The Role of Stress and the HPA Axis in Chronic Disease Management
Principles and Protocols for Healthcare Professionals

The Stress Response: Function and Dysfunction • How Stress Depletes Metabolic Reserve
Is it Really Adrenal Fatigue? • Genomics and Epigenetics of Stress • Modulating Cortisol Signaling
Neurosteroids and Neurotransmitters • Understanding Adrenal Hormone Testing
Avoiding Common Testing Errors • The Three-Stage Model of Stress Progression
Sample Patterns of Diurnal Cortisol and DHEA(S) • Addressing the Key Reversible Stressors
Nutrient Support Protocols • Adaptogens • And much more...

Thomas G. Guilliams Ph.D.
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# Table of Contents

**Lifestyle-Based Therapy: Our Core Philosophy**
- Physiological Resilience and Metabolic Reserve ................................................................. 10
- Prevention-to-Intervention Hierarchy .................................................................................. 13
- The Seven Spheres of Lifestyle Signals ............................................................................... 14

**The Role of Stress on the Human Condition**
- The Goal of the Stress Response ......................................................................................... 15
- Chronic Stress Depletes Metabolic Reserve ........................................................................ 16
- Conditions Related to HPA Axis Dysfunction ...................................................................... 17
- Hans Selye and His General Adaptation Syndrome .............................................................. 18
- Stress: Genomics, Epigenetics and the Rise of Chronic Disease ......................................... 20
- Reassessing the Nomenclature of HPA Axis Dysfunction (“Adrenal Fatigue?”) .................. 21

**The Stress Response System**
- Sympatho-Adrenomedullary System- LC/NE: An Overview ............................................... 24
- The HPA Axis: An Overview ............................................................................................... 25
- The Hypothalamus: Interpreter of Stress ............................................................................. 26
- CRH: Beyond the Hypothalamus .......................................................................................... 27
- The Pituitary: Controlling the Signals of the HPA axis ......................................................... 28
- The Adrenal Gland ............................................................................................................... 30
- Hormones of the Adrenal Cortex ......................................................................................... 30
- Reassessing the Notion of “Pregnenolone Steal” .................................................................. 32
- Hormones of the Adrenal Medulla ...................................................................................... 33

**Cortisol Signaling: Modulating the Target Tissue Response**.............................................. 34
- Cortisol Clearance and Metabolism Rate ............................................................................. 36
- Corticosteroid Binding Globulin and Cortisol Bioavailability ............................................. 37
- 11β-Hydroxysteroid Dehydrogenase: Controlling Intracellular Cortisol Concentration ....... 38
- Genomic Signaling: The Classic Cortisol-Signaling Effect ................................................. 40
- Heat Shock Proteins: Chaperoning the Cortisol Effect ......................................................... 42
- Non-Genomic Signaling of Cortisol ...................................................................................... 44
- DHEA: Modulating the Effects of Cortisol and More ............................................................ 45
- DHEA(S) as a Neurosteroid .................................................................................................. 47

**Laboratory Assessment of the HPA Axis**
- Measuring Cortisol (Serum, Urine, Hair) ........................................................................... 52
- Salivary Cortisol: The Preferred Method for Clinical Evaluation ......................................... 55
- Cortisol Awakening Response (CAR) .................................................................................. 56
- Diurnal Cortisol Testing/Precautions Using Standard Lab Testing ....................................... 57
- Cortisol Testing for Cushing’s, Pseudo-Cushing’s and Addison’s disease ............................. 58
- Glucocorticoid Therapy Increases Risk for Adrenal Insufficiency ..................................... 60
- Testing Salivary DHEA and DHEA-S .................................................................................. 61
- Cortisol: DHEA(S) Ratio ....................................................................................................... 62
- Salivary secretory immunoglobulin-A (sIgA) ....................................................................... 63
- Salivary alpha-amylase (sAA) ............................................................................................. 64

**The Three-Stage Model of Stress Adaptation (HPA Axis Dysfunction)** ............................. 66

**Sample Patterns of Diurnal Salivary Cortisol and DHEA(S) Results** ............................... 68
- Ideal Subject ......................................................................................................................... 68
- Hyper-Cortisol, Elevated CAR (only) .................................................................................... 69
- Hyper-Cortisol (with Diurnal Drop) .................................................................................... 70
- Hyper-Cortisol Spikes Due to Exercise ................................................................................ 71
- Late Evening Elevated Cortisol (Inflammation-Insomnia) .................................................. 72
- “Normal” Cortisol with Low DHEA(S), in Subjects with Signs of Perceived Stress ............ 73
Table of Contents

Blunted Morning Cortisol (only) .......................................................... 74
Hypocortisolism (General Pattern) ....................................................... 75

Provoking Psychosocial Stress: The Trier Social Stress Test (TSST) .......................................................... 78

