an individual.

Salivary Cortisol Measurements:

Over the past two decades the use of saliva, rather than blood or urine, to determine various hormone values has gained increasing attention. Salivary cortisol levels have been compared to serum cortisol levels in a variety of patients and found to be a very reliable measurement (1-7). The advantages of using salivary measurements are many. They include noninvasive sample collecting, sample can be collected anytime and anywhere (especially good for measuring circadian fluctuations), sample collection does not induce cortisol/stress (as with venipuncture), and more consistent responses to suppression tests (dexamethasone) or stimulation tests (CRF etc.).

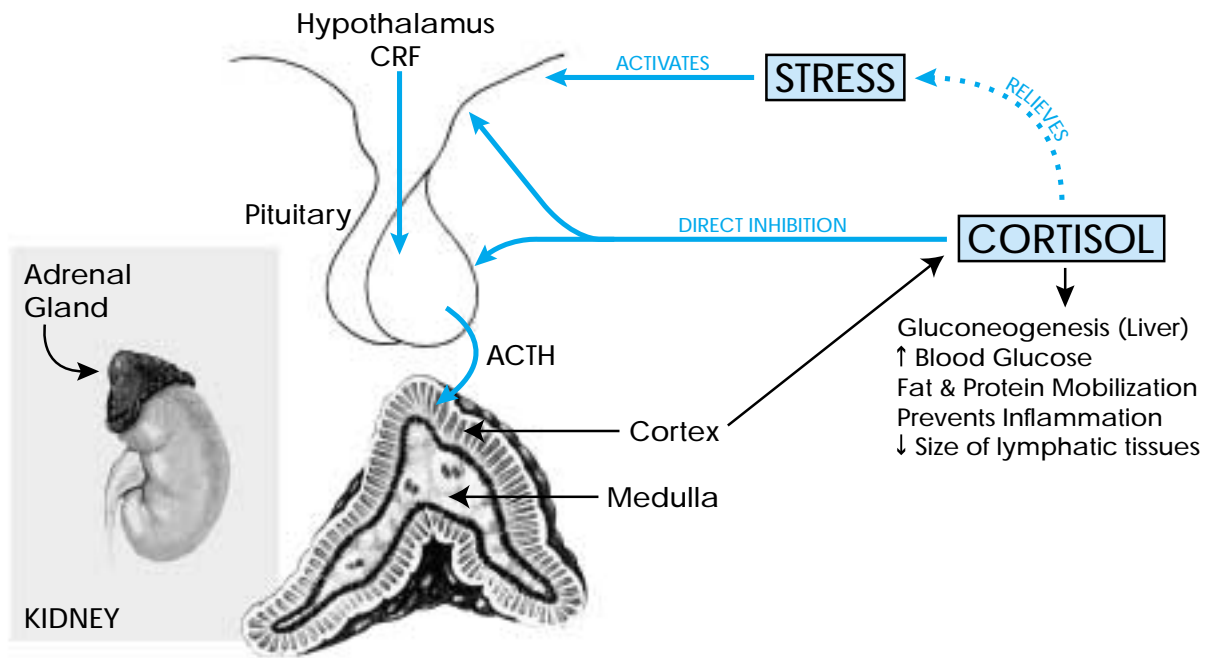
Cortisol enters the acinar cells lining the saliva glands via passive diffusion, and is not affected by the saliva flow rate. This passive transport prevents proteins or protein-bound molecules from entering the saliva. This means that

DHEA AND ADRENAL ACTIVITY

While the importance of cortisol has been relatively unheralded, the virtues of DHEA (Dehydroepiandrosterone) have made headlines for the past several years. DHEA and its sulfated metabolite DHEA-S are hormones secreted by the adrenal cortex in response to pituitary ACTH production. DHEA-S is the most abundant circulating steroid hormone in humans and the most abundant product of the adrenal glands. As such, its measurement has been of interest, especially since reduced levels of both DHEA and DHEA-S are associated with aging. Some have tried to use DHEA levels to devise a method to gauge relative biological (rather than chronological) age. One study showed that DHEA-S levels were significantly lower in nursing home patients who required total care versus individuals of similar ages who are able to care for themselves (30). Another study revealed that DHEA-S levels were lower in men with at least one coronary stenosis (greater or equal than 50%) compared to those without a similar arterial narrowing. Levels of DHEA-S were also inversely related to the number of diseased coronary vessels (31). While the cause-effect relationship with DHEA has yet to be determined, DHEA levels may be a marker for age-related chronic conditions. Perhaps the most interesting connection is the relationship between DHEA levels and incidence of Chronic Fatigue Syndrome (CFS). Several studies have shown that individuals with CFS are more likely to have low levels of DHEA and DHEA-S (32,33). This is probably the result of overall HPA or adrenal suppression, felt as general fatigue, accompanied by immune system irregularities and sensitivities. DHEA-S (but not DHEA) levels also seem to be associated with patients suffering from depression (32).

