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Conference highlights by Dr. Susan Berry

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Chronic Stress & the HPA Axis

This term is used by stressed individuals, usually those who experience long term or chronic stress. In today's 24/7 world, involving constant multi-tasking and a lack of work life balance for many individuals, I am seeing more and more patients with **HPA axis dysfunction (**see below) which impacts on the BHRT treatment protocols I use. These patients often present with exhaustion, insomnia, irritability, constant fatigue, poor focus, poor memory and depression amongst other symptoms. I perform salivary sampling for such patients alongside their hormone profile. This involves providing several saliva samples over a 24-hour period. It was confirmed at the BHRT San Francisco conference that this is the most reliable way of measuring adrenal hormone output and that this is preferable to a 24 urine collection as used by many physicians previously.

Human beings are designed to maintain a sense of normal homeostasis, a physiological state of balance. The term "stress" has been used to describe a "state of threatened homeostasis or disharmony". This must then be counteracted by a physiological response by the body to re-establish homeostasis or harmony, the so called "adaptive stress response". With regards to the way the body deals with stress, much attention has been paid to the **adrenal gland** and the production of the hormone cortisol. **Cortisol is the only hormone that increases with age, thus as we age we deal less well with stress.** It is important not to over work and take on too much responsibility as one ages if possible in order to protect the HPA Axis and prevent "adrenal fatigue" and burnout.

"**Adrenal fatigue"** has now become a popular term to describe the **physiological maladaptation to stress,** especially **hypocortisolism or low cortisol**. The key components of the stress response are the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS).

A vast amount of research has been conducted to understand the intricate cascade of events that occur once the brain detects a stressor, that is something that causes stress to the body. This stressor causes a disruption in homeostasis. This stress can take the form of fear, anxiety, embarrassment and can occur for example prior to public speaking and performance evaluations such as at work etc.

Hans Selye* has described the" the General Adaptation Syndrome" or G.A.S and its three stages of:

i) the alarm reaction stage
ii) the adaptation stage
iii)the exhaustion stage.

He describes ***4 categories of chronic HPA axis stress***. These are mental/emotional stress, sleep disorders, metabolic/glycemic dysregulation and chronic inflammation.

I)Mental/emotional stress is usually fairly obvious and is influenced by genetic predisposition and personality characteristics.

II)Sleep Disorders: during slow wave sleep, cortisol is normally suppressed by a rise in Growth Hormone. **Chronic stress exposure results in an abnormal HPA axis,** SNS activation and disruption of the normal diurnal pattern of hormone release (GH, CRH and ACTH). ***The result is a paradoxical rise in cortisol levels in the evening hours and initial phases of sleep. A vicious cycle ensues whereby high levels of night time cortisol (nocturnal hypercortisolism) causes sleep fragmentation, raising cortisol levels even further.*** Insomnia and depression are frequently observed consequences.

III)*Metabolic/Glycaemic disregulation.* *Under stressful conditions maintaining adequate levels of glucose for the brain and muscles is imperative. Cortisol secretion helps to maintain these levels by stimulating* ***gluconeogenesis*** *and in the process causes insulin resistance. These effects are intended to be short term only and to facilitate the "fight or flight" response. However, the consequences can be dangerous if this response is maintained in the long term. Individuals who regularly consume high glycaemic foods and/or are insulin resistant will often induce a "****hypoglycemic crash"*** *after a meal triggering the secretion of cortisol.* ***Cortisol can drive insulin resistance. Insulin resistant individuals or those with central adiposity should*** *be evaluated for HPA axis dysfunction and need to modify their lifestyle and diet to improve glycaemic control and so prevent the excess secretion of cortisol.*

IV)Inflammation. *Undiagnosed inflammation in the gastro intestinal tract such as food allergies, Inflammatory Bowel Disease and chronic inflammatory conditions such as joint inflammation and central obesity, can* **drive HPA Axis *dysfunction if not corrected or treated.***

Stress induced high adrenal output of cortisol *can* ***progress to low adrenal output of cortisol if the stressful situation lasts for a prolonged period of time.*** *This is thought to be an adaption response of the HPA Axis and is thus protective. This protective response ensures long term survival by preventing chronically high Cortisol levels from suppressing immune function. It represents an adaptation to chronic stress.*

It is important to note that hormones function as a symphony. If cortisol is increased, it causes a decrease in the production of progesterone and its activity. Cortisol competes with Progesterone for common receptors. When Cortisol is elevated, thyroid hormone is more bound and less active (seen in Hypothyroidism patients not responding to treatment). Decreased Oestradiol in women for example when a woman goes through the Menopause, is a stressor to her body which impacts her HPA axis and can also cause a decline in function of various neuro transmitters in the brain, such as Nor adrenaline, Serotonin, Dopamine and Acetylcholine.