Modifiable Categories of HPA Axis Stress ........................................... 80
Understanding and Assessing Perceived Stress .................................. 82
Perceived Stress Increases HPA Axis Activation .................................. 83
“Burnout” Associated with Decreased HPA Axis Activation .................. 84
Helping Patients Take “Control” ......................................................... 84
Neurotransmitters, Mood and the Perception of Stress ......................... 86
Depression and HPA Activation ......................................................... 86
Glutamate Activation ........................................................................... 87
Magnesium and Zinc Modulation ....................................................... 87
GABA and GABAergic Activities ....................................................... 88
Neurosteroids .................................................................................... 88
Monoamines and the HPA Axis ........................................................ 89
Supplementing 5-HTP ................................................................. 90

Circadian Disruption and HPA Axis Dysfunction ................................ 91
HPA and Molecular Control of Circadian Rhythm ............................... 92

Glycemic Dysregulation and HPA Axis Dysfunction ......................... 95
HPA Axis, Satiety and Comfort Foods ............................................... 95
Breaking the Cycle of Stress, Cortisol, Insulin, Adiposity and Inflammation .................................................................................. 96
Reducing Glycemic Impact of Diet .................................................. 96
Considerations for Supplementing Diet with Insulin-Sensitizing Nutrients .................................................................................. 97

Inflammatory Signaling and the HPA Axis ............................................. 98

Natural Therapeutic Strategies to Support HPA Axis Function .......... 102
HPA Axis Nutrient Support Formulary .................................................. 103

Supporting Nutrients: Evaluating the Evidence .................................. 104
Vitamin C (Ascorbic Acid) ................................................................. 104
B-Vitamins ..................................................................................... 105
Minerals ....................................................................................... 105
Phosphatidylserine (PS) .................................................................. 106
Glandular-Derived Supplements ....................................................... 106

Supplementing DHEA ...................................................................... 108
Sublingual vs. Oral Supplementation ................................................. 108
DHEA vs. 7-Keto Forms ................................................................. 109
DHEA Supplementation for Autoimmune Conditions ....................... 110

Supplementing Pregnenolone ......................................................... 111

Botanical Ingredients for HPA axis Support ....................................... 113
Adaptogens .................................................................................. 113
Eleuthero .................................................................................... 114
Schisandra .................................................................................. 114
Rhodiola (Rosenroot) .................................................................... 115
RSE: Combination Studies of Rhodiola, Schisandra and Eleuthero ........ 116
Ashwagandha .............................................................................. 117
Panax (American and Korean Ginseng) ............................................. 117
How We Think Adaptogens Work .................................................... 118

Other Botanicals .......................................................................... 119
Licorice Root Extract .................................................................... 119
Mucuna/Cowhage ......................................................................... 120

Physical Activity, Stress and the HPA Axis ......................................... 124

The Role of Stress and the HPA Axis in Chronic Disease Management  

Point Institute
Preface

In simple terms, this Road map is about the stress response system, primarily the HPA axis, and how a clinician can understand and apply the vast amount of recent clinical research to improve patient outcomes. I have been at the nexus between forward-thinking functional/integrative clinicians, the research world, and the investigation of lifestyle and natural-based clinical therapies for almost two decades, and this Road map is the synergy of those interactions; in keeping with the emerging standard for how such complex systems can be understood and applied in clinical practice. To do this, I have drawn from nearly a thousand published articles while staying ever mindful of the hundreds of questions asked by concerned and perplexed clinicians throughout the process.

I first became intrigued by the stress response and the HPA axis, and how they influence the progression of chronic disease (along with the utility of salivary cortisol and DHEA(S) testing), in the late 1990s, thanks to the late Bill Timmins. I have written and taught on this topic for years, but prior to the in-depth research involved in this project, I did not fully appreciate the widening gap between the vast expanse of stress-related research and the way in which the average clinician understood and applied stress-related therapies in their practice. This work is intended to help bridge that gap.

Unfortunately, many clinicians pay little attention to HPA axis function in patients unless they present with specific gross manifestations like Cushing’s disease or Addison’s disease. As this Road map will show, a healthy and functional HPA axis is an important buffer against a wide range of chronic diseases. Its function and status can be measured by the trained clinician and improved with appropriate interventions. Understood correctly, the HPA axis is truly one of the few systems that influences and controls, at least in part, nearly every other system in the body. Its influence on circadian regulation alone makes it one of the most powerful genomic regulators of the whole body.

On the other hand, many integrative, functional and alternative clinicians have oversimplified HPA axis dysfunction by using inaccurate or oversimplified terms such as adrenal fatigue. As this Road map will show in detail, much of the change in adrenal hormone output related to chronic stress comes from functional changes outside the adrenal gland, while only a small portion of the dysfunctions related to the HPA axis are related to a progressive loss of adrenal function. However, much is still unknown about the progression of changes that occur as the HPA axis adapts over years of challenges, including how the adrenal gland itself is affected by aging and stress. As with all things, our nomenclature must change as our understanding changes.

