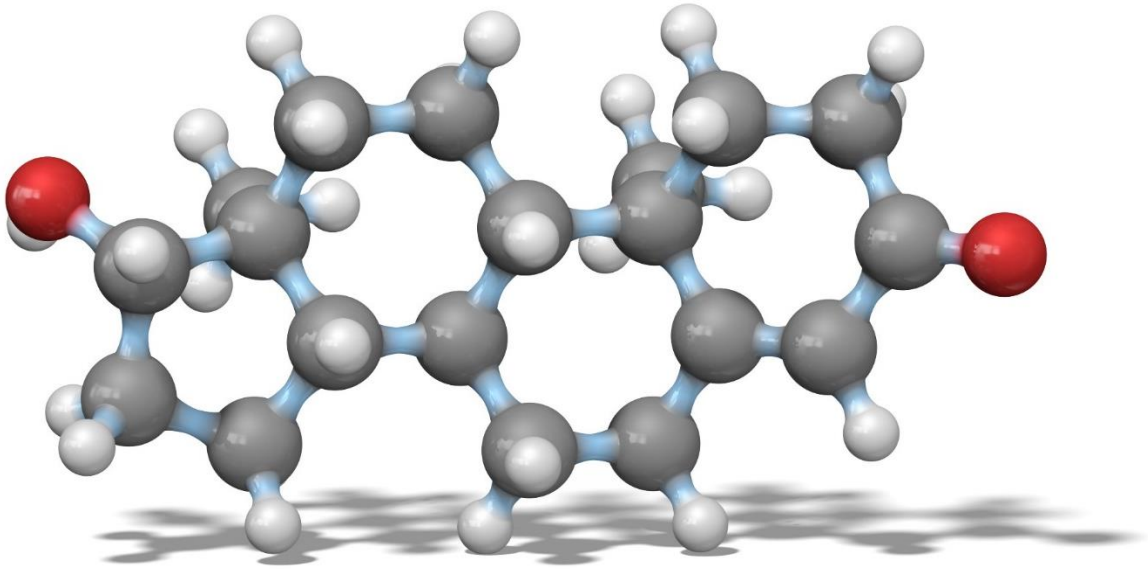
LP3 NETWORK™

FUNCTIONAL AND PERSONALIZED HORMONE RESTORATION THERAPY

HOME STUDY



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Dr. Tara Scott graduated from Northeast Ohio University College of Medicine and completed her residency with Summa Health Systems at Akron City Hospital in Ohio. She recently "retired" from OB/GYN after almost 20 years to focus on functional and integrative medicine. She is a Clinical Associate Professor at Northeast Ohio Medical University, where she teaches residents and is involved in clinical research.

Dr. Scott is a certified menopause practitioner with the North American Menopause Society and a fellow of the American College of Obstetrics and Gynecology. She first became involved with hormone and integrative medicine while practicing as an OB/GYN. Her empathy for patients experiencing hormone-related issues led her to become trained as an advanced fellow and certified by the American Academy of Anti-Aging Medicine. The evidence-based practices she employed helped many patients conquer chronic wellness issues. She then started Revitalize Medical Group, where she serves as the Chief Medical Officer. In 2016 she obtained an additional board certification in Integrative Medicine. Dr. Scott is passionate about educating the medical community on the advances in evidence-based hormone therapy. She lectures around the community to raise awareness about wellness and hormone balance.

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Dr. Ken Speidel is recognized for his broad experience in pharmacy practice and education, including his national recognition as a pharmacotherapeutic specialist in endocrinology and pain management. In addition, Dr. Speidel provides expert training in sterile and non-sterile compounding processes in the acute care, community, outpatient, and 503A/503B practice sectors. He has been instrumental in the development of national standards for pharmacy compounding practices and provides consulting services to many organizations including boards of pharmacy as well as hospitals and health systems in the United States and abroad.