*It is to be noted that under stressful situations the hormone ACTH will drive high Cortisol levels and begin to deplete DHEA production through what is often termed "****Pregnenolone steal"****. It is also to be noted that in some patient's absolute cortisol levels will fail to detect an HPA axis dysfunction, while a* ***Cortisol: DHEA ratio*** *will.*

Functions of Cortisol:

- *Balances blood sugar*
- *Weight control*
- *Immune system response*

- *Stress reaction*
- *Sleep*
- *Protein synthesis*
- *Mood & thoughts*
- ***Influences testosterone/oestrogen ratio***
- ***Influences DHEA/insulin ratio***
- ***Affects pituitary /thyroid /adrenal system***
- *Participates with aldosterone in sodium reabsorption*
- *Is an anti-inflammatory*

Consequences of high cortisol:

- ***Low energy***
- ***Sleep disturbance***
- ***Binge eating***
- ***Increased blood pressure***
- ***Increased cholesterol & triglycerides***
- ***Increased blood sugar***
- ***Increased insulin/insulin resistance***
- ***Decreased immune function with susceptibility to infection***
- ***Weight gain around the middle (central obesity)***
- ***Impaired hepatic conversion of thyroid hormones T4 to active T3***

DHEA (Dehydroepiandrosterone)

Much research has been done into this critically important hormone which is produced mostly in the adrenal gland. It's production declines sharply as we age however. By the time one reaches 70, one's DHEA level is likely to be 75-80% lower than when it was at its peak. DHEA facilitates healthy aging in part by improving cardio vascular health. New studies have shown that DHEA mounts a three pronged attack against three of the most prominent risk factors for cardiovascular (CVS) disease:
Atherosclerosis ("hardening of the arteries").
Endothelial dysfunction (poor function of the lining of the arteries).
Metabolic syndrome (the combination of central obesity, poor blood sugar control, high blood pressure, abnormal blood lipids).

Large scale studies show a correlation between low DHEA levels and increased risk of death in older men. A careful designed 2010 study demonstrated that women are also vulnerable to the effects of lower DHEA levels. In that study, among women who were already at high risk for CVS disease, those with the l**owest one third of DHEA levels had a significant 155% increase in the risk of dying from CVS disease.** (Journal of Clin Endocrinol Metab 2010 Nov;95 (11):4985-92).

Another study showed that in women with the **lowest 25% of DHEA levels have a 41% increase in the risk of stroke**.
In addition, low DHEA-S levels in women have been found to correlate with significant increases in arterial wall thickness and reductions in blood flow. (Stroke 2013 Jul;44(7);1784-9). (Endocr J 2008 Aug;55 (4):667-75).

A study in female rabbits whose ovaries had been removed (simulating menopause) showed that DHEA efficiently reduced early signs of atherosclerosis and increased beneficial **nitric oxide** levels. **Endothelial nitric oxide is a chemical signal that tells blood vessels to relax, thus widening arteries and allowing increased blood flow through the artery.** (Atherosclerosis 2011 Jan;214 (1);47-57)

DHEA supports a healthy immune system. The immune system wanes with age, resulting to increased vulnerability to infections and cancer. This is called **immune senescence.** DHEA is increasingly recognized as a means of improving the immune response in older adults (Appl Physiol Nutr Metab 2008 Jun;33 (3):429-33). (J Steroid Biochem Mol Biol 2010 May 31;120 (2-3);127-36).

Other functions of DHEA include increased sense of wellbeing, helps one deal with stress, promotes insulin sensitivity, benefits the normal aging brain, improves mood, protects hip bone and spinal mineral density, enhances muscle mass.

Doses of DHEA supplementation vary between 15-50 mg once daily depending on age, sex and symptoms. DHEA is contra indicated in the presence of any hormone dependent tumor e.g. Breast, uterus, prostrate. Blood test monitoring is important. It must be remembered that DHEA is metabolized to Testosterone (hence it can improve low libido in a woman with low Testosterone) and Oestradiol.