This Road map is intended to teach the core principles of the stress response system to the busy clinician with little time to stay current with this area of science. Having spent years discussing this topic with clinicians and laboratory experts, I have specifically attempted to cover areas where many of the difficult clinical questions persist. In attempting to find the substantiation for some commonly held beliefs and clinical conundrums, I often found that the evidence was lacking or challenged those notions (i.e., pregnenolone steal). I have done my best to explain these issues, as well as introduce what I believe is more appropriate nomenclature to communicate these phenomena within the functional/integrative medicine community. In doing so, I hope these changes introduce more robust explanations for how and why certain HPA axis manifestations occur, and allow clinicians a better foundation upon which to create intervention strategies. These ideas will be less difficult for those learning these concepts for the first time, and a bit more challenging for those who may have learned (and taught) some of the ideas we challenge or nomenclature we suggest moving away from.

This Road map will also challenge the laboratories offering various tests intended to measure HPA axis function (mostly by measuring adrenal hormone output in the saliva, urine or serum), especially since many clinicians
first learn about the clinical aspects of measuring HPA axis function through laboratory training. Basically, the tests currently offered by most of these labs need to be significantly updated or changed altogether. In reviewing the salivary cortisol and DHEA(S) instructions of nine different labs (including reference ranges, hormone units and interpretive explanations) available as of May 2015, there were not two that reported findings in a similar way throughout. Often, they were so dissimilar it would leave the impression that there was limited scientific foundation for the reported information. Within this text, we propose several different ways a clinician might add more information and precision using the currently available tests, though we hope forward-thinking laboratories will begin to offer tests incorporating the latest clinical research. Providing tests for cortisol awakening response (and/or including CAR analysis into a standard diurnal cortisol test), reporting DHEA or DHEA-S in a manner that allows for diurnal analysis, and/or providing DHEA(S) reference ranges for different age/sex are good places to start.

The Scope of This Project

In this first edition (we hope there will be future expansions), the scope was intentionally limited narrowly around the HPA axis and the stress response system. Since the HPA axis interacts with nearly every other function of the body, it was difficult to keep this narrow focus (though the looming deadlines were a helpful reminder). As even most casual observers will note, there are many potential additions we could have included, such as chapters that define the relationship of the HPA axis to thyroid function or female and male sex hormones. Likewise, each facet of this vast subject could easily have been expanded with more background perspectives and more detailed information. The goal was to strike a balance between oversimplification and clinical irrelevance, and focus on those principles most needed for applying the information within a clinical setting. We have listed key references in each section allowing the enterprising student to dig into more details, evaluating whether the goal of balancing these extremes has been met.

In addition, the range of therapeutic solutions evaluated herein is also limited. For the most part, only lifestyle and nutrient approaches are evaluated- the primary purpose of this Road map. Our approach is “Western” and “modern” in nomenclature and therapeutic perspective. While we acknowledge that there are other healing traditions that incorporate diagnostic and therapeutic categories related to “stress” (such as Traditional Chinese Medicine, Ayurveda, and indigenous herbal traditions worldwide, etc.), discussions of these are best left to the experts in these traditions (which I am not) and in texts designed to teach the fundamental framework of these traditions. Absence of the discussion or mention of any other therapeutic strategies (including pharmacotherapy) within this text should not be viewed as an endorsement or a rejection of such strategies, but simply an intentional limitation of the scope of this Road map.

Finally, scientific research and the interpretation and application of that research is constantly changing or in dispute. If any reader of this text has knowledge of reputable scientific information that would challenge or modify the conclusions or recommendations made here, they should contact us at info@pointinstitute.org so we can evaluate the information and consider incorporating it into future editions. Before doing so, please be sure you have the most recent edition of this Road map, or have read any updates or addendums posted on our website (www.pointinstitute.org). If the information provided in this Road map helps advance the understanding of how stress impacts chronic disease, while empowering clinicians (and patients) to diminish that impact, it will have been worth the effort.
Cortisol Signaling: Modulating Target Tissue Responses

Up to this point, we have described the HPA axis primarily as a way to regulate the adrenal production of cortisol through a complex set of positive signals and feedback inhibition loops controlled by circadian and "stress" signals consolidated in the brain. The synthesis and circulation of cortisol is, however, just the beginning of understanding how the HPA axis controls target tissue responses. Since cortisol is a very potent steroid hormone, there are several ways to buffer and modulate its effects on different target tissues. In the next sections, we will discuss the variety of mechanisms used to modulate the cellular actions of cortisol. Understanding these mechanisms can allow the clinician to leverage specific therapeutic interventions that may mitigate the damage of, or improve the adaptation to, cortisol production and chronic stress. Figure 14 shows a schematic diagram of several specific mechanisms that affect the cortisol signaling process. Each will be described briefly here and unpacked further in each of the next sections.