Because DHEA-S is so abundant and has such a long half-life, it is rather easy to detect in saliva samples and does not have a noticeable diurnal cycle like cortisol or DHEA. For this reason it can be used in combination with a cortisol rhythm to detect HPA irregularities. The cortisol/DHEA-S ratio can be a valuable tool in determining the need for pregnenolone, DHEA, and stress management treatments. Since the salivary detection of DHEA and DHEA-S is more novel, check with your lab to determine the availability and normal ranges using their technique. Remember, only individuals with lower than average DHEA/DHEA-S levels should be given supplemental DHEA, as it is a sex steroid molecule.

CONTROLLING THE HYPOTHALAMIC - PITUITARY - ADRENAL AXIS



BIOSYNTHESIS OF CORTICOSTEROIDS (ADRENAL CORTEX)

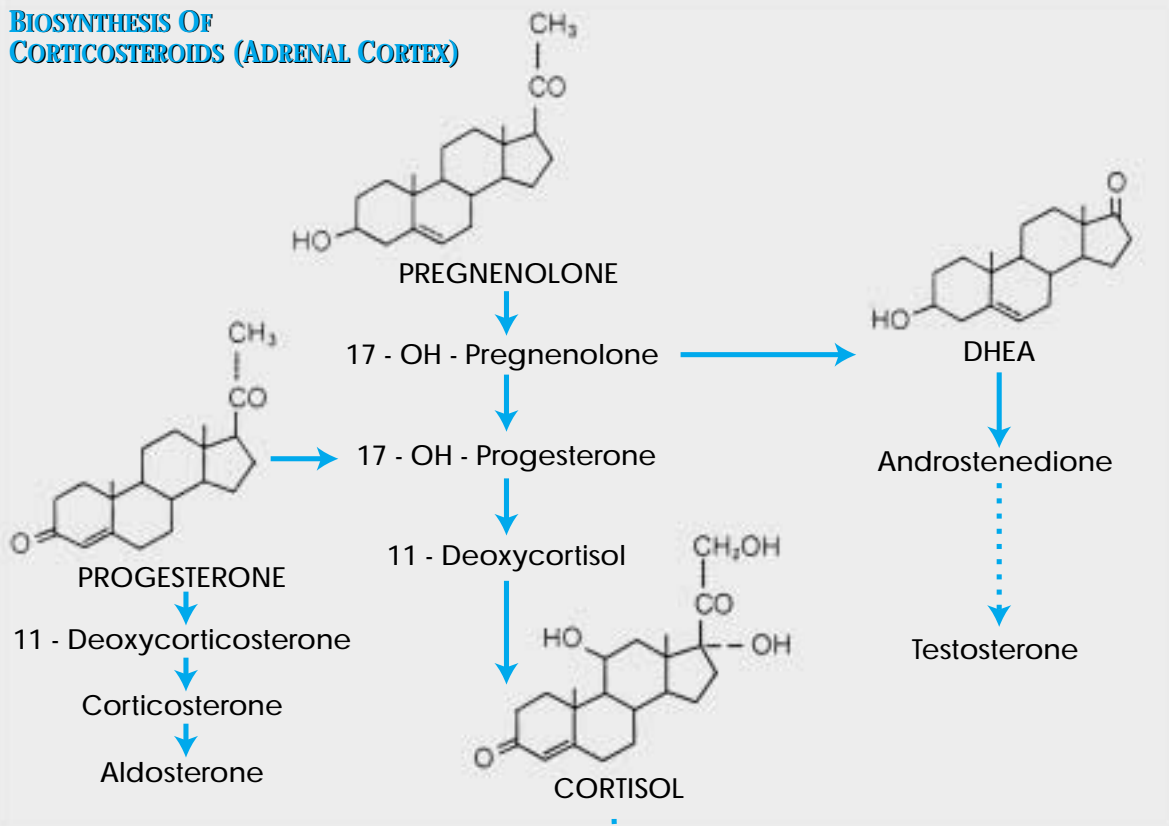


Figure 1

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the cortisol measured in the saliva is the active “free” fraction. When serum levels are measured, free cortisol must be measured in the milieu of large amount of “bound” cortisol (inactivated) and the available literature clearly suggests that saliva cortisol is more closely correlated with the free cortisol fraction in serum compared to total serum cortisol (2). Furthermore, salivary cortisol levels are very stable at room temperature and through the mail, making this method ideal for out of office sampling and shipment to labs for measurements (8).