Symptoms of DHEA excess include fatigue, anger, depression, deepening of voice, insomnia, mood changes, weight gain, facial hair, acne, sugar cravings, restless sleep, irritability.

FEMALE SEXUAL DYSFUNCTION / *LOW LIBIDO/ NITRIC OXIDE (NO) INSUFFICIENCY.*

More than 30% of the female population experience some sort of sexual dysfunction. Low libido is a very common complaint from my patients and often causes much distress and can affect relationships. In Menopausal women, the problem principally manifests as **Female Sexual Arousal Disorder (FSAD).** FSAD is defined as the "inability to achieve and maintain sufficient sexual excitement, expressed as a lack of genital or other somatic (refers to the body) responses". ***Loss of oestrogen in menopause results in decreased nitric oxide production and so a reduced/absent sexual response. As women enter the peril-menopause/menopause, declining hormone levels of hormones are one of the factors causing a precipitous decline in Nitric Oxide (NO) levels which is of crucial importance in the female sexual response.*** Low NO levels cause sub optimal circulation through the body, as well as to the vulva, vagina and clitoris. **Furthermore, low oestrogen also exacerbates the circulation problem by causing vaginal dryness and vaginal atrophy** (shrinkage of tissue). So one can see, that the several factors contribute to the reduced sexual response in peri menopausal/menopausal women.

There are several hormones involved in the healthy female sexual functioning and are as follows:

- Progesterone
- Oxytocin
- Thyroid
- Oestrogen
- Cortisol
- Testosterone
- DHEA

- Pregnenolone
- Prolactin

Oestrogen and Testosterone are very important as they can promote the expression of Nitric Oxide Synthetase, an enzyme which promotes the production of Nitric Oxide. **Oestrogen positively affects Nitric Oxide production.** It is also important to appreciate that Testosterone enhances vaginal blood flow and lubrication which may be due to a local conversion effect from Testosterone to Oestradiol. There are Testosterone receptors in the vaginal mucosa hence the effect of Testosterone in the vagina. Oestradiol is effective to treat vaginal dryness and vaginal atrophy which is very common in menopausal women. As many of my patients know, I often use DHEA which is metabolized to Testosterone and hence has the above desired effect and is also metabolized to Oestradiol. However, it must be born in mind that DHEA is contra- indicated as stated above, if there is any hormone dependent tumour e.g. Breast and uterine cancer as stated on my website. Monitoring is essential.

Optimal sexual function is a complex neuro-vascular process that is affected by hormonal and psychological input. **Stress is an intimacy killer.** ***Many of my patients feel overwhelmed with their responsibilities…. mother, wife, carer for elderly parents, home maker, holding down a job whilst going through the peri-menopausal/menopausal years. Often a woman is not taking care of herself, in that she is taking on too much and not saying "NO" often enough. Is it any wonder she is always just too tired for sex and would rather have an early night?!!***

Emotional factors play a very strong role in the female sexual response. Of almost 1,000 women 20-65 years the 2 strongest predictors of sexual response were

- Emotional relationship with partner
- Own emotional health

Relationship difficulties adversely affect a healthy sexual response. The relationship difficulties must be addressed first. It must also be remembered that mental health is a huge indicator of sexual function also. Anxiety, depression, poor self-esteem, dysmorphic body disorder and a range of mental health disorders affect sexual functioning and need to be addressed.

There are thus multiple physiological, psychological, hormonal, neurological and anatomical considerations that affect sexual function. All of these processes lead to an **increase in blood flow to the vagina resulting in clitoral engorgement and ultimately orgasm. It is nitric oxide that facilitates this mechanism. The control of blood flow is dictated and determined by the production and regulation of nitric oxide. Nitric oxide is a potent vasodilator i.e. it dilates blood vessels, allowing increased blood flow.**

Professor Nathan Bryan, Professor of Molecular Medicine at the University of Texas states that males or females with **endothelial dysfunction are unable to generate sufficient NO and are therefore unable to attain a normal sexual response. As is already well known in the medical profession, Erectile dysfunction (ED) is classified as a vascular disorder that is a red flag for the presence of underlying endothelial dysfunction and the development of cardiovascular disease. Although ED is typically classed as a male symptom or disease, it also affects females.**

ENDOTHELIAL DYSFUNCTION IS DEFINED AS THE LOSS OF NITRIC OXIDE BIOAVAILABILITY, AND SO ERECTILE PROBLEMS PRESENT A CLEAR INDICATION OF THE NEED FOR NITRIC OXIDE.