Figure 14: Cortisol Signaling Modulation. This figure depicts the major ways in which the cortisol effects on target cells can be modulated. See text on the adjacent page and following sections for details and context for each of these mechanisms.
Cortisol Metabolism Rate
Like all steroid hormones, cortisol is metabolized and removed from the body. The clearance rate and detoxification of cortisol (and its intermediate metabolites) are potential factors that alter its target tissue effects.

Free vs. Bound Cortisol
Approximately 95% of the cortisol in the serum is bound to either cortisol-binding globulin (~80%) or albumin. Only free cortisol appears to have cell-signaling effects. Cortisol binding globulin may also act as a transport molecule to help concentrate cortisol to tissues where it may be needed (e.g., inflamed tissues).

11β-HSD (1 and 2)
11-β hydroxysteroid dehydrogenase enzymes 1 and 2 facilitate the inter-conversion of cortisol (active) and cortisone (inactive). The polymorphisms, expression, activation and inhibition of these two enzymes can greatly affect the intracellular concentration of active cortisol available for signaling within the cell.

Classic Genomic Glucocorticoid Signaling
The genomic effects of cortisol are mediated through glucocorticoid (cortisol) receptors. The different receptor isoforms and splicing variants, along with multiple forms of dimerization, help determine the genomic activation or repression of glucocorticoid responsive genes. Most of the known effects of cortisol are mediated through genomic signaling.

Heat Shock Proteins and Co-chaperones
Like most nuclear regulators, cortisol receptors are sequestered within the cytoplasm in the absence of cortisol by a group of chaperone proteins called heat shock proteins. Heat shock proteins and related co-chaperones can profoundly influence the binding affinity and signaling effects of cortisol. Their expression can be modulated by stress as well as other lifestyle and environmental influences.

Direct Non-genomic Signaling
Though best known for its genomic effects, several signaling pathways have been described for cortisol that appear to be mediated by membrane-bound receptors or directly through other cytoplasmic signal transduction pathways (independent of the nuclear/genomic signaling pathways and receptors).

Adrenal (or Brain) DHEA Production
DHEA appears to function as an anabolic counter-regulatory hormone to the catabolic effects of cortisol. Low levels of DHEA allow for more “unopposed” cortisol signaling within tissues. Though the production and release of DHEA and DHEA-S in the adrenal gland is, in part, managed by the HPA axis and “stress” signaling, there are other factors (e.g., aging) with a strong influence on production. In addition, DHEA and DHEA-S can be synthesized in the brain (as neurosteroids) where they act to protect sensitive CNS tissues from the effects of cortisol.

Feedback Inhibition and Target Tissue Function
While considering these different ways that cortisol signaling is modulated at the level of various target tissues, it is important to remember that some of these effects are systemic, while many are tissue-specific. Additionally, recall that changes to target-tissue responses to cortisol signaling also impact tissues involved in cortisol feedback inhibition (e.g., amygdala, hippocampus, hypothalamus and pituitary), so that changes that increase cortisol signaling in these tissues will result in a more profound feedback inhibition (e.g., the use of dexamethasone to suppress the HPA axis and cortisol secretion). Clinicians should keep in mind the tissue-specific cortisol sensitivity and feedback inhibitory dynamics when seeking to diagnose patients based on measured cortisol levels, or in attempting to use supplemental glucocorticoids or agents designed to alter glucocorticoid signaling (see glucocorticoid-induced adrenal insufficiency on page 60). Elevated serum or salivary cortisol levels may be compensated by glucocorticoid resistance in specific tissues and, conversely, low cortisol levels may be compensated by hypersensitivity in specific tissues. Both may explain anomalies between measurements of cortisol circulation and apparent cortisol tissue effects.
an exercise session will likely result in an elevation in the total cortisol, the magnitude of which is dependent on exercise duration and intensity. Depending on the purpose for which clinicians are testing HPA axis function, they may choose to ask patients to refrain from all exercise on the day of testing, ask them to record the timing and intensity of their exercise on the day of the test, or intentionally sample at the end of their exercise sessions to record HPA axis response to their routine exercise sessions. Note that this last option, while it gives the clinician an uncontrolled HPA axis provocation and may add interpretive value, may be interpreted by the laboratory report inappropriately as “hypercortisolism” or a diurnal dysrhythmia.

Cortisol Awakening Response (CAR)

One of the most distinctive features of the 24-hour circadian rhythm of cortisol secretion is missed by nearly all laboratory cortisol tests designed to detect circadian function of the HPA axis. This is the predictable increase of cortisol that occurs in the morning, just after awakening, called the cortisol awakening response (CAR). This feature is a result of two phenomena: the first is the momentum of rising cortisol levels that begins several hours before awakening due to normal circadian HPA axis activities (ACTH); the second, a transient (30 to 45 minute) additional increase of up to 50% in cortisol secretion due to light activation of the suprachiasmatic nucleus (there is no similar rise when waking from a nap). The CAR has been used significantly more than the overall diurnal salivary cortisol in the clinical literature to define specific stress-related HPA axis abnormalities that affect cortisol output.