Measuring salivary cortisol levels is an excellent tool to measure HPA axis activity. Figure 2A shows the normal diurnal ranges one would expect from measuring salivary cortisol. The ideal morning levels range from 12-22 nM, drop to a range of 4-7 nM at noon and stay steady throughout the afternoon (4-6 nM) and then drop again to a range of 1-3 nM in the late evening before midnight (1,9). There is little statistical difference in the diurnal patterns between men and women. One note of caution: a comparison of absolute hormone concentrations between laboratories is sometimes difficult depending on the assay system for measurement being used. It is important for each clinician to become well acquainted with the “normal” ranges used in the lab they are using. It is also critical to ensure that the individuals taking the test, do so on a day that is as typical (stress-wise) as possible to avoid measuring anomalies caused by sudden or anticipated physical or emotional stress.

When the diurnal pattern of cortisol production is altered, it is often the result of some type of stress on the HPA. Figure 2B represents 3 frequent variations to the normal diurnal pattern. Pattern 1 represents a hyperadrenal curve where the secretion of cortisol does not shut down throughout the day. This may be due to an ongoing acute stressor (Selye’s alarm reaction) or a resistance to cortisol feedback by the hypothalamus and pituitary. Pattern 3 represents a hypoadrenal curve. There might be a slight diurnal nature to the curve, but the overall production of cortisol is so low that it is of little consequence. The HPA is unable to respond adequately during the sleep cycle and is not triggered by awakening (Selye’s stage of exhaustion). Patients with Addison’s disease would essentially be 0 for each measurement. Pattern 2 represents one of a number of odd diurnal patterns that may cause disturbance in sleep patterns (this person probably has trouble getting to sleep at night, or