Whether it is the male penis or in the female clitoris and vagina, erections are initiated through increased blood flow into the corpus cavernosum of the male penis and clitoral engorgement due to increased blood flow in women. Of importance is the fact that **sexual dysfunction is linked to cardiovascular disease in both men and women. ED (Erectile Dysfunction) in both men and women is associated with increased all-cause mortality primarily due to increased cardiovascular mortality. Sexual dysfunction is now considered an early marker/risk factor for cardiovascular disease. All patients therefore need to be screened for cardiovascular disease.**

Oestrogen positively affects Nitric Oxide production as stated above. This may be responsible for the ANTI-ATHEROSCLEROTIC EFFECTS OF OESTROGEN. During menopause, Oestrogen production declines in women and this leads to LOSS OF ACTIVATION OF ENDOGENOUS NITRIC OXIDE PRODUCTION. Multiple studies now show that Oestrogen replacement therapy increases Nitric Oxide availability and production in post-menopausal women. (Ameer J Obstet Gynecol. 1999: 180:334-339). Without Estrogen production, there is less Nitric Oxide resulting in reduced blood flow creating the inability to produce and sustain an erection and orgasm in women.

Loss of Nitric Oxide production not only leads to sexual dysfunction but is recognized as the earliest event in the onset and progression of cardio vascular disease.

As many of you know, my main research interest is in the prevention of cardiovascular disease in men and women and for the reasons discussed above, I treat sexual dysfunction seriously and initiate more sophisticated testing of cardiovascular function.

NITRIC OXIDE: TOO MUCH OF A GOOD THING?

The Nobel prize was awarded in 1998 for the discovery of the **crucial signaling molecule called Nitric Oxide. It plays a central role in human health and disease. The loss of Nitric Oxide has been linked to many symptoms of ageing such as Dementia, Insomnia, Hypertension, Atherosclerosis, Diabetes, poor transmitter function etc, etc.**

A healthy level of the trace mineral Selenium has been shown to lower the risk of cancer. But that healthy level has been measured in micrograms not milligrams. Ingesting even 5 milligrams daily can poison you, creating a condition called **Seleniosis** which causes symptoms of fatigue, hair loss and brain damage if you ingest enough.

Nitric oxide is no exception to this natural phenomenon according to Dr. Bryan. Surprisingly, **Nitric oxide is a free radical, that is it is a molecule with an unpaired electron. A free radical attack is responsible for a process called oxidation. Free radicals are also called reactive oxygen species or ROS.** In normal quantities Nitric Oxide is good and acts a crucial signaling molecule. It is a master of **homeostasis, that is of balance and good health. However, when Nitric Oxide is overproduced because of infection, inflammation or other causes, it can wreak havoc in the body.**

How to maintain a "just right" level of Nitric Oxide? In brief it's a balanced lifestyle.
In brief this includes:

- Eat a diet **rich in nitrate** packed leafy vegetables e.g. Spinach.
- Emphasize foods and beverages **rich in polyphenols** such as dark chocolate, green tea, red wine in moderation.
- Drink lots of water-hydration helps cells manufacture Nitric Oxide.

- Consider taking a Nitric Oxide increasing supplement, particularly if you are over 40 as ageing reduces the body's production of Nitric Oxide. (NEO 40 daily, available in the USA and manufactured by Neogenis Labs).
- Get regular Nitric Oxide producing exercise.
- Create an environment and a schedule that ensures you get enough Nitric Oxide restoring sleep.
- **Control Nitric Oxide-depleting stress, through deep breathing and other stress reduction techniques.**

OESTROGEN METABOLISM

It is not simply the total amount of Oestrogen circulating in the body that is critical for optimal health according to Dr. Pamela Smith, Director of the Centre for Healthy Living and Longevity, Michigan, USA. How Oestrogen is broken down or metabolized in the body may also play an important role in the cause of a variety of Oestrogen dependent conditions.