CAR is influenced by overall HPA reactivity as well as a person’s anticipation of stress. In other words, waking acts as a mini “stress test” for the HPA axis. For instance, a lower cortisol response to awakening is seen in subjects with a high amount of psychosocial burnout, chronic fatigue and PTSD, while it is higher in subjects with ongoing job-related and perceived stress. Also, in subjects experiencing high work stress, the CAR is significantly higher on workdays than weekends, suggesting that daily CAR is partly dependent on the anticipation of stress. While general depression disorders often result in a higher CAR, individuals with seasonally affected disorders have a lower CAR, though only during the winter months. Finally, CAR is significantly elevated during ovulation, as compared to the other phases of the menstrual cycle.

It is difficult to capture the CAR when following the current saliva collection instructions provided by most laboratories. Many only suggest a window of time (e.g., 6 a.m. to 8 a.m.) with no regard to waking time. Others suggest a time after awakening that is much too late to sample the CAR (e.g., >60 minutes after awakening), while some suggest that the first sample be taken upon awakening (before the cortisol reaches its peak). Since the morning cortisol sample is likely to account for more than half of the total cortisol measured using a standard four time-point “diurnal” cortisol test, failing to capture the CAR within the first morning sample can result in over-diagnosis of either hypocortisolism or a flattened circadian profile (see page 74). In individuals working the nightshift for long periods of time, testing should commence upon awakening, as the CAR is shifted to the evening (though usually blunted in most nightshift subjects).

Clinicians can use a standard four time-point cortisol collection strategy to obtain a
Glucocorticoid Therapy Increases Risk for Adrenal Insufficiency

Exogenous corticosteroids such as prednisone are more powerful than endogenous cortisol (or exogenous hydrocortisone) in both target tissue signaling and HPA axis feedback inhibition. The down-regulation of ACTH secretion causes atrophy of the zona fasciculata—condition that may become permanent over time, requiring long-term hydrocortisone therapy. Though we have pointed out that low cortisol output (hypocortisolism), as a consequence of chronic stress, is not properly defined as “adrenal fatigue” or “adrenal insufficiency,” it is important to note that the common use of corticosteroid therapy for transplants, certain cancers, rheumatic and atopic disorders, inflammatory bowel disease, asthma, sinusitis, and allergic rhinitis is the most common cause of true adrenal insufficiency. Often times, neither the prescribing physician nor the patient realize they may be at risk, and these subjects may be “discovered” through routine adrenal hormone output testing designed to evaluate stress and the HPA axis.

A recent (and first of its kind) meta-analysis of over 40 years of corticosteroid therapy publications shows that adrenal insufficiency occurs in a dose and route-dependent fashion. For instance, adrenal insufficiency occurs in about 4.2% of subjects given corticosteroids via nasal administration, 7.8% using inhaled corticosteroids, 4.7% using topical corticosteroids, and as high as 48.7% and 52.2% in subjects receiving oral or intra-articular injections (injections suppress cortisol for 24 to 48 hours, and recovery occurs only after one to four weeks). In asthma patients, subjects given a low, medium or high dose of corticosteroids had a 2.4%, 8.5%, and 21.5% occurrence rate of adrenal insufficiency, respectively. Those on short, medium or long-term therapy had an occurrence rate of 1.4%, 11.9%, and 27.4%, respectively.

According to NHANES data collected from 1999–2008, it is estimated that the prevalence of glucocorticoid use in the United States is 1.2%, with a long duration of use (29% of users reported use of >5 years). Clinicians should ask about previous corticosteroid use in all subjects with a flattened hypocortisol salivary profile, especially in those with conditions for which these drugs are commonly used. Depending on the dose and duration of use, the HPA axis may normalize after corticosteroid-induced adrenal insufficiency using slow withdrawal of glucocorticoid treatment over nine to 12 months. Glucocorticoid withdrawal, especially in subjects with long-term therapy, will often precipitate an acute adrenal crisis and must be managed carefully.

Glucocorticoid therapy can also alter DHEA(S) levels and diurnal rhythm. In healthy young male athletes (mean age 20, mean BMI 22) given 60 mg of prednisone daily for six days, diurnal DHEA levels (measured in saliva) were completely blunted and only returned to baseline after three days of no therapy. See page 110 for a discussion of DHEA supplementation in subjects with adrenal insufficiency or glucocorticoid-induced loss in bone mineral density.