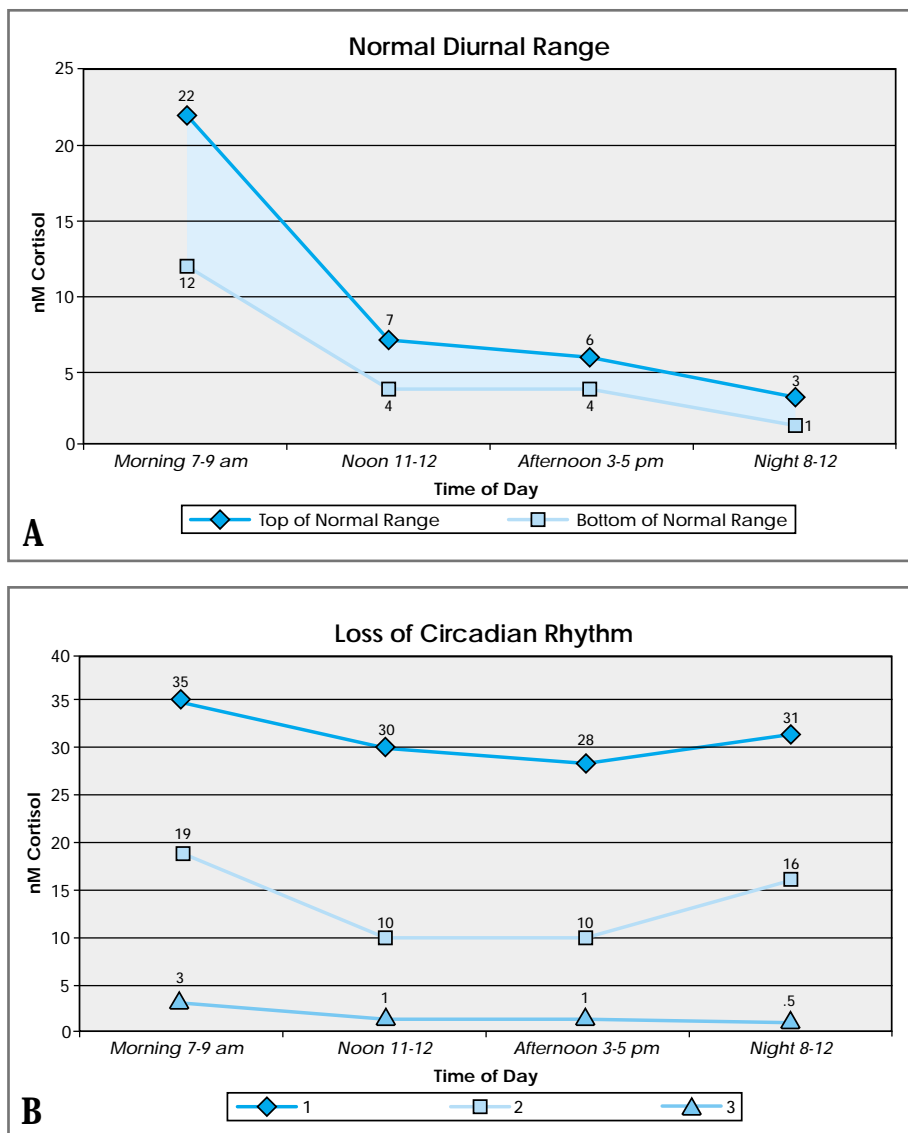


Figure 2

Normal (A) and various abnormal (B) diurnal rhythms measured in salivary control. See text for further information.

finds sleep less than restful) or depression. One study found that when diurnal salivary cortisol of individuals with major depression were compared with controls, evening cortisol levels were significantly increased (10). This may be tied to the relationship between cortisol levels and the endogenous inhibitor to monoamine oxidase A (11).

While the primary understanding of the HPA can be gained by taking 3 or 4 salivary cortisol measurements throughout the day, the morning measurement may be the most informative for long-term studies. Put simply, awakening stimulates the HPA and acts like a mini HPA stress test everyday (with the assumption that it shuts down at night). Several studies have shown that the HPA activity (as measured by salivary cortisol levels) increases 50-75% within

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the first 30 minutes after awakening, analogous to other HPA challenges (CRF or ACTH challenges) (12,13). Chronic stress and burnout significantly alter morning cortisol levels (14, see Stress and Burnout sidebar).

Treatment:

Glycemic control:

Of great importance to the patient is the control of blood glucose levels. Because cortisol is a glucose-regulating molecule its levels are greatly influenced by blood glucose levels. As the levels dip below 70mg/dl, the cortisol levels rise until the blood glucose levels are stabilized. It is important for proper HPA control to maintain blood sugar homeostasis throughout the day. This means that meals should contain glucagon stimulators (protein) with insulin stimulators (carbohydrates) to maintain a homeostasis in blood sugar. For many people this may mean having small glycemicly balanced snacks between meals to prevent the need for HPA activation just prior to each meal to increase blood glucose levels.

Lifestyle management:

Included in this category are a number of "controllable" factors. Stress analysis (via questionnaire) and management tools are an obvious start for those whose lifestyle includes avoidable stress. Job stress (including shift-work) should be considered avoidable if significant enough. Regular sleep, work, and eating patterns should be considered to avoid increasing stress and regular daily, weekly, and yearly patterns of relaxation should be maintained for optimal health. Moderate, non-competitive exercise can be a valuable stress reducer, not to mention the other healthy benefits.

When it comes to unavoidable stressors, our response becomes the key. If anger, fear, anxiety, and depression are typical responses to unavoidable situations, adrenal stress is sure to follow. Learning to perceive and respond to stressful situations in ways that do not stimulate the HPA is one of the keys to preventing adrenal malfunction and eventual exhaustion.

Phosphatidylserine:

Phosphatidylserine (PS) is a naturally occurring phospholipid, essential for the membranes of all cells, particularly brain cells. Among the many therapeutic uses for PS, it has some promising effects in HPA modulation. Two recent studies from Italy have shown that PS is able to blunt the ACTH and cortisol response to stressors (34,35). This means that individuals whose HPA is overstimulated (high salivary cortisol, no diurnal drop) may be able to take oral PS to reduce this response. They found that in just 10 days, a dose of 800mg/day was sufficient to drop both ACTH and cortisol under stressors that induce significant increases of both. Most

individuals would use 200-400 mg and see results in 6-8 weeks (a good time for retesting salivary cortisol).