In addition to his worldwide consulting and educational work, Dr. Speidel is a retired Professor of Pharmacy Practice from the University of Findlay. He has also assisted in the development and facilitation of many nationally recognized educational programs, approved by the Accreditation Council for Pharmacy Education (ACPE). Moreover, Dr. Speidel was an advisor for the development of the Pharmacy Compounding Accreditation Board (PCAB) and remains a surveyor and accreditation expert for PCAB/ACHC (Accreditation Commission for Health Care). Dr. Speidel has served as multi-term president of the National Home Infusion Association (NHIA) as well as president of the Hospice of Portage, a large hospice program in the United States.

Dr. Speidel received a Bachelor of Science and Doctor of Pharmacy from Ohio Northern University and has completed postdoctoral training in nutritional support and functional medicine. He has been awarded Fellowship status with the International Academy of Compounding Pharmacists (IACP) as well as the American College of Apothecaries (ACA).

Accreditation

Pharmacists

Total CPE Credits: **25 CPE Hours** = 2.5 CEUs

Home Study: Knowledge-based
Home Study UAN: 0012-9999-17-212-H07-P
Home Study CPE credits: 9 CPE hours = 0.9 CEUs
Release date: August 1st, 2017
Expiration date: August 1st, 2020

Live Activity type: Practice-based
Live activity UAN: 0012-9999-17-212-H07-P
Live Activity CPE credits: 16 CPE hours = 1.6 CEUs
Release date: August 1st 2017
Expiration date: August 1st, 2020

UF College of Pharmacy UNIVERSITY of FLORIDA

The University of Florida College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Completion Requirements

1. Complete home study learning assessment with a score of 70% and submit a completed home study evaluation online.

2. Attend the live component in full (sign-in and sign-out on each day) and demonstrate satisfactory participation.

3. Submit a completed live activity evaluation online.

4. When the aforementioned steps have been completed and approved:

- Participants registered in the United States: The University of Florida College of Pharmacy (UFCOP) will report CPE credits to the CPE Monitor. A paper copy of a statement of credit may be obtained from your NABP e-profile. For participants registered in the state of Florida, UFCOP will report credits to CE Broker.

- Participants registered other than in the United States will receive a statement of credit by email.

International participants should verify with their respective governing board for accreditation equivalency

Naturopathic Doctors

Ontario

For members of the College of Naturopaths of Ontario (CONO)
Live Event: **15.5 Category A Credits (12 Pharmacology)**

The College of Naturopaths of Ontario

Completion Requirements

1. Completion of home study is not required to receive Category A Credits. It is the participant's responsibility to contact LP3 Network to bypass online home study (required by default).
2. Attend the live component in full (sign-in and sign-out on each day) and demonstrate satisfactory participation.
3. Submit a completed live activity evaluation online.
4. When completed/approved, participants will be sent an email to access their Category A Credit certificate online. It is the participant's responsibility to submit the certificate to CONO to claim credits.

Home Study: **Category B Credits**

Application process:

It is the participant's responsibility to determine whether or not this self-directed home study (9-hour activity) falls within the scope of practice and relates to the clinical competencies of the profession. For more information on attaining self-directed Category B Credits, please see the College's website.

British Columbia

For members of the College of Naturopathic Physician
Live Event: **15.5 Category A Credits (12 Pharmacology)**

COLLEGE OF NATUROPATHIC PHYSICIANS OF BRITISH COLUMBIA

Completion Requirements

1. A maximum of 10 Category F CE Hours can be claimed every 2 years. Therefore, completion of home study is optional*. It is the participant's responsibility to contact LP3 Network to bypass online home study (required by default).
2. Attend the live component in full (sign-in and sign-out on each day) and demonstrate satisfactory participation.
3. Submit a completed live activity evaluation online.
4. When completed/approved, participants will be sent an email to access their Contact Hours certificate online. It is the participant's responsibility to submit the certificate through CNPBC's Registrant Online Self-Service system to report CE hours.
   **Additional CE hours accrued from live activity or from home study (if completed) can be applied to other continuing education categories, as appropriate.*

Physicians

American Physicians: On their own accord, they may assess this activity for its educational value and learning experience in order to determine if this activity is appropriate for claiming AMA PRA Category 2 Credits™ under the American Medical Association (AMA) Physician's Recognition Award (PRA) and credit system.