References

Subject Type: Elevated CAR is found in many subjects with high levels of anticipated daily/job stress, though usually not on weekends (see page 84). Many people typically labeled as “Stage 1” within the three-stage model of stress progression will have elevated CAR. Pre-menopausal women may have elevations of CAR during ovulation. Subjects with melancholic depression will also often have elevated CAR. Subjects with some sleep issues may have elevated CAR, though sleep apnea and late-night (short-sleep duration) is often correlated with a blunted CAR.

Cortisol: Diurnal pattern (after awakening) may show morning cortisol level in the upper portion of the reference range or higher depending on when the first sample was taken. Overall, cortisol levels will typically be higher in older subjects and those with higher levels of perceived stress.

CAR (if measured): Waking levels may start higher and the dynamic increase may exceed 60% in subjects with higher perceived stress. Older subjects will have higher morning cortisol levels, though the dynamic changes from waking to +30 minutes is often less (by percent). Elevated CAR is often partially captured even when the first morning saliva sample is taken an hour after awakening, though it is difficult to quantify.

DHEA(S): DHEA or DHEA-S measurements are not diagnostically correlated with CAR, although a robust, dynamic CAR (in young subjects) is associated with a higher waking DHEA(S), which drops rapidly during the first hour after awakening.

Diagnostic and Therapeutic Strategies:
- Help identify avoidable perceived job/life stressors
- Ask about normal sleep time, duration and quality, and advise where appropriate
- Consider general HPA axis nutrient support for hyper-cortisol (see page 103)
  - Glycemic-supporting nutrients
  - Vitamin/mineral support
  - Adaptogens (avoid licorice root extract in a.m. and in salt-sensitive hypertensives, see pages 113-120)
  - Additional phosphotidylserine (PS) may improve feedback inhibition
  - Consider supplementing DHEA only if DHEA(S) measures are low (see page 108)
The stress response is designed to help us avoid danger and things that might harm us. Therefore, our brains are wired to assess the threats around us using visual, auditory, olfactory and other sensory information, combining that information with the memories of previous events that were harmful (or stressful) to decide how to respond. Like other animals with instinctual or learned behaviors, humans are relatively good at recognizing physical dangers such as height, heat, cold, or menacing animals or humans. This is best described by the idea of the “fight or flight” response, which assumes we recognize a reason to flee or defend ourselves (e.g., being chased by a grizzly bear). Assuming these dangers are real, the stress response will either help us avoid injury or help us cope with the injury once it has been inflicted.

Unfortunately, the stress response does not easily distinguish between real threats and those that are only perceived as threats. Often these might be called mental and emotional or psychosocial stressors. These are responses that are greatly influenced by past history of stress or trauma, by learned behaviors, by personality traits, or perhaps, by neurotransmitter imbalances. Patients might describe this type of stress with words like fear, worry, anxiety, anger, pressure, hopelessness, or anger. The most common sources of perceived threats are usually related to employment, relationships, financial issues, traumatic memories or social life. Whether or not these events will actually cause harm, the pathophysiological changes that occur during HPA axis activation are the same.

If these stressors are only perceived, how can clinicians gauge their impact on a patient’s health and what can be done to limit their health consequences? This requires two separate lines of inquiry. The first is to define the extent to which the patient is experiencing perceived stress, and the second is to help them identify the most profound source(s) of that stress.

Research in this area has defined four key factors determining the magnitude of the HPA axis response to a mental/emotional stressor. They are: 1) novelty of the event; 2) the unpredictable nature of the event; 3) perceived threat to physical body or ego; 4) a sense of loss of control. Sometimes referred to by the acronym N.U.T.S. (i.e., Novelty, Unpredictability, Threat, Sense of no control).

Individual characteristics of the patient are also profoundly influential. Innate qualities such as age, gender (female preponderance), and hereditary predisposition coupled with personality characteristics (i.e., introversion and low self-esteem), as well as prenatal and early childhood experiences serve to further individualize and amplify each patient’s unique stress response. In stress research studies, a variety of surveys and questionnaires are used to create objective criteria for psychosocial stress/perceived stress and HPA axis status, many of which are available to clinicians online.

One of the most popular ways to measure perceived stress is the Perceived Stress Scale (PSS), originally proposed by Cohen et al. in 1983. The original version contains 14 questions (PSS-14) to assess how subjects feel about the control in their lives over the past month, with options of never, almost never, sometimes, fairly often, and very often.

For printable copies of the PSS-14, PSS-10 and PSS-4 in English and 25 other languages, along with scoring instructions and other research tools, visit Dr. Cohen’s website: www.psy.cmu.edu/~scohen/scales.html

Understanding and Assessing Perceived Stress
Control Relational Stress
Some of the greatest pleasures and some of the worst experiences in life involve relationships. Few things can lift our spirits like being with someone we love; few things can damage our spirits more than a relationship full of tension and strife. Clinicians need to be aware of the relational dynamics of any individual being assessed for HPA axis dysfunction, recognizing that these issues can be very intense and difficult to control. Using a life stress inventory with a list of events, such as divorce, marital separation, sexual difficulties, or spousal arguments, may be an easy way to start the conversation. In addition, clinicians should not overlook the burden caused by daily caregiving to chronically ill parents, spouses or children. A list of competent individuals (e.g., medical doctors, clergy, etc.) should be readily available to refer patients.