Pregnenolone and DHEA:

The use of oral or sublingual doses of pregnenolone and/or DHEA may be warranted in order to help support an abnormal HPA. Pregnenolone is a precursor to all of the corticosteroids (See figure 1) and is of great benefit in both hyperadrenalism as well as hypoadrenalism. When levels of cortisol are high and DHEA levels are normal or low, pregnenolone is often shunted to the cortisol pathway, depleting the other pathways. When cortisol is low and DHEA levels are normal or low, pregnenolone may be in a state of deficiency. When DHEA levels are high, the use of pregnenolone would be less necessary, may confuse the therapeutic response and would not usually be recommended. Physiological (rather than pharmacological) doses of 10-50 mg/day (sublingual) of pregnenolone in divided doses are very adequate for most individuals. Physiologic doses of sublingual DHEA (5-15 mg/day) would be used when DHEA levels are low (See DHEA panel). When using micronized oral products, doses should be doubled, when compared to sublingual doses, to account for lowered absorption.

Licorice Root Extract:

Licorice (*Glycyrrhiza glabra* L.) root was once used to make the candy of the same name, but has since been replaced by anise and corn syrup. Glycyrrhizin, one of the major components of licorice root has a structure very similar to corticosteroids. These compounds have been shown to block 11- β -hydroxysteroid dehydrogenase, the enzyme responsible for the conversion of cortisol to the inactive cortisone (15-18). The result is increased cortisol levels. Chronic high levels of licorice have been known to raise blood pressure by causing increased cortisol binding to the mineralocorticoid receptors in the kidney, increasing water retention and blood volume. When taken in smaller targeted doses, licorice root extracts can be used to support adrenal activity. Licorice root extract should be used only in hypoadrenal states. Sublingual (tincture) doses should be taken several hours before the cortisol levels drop below normal. For instance if morning cortisol levels are normal or high but the noon levels are below normal, 5 drops of licorice root extract (equal to about 50 mg of root) would be taken between 10-11 am. This will maintain or boost cortisol levels for several hours. Additional doses can be taken in the mid afternoon if the 4-5pm cortisol levels are reduced. Severe hypoadrenalism may require 3 or 4 separate doses throughout the day and may also necessitate taking up to 10 drops at each dosing. While these amounts may seem rather low, they are intended to be subtle and used in combination with glycemic control and vitamin/mineral support products. Even at these levels, caution should be taken with individuals having high blood pressure.

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Vitamins and Minerals:

The synthesis and secretion of cortisol is dependent on adequate supplies of various vitamins. Vitamin C is needed for steroid biosynthesis and is depleted from the adrenal cortex upon high cortisol secretion. Niacin derivatives are also necessary cofactors for steroid biosynthesis. Pantothenic acid and folic acid are vital to maintain steroid secretion from the adrenal cortex. The effects of pantothenic acid deficiency has been specifically linked to decrease adrenal function in both animals and humans (19,20,21). Likewise, adrenocortical insufficiency has also been noted during biotin deficiency.

The relationship between the adrenal cortex and minerals is quite complex. Aldosterone (mineralocorticoid), made by the adrenal cortex, has a profound effect on the regulation of minerals. Both aldosterone and cortisol are stimulated by stress (ACTH) and increase the amount of potassium released. Under stress, calcium may be depleted in adrenal tissues as it is required for the secretion of both

hormones. Serum levels of potassium, zinc, iron and copper are reduced under cortisol secretion. A balanced vitamin and mineral supplement regimen is critical when addressing adrenal regulation. There are several products specifically designed to support adrenal function that may be used in addition to a general multivitamin and mineral supplement.

Glandulars:

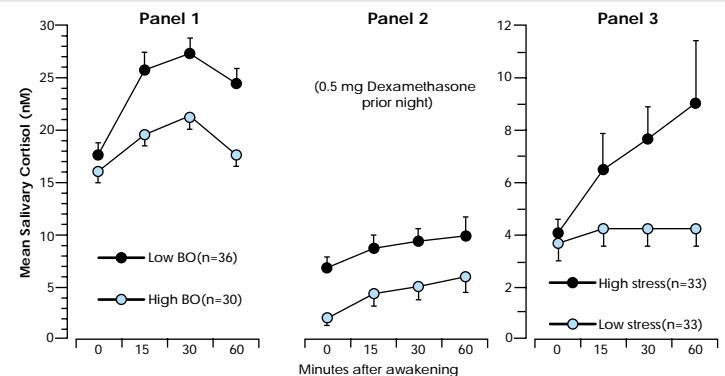
Using glands and organs as supplemental ingredients may be new to some, but the concept is ancient. Dietary use of organ meat for therapeutic functions has been going on in many cultures for centuries. The concept of glandular therapy is simple, like organs help each other. Vitamin, mineral, and hormone concentrations are unique to each organ. Ingesting organ products similar to those in our own system (bovine, porcine etc) has been shown to stimulate the activity of these organs. While this may be beneficial in the event of reduced activity (diurnal hypoadrenalism), inadvertent over-