Oestrogen is metabolized in the 2 following ways:
There are 2 major competing pathways
- 2-hydroxyestrone. (2-HO)
- 16-hydroxyestrone (16-HO)

1 minor pathway
- 4-hydroxyestrone. (4 -HO)

2-HO is sometimes called the "good Oestrogen". It does not stimulate the cells to divide which can cause damage to DNA and cause tumour growth.

The other major pathway whereby Oestrogen is metabolized is the 16-HO pathway. This metabolite is much stronger and much more powerful. **16-HO** has a stimulator effect. 16-HO binds strongly to special receptors inside the cells that can increase the rate of DNA synthesis and cell multiplication. **Consequently, 16-HO is proposed to have significant Estrogenic activity and to be associated with an increased risk of breast cancer. Furthermore 16-HO binds long term to the Oestrogen receptor whereas others Oestogens bind briefly and then are released. This may also be a reason why 16-HO is associated with an increased risk of cancer.**

HIGH LEVELS OF 16-HO ARE ASSOCIATED WITH:
- **OBESITY**
- **HYPOTHYROIDISM**
- **PESTICIDE TOXICITY**
- **OMEGA -6-FATTY ACID EXCESS**
- **INFLAMMATORY CYTOKINES**

Therefore if a patient metabolizes a larger proportion of her endogenous and exogenous Oestrogen through the 16-HO pathway, she may be at an increased risk of breast cancer than if she metabolizes more oestrogen through the 2-HO pathway. Recent studies have shown that a low 2:16 HO ratio is associated with an increased risk of breast cancer. This ratio can be measured in the urine and is a good gauge of the body's ability to methylate. Another way of measuring this ability is by measuring Homocysteine levels.

FACTORS THAT STIMULATE METHYLATION ARE NUMEROUS AND INCLUDE:

- **SAMe**
- **METHIONINE**
- **B2, B6, B12**
- **FOLIC ACID**
- **REDUCING CATECHOLAMINE PRODUCTION BY DECREASING STRESS.**

A minor pathway of Oestrogen metabolism is **4-HO. It may also enhance cancer development as 4-HO may directly damage DNA by causing breaks in the molecular strands of DNA. Moreover 4-HO has the ability to convert to metabolites that react with DNA and cause mutations that can be carcinogenic. OF NOTE IS THAT EQUINE OESTROGENS SUCH AS PREMARIN, INCREASE METABOLISM INTO 4-HO.**

THEREFORE, THE METABOLISM OF OESTROGEN VIA THE 2-HO PATHWAY IS OF CRITICAL IMPORTANCE in lowering the risk of cellular damage and consequently cancer risk.

NATURAL APPROACHES THAT RAISE 2-HO:

- **MODERATE EXERCISE**
- **CRUCIFEROUS VEGETABLES EG. BROCCOLI**
- **FLAX**
- **ROSEMARY**
- **TUMERIC**
- **WEIGHT LOSS**
- **BROCCOLI DERIVATIVES EG. INDOLE-3 CARBINOL (I-3-C)**
- **HIGH PROTEIN DIET**
- **SOY**
- **OMEGA 3 FATTY ACIDS**
- **VITAMINS B6, B12 AND FOLATE.**

There are other factors that affect how the body metabolizes Oestrogen. The first is **Obesity.** The second factor is the presence of **xenoestrogens which are toxic to the body.** Researchers have identified several chemicals that **imitate Oestrogen. These are called xenoestrogens sources of which are:**

- **Pesticides**
- **Synthetic hormones fed to animals**
- **Plastics**
- **Cosmetics.**

Thirdly, alcohol interferes with the body's ability to detoxify Oestrogen and increases Oestradiol levels and the risk of breast cancer.

Lastly, even antibiotics found in food may be associated with an elevated risk of breast cancer by changing gut flora involved in the enterohepatic circulation of Oestrogens.

The BHRT conference in San Francisco was for 3.5 days and covered a large amount of information as one can appreciate, much of which you may have already read on my website previously. Time does not allow me to comment on any more topics unfortunately. However, I will of course be incorporating new research into my BHRT protocols and into my daily practice. Unfortunately, time does also not allow me to answer any e-mail questions on the above information. I am always happy however, to answer questions during the consultation.

Dr. Susan Berry

*https://en.wikipedia.org/wiki/Hans_Selye