Neurotransmitters, Mood and the Perception of Stress

When we talk about “stress,” or allostatic load, in terms of the perception of an event, we must realize that these “events” must first be translated into neurochemical signals before they trigger the HPA axis. Therefore, the sensitivity and outcome of translating these events (whether they are ongoing events, memories of past events, or stressful anticipation of unrealized events), is highly dependent upon signaling from other neurotransmitters. In fact, the signaling neurotransmitters that manage mood and affect often overlap with measures of HPA axis activation, and cannot be easily distinguished in some subjects. While the detailed influence of neurotransmitters, such as GABA, glutamate, serotonin, norepinephrine, dopamine and a host of neurosteroids, on the HPA axis is beyond the scope of this Road map, we will outline some of the fundamental activities clinicians should keep in mind when evaluating patients for HPA axis dysfunction.

Anxiety disorders are the most common mental illness in the United States, affecting 40 million adults age 18 and older (18% of the population). Major depressive disorder (MDD) is the leading cause of disability in the United States for those age 15 to 44. MDD affects approximately 14.8 million American adults age 18 and older each year, or about 6.7% of the population. These disorders are often associated with abnormal amounts, ratios or activities of various neurotransmitters. For this reason, more than 1 in 10 Americans are prescribed a medication intended to modulate or mimic neurotransmitter function with a variety of outcomes and side effects.

The manifestations of HPA axis dysfunction caused by stress, such as a feeling of a loss of control, burnout-withdrawal, and worry, overlap with those of both anxiety and depression. For this reason, it is often difficult to separate the diagnostic and treatment approaches in such individuals. It is common for researchers to use depression scales (e.g., Hamilton Depression Scale) along with perceived stress scales in subjects undergoing HPA axis function testing. It is also well-known that the brain regions most responsible for interpreting perceived stress (i.e., hippocampus, prefrontal cortex, amygdala and hypothalamic PVN; see page 27), are highly influenced by neurotransmitter-signaling, though these interactions are multi-layered and not well-understood.

Depression and HPA activation

A recent summary/meta-analysis of the past 40 years of research has affirmed that elevated activity of the HPA axis during depression is one of the most reliable findings in biological psychiatry. Higher cortisol levels are most pronounced in subjects with more severe depression symptoms, especially if the patient is hospitalized due to depressive symptoms. Melancholic and psychotic depression are linked with notably higher average cortisol than those with regular depression. Atypical depression, characterized by hypersomnia, fatigue and hyperphagia, does not appear to cause elevated cortisol levels, and in some studies, correlates with lower cortisol output. ACTH output, when measured, also mirrors most of these findings, as it is elevated in more severely depressed subjects.

HPA hyperactivity in depressed subjects appears to be caused, at least in part, by impairment within the negative feedback inhibition process. Essentially, the feedback inhibition is less sensitive to elevated cortisol secretion, which prevents appropriate down-regulation of the HPA axis. Research has primarily focused on the function and polymorphisms of the glucocorticoid receptor (GR) and its co-chaperones within the hippocampus, amygdala, hypothalamus
Natural Therapeutic Strategies to Support HPA Axis Function

Supporting the HPA axis is a critical component to chronic disease management, but it involves organizing therapies around known processes within the brain, the adrenal gland and the way in which cortisol signaling functions within target tissue. This section summarizes some basic protocols that can be used in most patients with HPA axis dysfunctions giving nuanced applications based on measured cortisol levels (see also pages 66-76). This is followed by summaries of the key nutrients, herbs or dietary supplement ingredients that have the potential to improve HPA axis outcomes.

It is important to always remember the big picture when addressing stress and HPA axis support protocols. Fundamental to uncoupling the chronic disease consequences of stress, even without discovering or removing a known stressor, is to build the metabolic reserve of all tissues through proper diet and lifestyle inputs. Obviously, removing known stressors that lead to HPA axis dysfunction/maladaptation is also profoundly beneficial. In both of these strategies, building metabolic reserve and reducing known HPA axis stressors, there is a wide range of non-pharmacological options available to the clinician.