“STRESS, BURNOUT, AND HPA ACTIVATION.”

Valuable information can be gained by intentionally activating or suppressing the HPA, and then monitoring its reaction via salivary cortisol levels. A group of researchers at the University of Trier in Germany have developed several ways to stimulate salivary cortisol levels using various stressors. One method measured salivary cortisol levels every 20 minutes throughout a day that included three consecutive parachute jumps (28). They found that salivary cortisol levels peaked (raising some 50nM) 30 minutes after each jump, although less so on the third jump. They also created a brief psychosocial stress test called the TSST (Trier Social Stress Test), which involves free speech and mental arithmetic in front of an audience for 15 minutes (29). They found that salivary cortisol levels rose 2-4 fold above baseline during the test, but found that men had 1.5 to 2 fold higher responses than women (in anticipation and during the test). Psychological stress, they concluded, increases when there is high ego-involvement (men vs. women, athletes etc.), low predictability, low controllability, or novelty (2).

Recently they published research on the cortisol responses to awakening in a group of teachers with stress and/or burnout (14). They divided the teachers into high burnout/low burnout groups based on statistical variations of 3 separate questionnaires; and high and low perceived stress based on the Perceived Stress Scale (questionnaire). Salivary cortisol levels were taken upon awakening and 15,30 and 60 minutes after awakening. Panel 1 shows the difference in salivary cortisol levels upon awakening in high and low burnout individuals. The HPA activation of low burnout individuals shows a typical 50-75% increase in the first 30 minutes after awakening while this is blunted in the high burnout individuals. This is a sign of HPA exhaustion. Upon taking a 0.5mg dexamethasone suppression test (oral in the evening prior) the high burnout HPA shows a stronger suppression, but similar curve as those in the low burnout group (Panel 2), confirming the lower HPA activity in high burnout individuals.

Interestingly, when divided by perceived stress, there is a dramatically different response to dexamethasone suppression. Panel 3 shows that while both groups are equally suppressed upon awakening, those with high perceived stress are able to “break-through” the suppression while those with low perceived stress are not. This would fall into a classic “alarm reaction” where stress is over-riding the HPA feedback mechanisms. This information should be used to design laboratory tests that will allow fairly accurate portrayals of the HPA system by performing multiple morning cortisol levels in combination with oral dexamethasone challenges.



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stimulation is possible. The use of adrenal glandular products has become very popular to help regulate the adrenal gland. Without a proper balance of vitamins, minerals, and adaptogenic herbs; the use of adrenal, pituitary, or hypothalamic tissues may act to prevent proper regulation, over-stimulating an exhausted system. When using glandulars, one should look for a product that is formulated with these considerations in mind.

Adaptogenic Herbs:

The use of adaptogenic herbs in humans is fascinating and is much more involved than we can discuss here. An adaptogen is primarily a substance that increases the body's ability to resist stress and exerts a balancing effect on various systems of the body (immune, central nervous, cardiovascular etc.). Adaptogens may be able to stimulate or inhibit the activities of these systems, depending on the system's need (23).

Of the many adaptogens used, Siberian Ginseng and Panax Ginseng are the best known. While having very different active principals (eleutherosides vs. ginsenosides) and being of different plant genus families (*Eleutherococcus senticosus* vs *Panax ginseng*) they have had similar uses for centuries, particularly in the Orient and Russia. Extracts of both were found to have binding affinity to glucocorticoid, mineralocorticoid and progesterin receptors (22). The differential binding affinities (as compared to the

endogenous hormone) may explain the balancing effect on the stress mechanisms much like the phytoestrogens do in female hormonal cycle regulation. The effect of adaptogens in combination with vitamins and minerals has been shown to be additive and very beneficial in relieving adrenal stress (24,25). Some other adaptogenic herbs include Astragalus, Ashwagandha, Schizandra, Wild Yam, Dandelion Root, and of course Licorice Root.