### Strategies for Supporting HPA Axis Function

#### CNS Support
- Maintain Appropriate Hypothalamus Response to Stressors
  - 1. Glycemic Dysregulation
  - 2. Perceived Stressors
  - 3. Inflammatory Signals
  - 4. Circadian Signals
  - Sleep Therapy
  - Light/Dark Entrainment
  - Meal Timing
- Balance Neurotransmitters/Neurosteroids
  - Consider Supplementing Precursors and Cofactors for Neurotransmitter Synthesis
  - Consider Supplemental DHEA & Pregnenolone
- Balance Cortisol Feedback Mechanisms
  - Consider Phosphatidylserine
  - Consider Adapto gens

#### Adrenal Support
- Protect the Zona Reticularis
  - Antioxidants
  - Adapto gens (?)
- Nutrient Support for Adrenal Steroidogenesis
  - Vitamin C
  - B-Vitamin (general)
  - Pantothenic Acid
  - Niacin
  - Minerals (general)
  - Magnesium/Zinc
  - Glandulars (Adrenal)

#### Target-tissue Cortisol Modulation
- 11β-HSD Activity
  - Reduce Inflammation
  - Reduce Insulin Resistance/Insulin
  - Reduce Central Adiposity
  - Consider Physical Activity (not intense)
- HSP Modulation of GR
  - Consider Adapto gens
  - Consider Physical Activity (not intense)
- DHEA's Anti-Glucocorticoid Activity
  - Consider Suplemental DHEA
adaptogenic). Clinicians who are unfamiliar with the clinical use of ginseng preparations, especially as an adjunct to stress and fatigue-related therapies, should find additional information about the type and dose of the products they wish to use, as well as the type of patient best suited for this support.

How We Think Adaptogens Work

The proposed mechanisms explaining how certain botanical extracts, or their chemical constituents, trigger a non-specific resistance to stress, sometimes up-regulating and other times down-regulating cellular functions, are difficult define. This is partly due to the fact that finding agreement on the exact limits on what defines a “non-specific” adaptogenic effect, requires some actual specifics. Years ago, Brekhman and Dardimov listed these four criteria for defining an adaptogenic response:129

- Adaptogens must reduce stress-induced damage, thus presenting stress-protective effects such as anti-fatigue, anti-infectious, anti-depressant and restorative activities.
- Adaptogens must exhibit stimulating effects, both after single and multiple administrations, leading to increased working capacity and metal performance against a background of fatigue and stress.
- The stimulating effect of adaptogens must be different from those of conventional CNS stimulants and anabolics that deplete the energetic and plastic resources of the organism and give rise to negative side effects such as drug withdrawal syndrome.
- Adaptogens must be innocuous and must not perturb body functions from their normal levels but rather exert a normalizing influence on a pathological state, independent of the nature of that state.

Leading researchers in this area now consider adaptogenic activities much like a mild stress-mimetic, in that they appear to trigger some of the same biological and cellular functions needed under stress, without adding to the allostatic load themselves. Some 45 years after these early parameters for defining adaptogenic activities, modern molecular biological and genomic techniques are helping to elucidate what may be happening at the organ, tissue, cellular and molecular levels.130,131 Here are the leading mechanisms described for adaptogens and/or some of their specific constituents:

- **Modulation (increase) of heat shock protein expression**132,133,134 Stress-induced denatured proteins can lead to non-specific damage within cells, contributing to increased inflammatory and immunological burden, as well as mitochondrial stress. Heat shock proteins (HSPs) act as molecular chaperones to help proteins fold, especially when cells are under metabolic stress. HSPs may also be important to help signal cell stress to adjacent cells. HSPs are also important in the management of the glucocorticoid receptor itself (see page 42). In essence, HSPs manage the folding, affinity, nuclear transport, genomic signaling and half-life of these cortisol receptors, critical for the stress response and circadian functions of most cells. Animal and cell-culture data have revealed upregulation of several HSPs (especially Hsp72) associated with many adaptogenic extracts or constituents.

- **Increase in the neuropeptide Y (NPY) expression and release**135 Neuropeptide Y is a stress-responsive hormone found in both the central and peripheral nervous system.136 Found at high concentrations within the amygdala, hypothalamus and in peripheral sympathetic nerve endings, NPY is released following both physical and psychological stress. NPY can act synergistically with cortisol and catecholamines in peripheral tissues, while inhibiting the activation of the HPA axis at the same time. Overall, it appears to buffer and modulate the quick resolution of the stress response. Animal and cell-culture data have revealed NPY upregulation associated with several of the primary adaptogenic extracts or their constituents.

- **Genomic signaling of genes within core metabolic pathways**137,138 Modern molecular biology techniques allow researchers to detect changes in genetic expression (i.e., RNA transcripts, proteins or both) in specific cells when treated with a range of adaptogenic extracts or isolated constituents. This research has primarily been done in isolated neuroglial cells. Through these methods, researchers have noted significant genomic responses in well over 500 different genes associated with each extract or constituent tested, several hundred of which are regulated in similar ways by most of the substances tested; suggesting some common pathways for adaptogenic modulation. Most of these genes are involved with various cell-