Conclusion:

As the number of individuals with chronic conditions increases year-by-year, healthcare professionals need to discern the role of stress in their patients suffering from these conditions. We have explored the use of a simple measurement, salivary cortisol and DHEA levels, as a tool to gauge the function of the hypothalamic-pituitary-adrenal axis. We have shown the implications of both the overall levels as well as the diurnal nature of these measurements to determine the patient's level of stress (physiological and psychological) and adrenal exhaustion. With this valuable tool, assessing chronic complaints takes on a new dimension and allows a very targeted therapeutic approach. Underlying conditions may disappear or be brought to the fore, where they can be dealt with directly. For those who are serious about the overall health of their patients, helping them measure and manage adrenal stress can be extremely rewarding; not to mention what it can do for the patient!

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IN MY OPINION

I was very intrigued as I was putting this review together by the various chronological cycles there are in our bodies. There are the obvious daily cycles of sleeping and waking, diurnal hormone cycles like cortisol and human growth hormone, and body temperature. Cycles of greater length also exist, most notable the menstrual cycle which averages 28.5 days (the exact length of the lunar phase), and annually (most profound in the plant and wild animal communities). It has only been within the past several decades that some of these annual changes have been detected in humans; such as changes in hormone levels that lead to increased conceptions in late summer/fall (childbirth increasing in late spring), seasonal affective disorder ("winter blues"), and changes in metabolism. Lifetime cycles are well characterized in a number of profound ways: decreasing/increasing levels of hormones; stages of puberty, fertility, and menopause in women; and the numerous physical characteristics that make chronological age so apparent.

Each of these timeframes seems to have both an internal and an external pacemaker. The external are rather obvious, the sun keeps a daily rhythm, the moon the monthly rhythm and the combination of sun, stars and seasons give continual external cues to keep these cycles regular. Chronobiologists call these zeitgebers from the German word meaning synchronizer. It is apparent from recent research that even without these external cues, the body has an internal pacemaker as well. When given no daily external cues, circadian rhythms regulate to just over 24 hours; and monthly cycles seem to be set, apart from external zeitgebers. Most confounding to scientists in recent years is the phenomenon of a circaseptan (7 day) cycle that has been noted in a number of plants, animals and humans. Most profoundly is the 7-day cycle associated with organ transplant rejection, possibly correlated to pattern of corticosteroid metabolism, which also shows a circaseptan rhythmicity. Let us consider two questions.

What are the consequences of ignoring or altering these biological rhythms?

The inventions of electric lights and air travel have made it possible to put our internal biological rhythms in conflict with the natural zeitgebers. No longer do we need to stop working when the sun sets, we can work at anytime of the day or night and sleep whenever we can. Shift-work and especially swing-shifts have radically stressed the body's ability to reset the "clock" on a weekly basis. The consequences of air travel through several time-zones (known as jetlag) can create a profound effect on the body requiring several days to weeks to fully adjust, depending on the direction and number of time-zones traveled.

It is my contention that the more often we ignore the natural zeitgebers of daily, weekly, monthly, and yearly patterns; the more susceptible we will be to chronic and debilitating diseases. The increase in chronic illnesses in the past century, especially in western societies, has as much to do with this phenomenon, as it does to diet and other lifestyle factors. This aspect of lifestyle management should not be overlooked when assessing the changeable factors in the patients stress level.

How is it possible that humans (or plant or animals) are programmed to cycle at these various nested rhythms apart from these external cues, and yet are kept in proper sync by the geologic rhythms of the universe?

I would like to suggest that a clue to answer this may come as we read one of the most ancient descriptions of the creation and purpose for man and these other geological bodies. "Then God said let there be lights in the expanse of the heavens to separate the day from the night and let them be for signs, and for seasons and for days and years...and God made the greater light to govern the day and lesser light to govern the night; the stars also." (Genesis 1:14-16). We might say, these were made specifically as zeitgebers; regulators of times and seasons. Considered myth by many, is it not curious that while we have no scientific understanding of the relevance of a 7-day cycle, or how such a thing could have appeared without external cues, this same Creator instructed mankind that such a pattern exists nearly 4 thousand years ago, and claims to have followed it Himself as he created the universe. The daily, monthly, and yearly rhythms may be more integral that we had previously considered. Is it any wonder why our health suffers when we ignore such cues.