Canadian Physicians: Physicians of the College of Family Physicians of Canada (CFPC) may be able to claim Mainpro-M2 credits for self-directed or non-CFPC-accredited learning activities (i.e., programs that are not Mainpro-M1 or Mainpro-C accredited).

Declarations and Disclosures

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Activity Description

The roles that hormones play in body physiology and pathology are intricate, complex, and multifaceted. These communicatory molecules are central players in the maintenance and regulation of multi-organ systems and functions, including digestion, metabolism, sexual reproduction, lactation, growth, development, sleep, and stress, among much more. Hormonal actions are specific as well as interactive and diverse. With their critical roles in whole-body homeostatic maintenance, even the most subtle deviation in hormonal levels has the potential to produce vast multi-system changes that can clinically emerge as a variety of symptoms. To further complex the matter of hormonal systems, there exists substantial variations in individual hormone levels required for maintaining individual set-points. What may be normal for one, may be abnormal for another.

The intent of this home study component is to review clinical, physiological, and pharmacological principles pertinent to hormone restoration therapy. This includes endocrine organs and hormone functions, female and male reproductive systems, adrenal and thyroid functions and dysfunctions, and fundamental principles and personalized approaches applied in hormone restoration therapy. To complement material found in this home study, participants will be referred to four supplementary readings that provide current empirical evidence on hormone system dysfunctions and opportunities for customized care. To ensure competency and satisfactory understanding of the material discussed in this activity, participants will complete a learning assessment that tests their knowledge on material discussed in this manual as well as the material discussed in the four supplementary readings. Completion of this home study activity will provide participants with the fundamental basis upon which the live component of this program is based. It is encouraged that the participant well review this material prior to attending the live component so that the live component can focus largely on clinical decision-making processes and personalized therapeutic opportunities in the form of case studies and interactive activities. This will maximize the learning experience and ultimate competency of the participant.

Learning Outcomes of Home Study Activity

1. Review hormones and hormone system functions.
2. Describe the hormone cascade.
3. Explain female and male reproductive hormone system lifecycles.
4. Discuss and evaluate the risks and benefits of hormone restoration therapy.
5. Review adrenal system functions and dysfunctions related to chronic stress and adrenal insufficiency.
6. Review thyroid system functions and dysfunctions related to hypothyroidism.
7. Recognize the fundamental principles and personalized approaches of hormone restoration therapy.

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SECTION I: Hormones and Hormone System Function

Abbreviations

- Adrenocorticotropic Hormone (ACTH)
- Corticotropin-releasing Hormone (CRH)
- Cortisol (C)
- Estrone (E1)
- Estradiol (E2)
- Estriol (E3)
- Dehydroepiandrostenedione (DHEA)
- Dihydrotestosterone (DHT)
- Follicle Stimulating Hormone (FSH)
- Gonadotropin-releasing Hormone (GnRH)
- Insulin (I)
- Luteinizing Hormone (LH)
- Progesterone (P)
- Testosterone (T)
- Thyroid (Th)
- Thyroid Stimulating Hormone (TSH)
- Thyroxine (T4)
- Thyroxine Binding Globulin (TBG)
- Thyroxine Binding Pre-albumin (TBPA)
- Triiodothyronine (T3)
- Sex Hormone Binding Globulin (SHBG)

Hormones

Adrenocorticotropic Hormone (ACTH):

- Synthesized and secreted by the anterior pituitary
- Stimulates glucocorticoid and mineralocorticoid and androgen synthesis and release from adrenocorticoid cells

Aldosterone:

- Synthesized and secreted by the adrenal cortex
- Mineralocorticoid
- Regulates salt and water balance

Androgens (DHEA and T):

- Synthesized and secreted by the adrenal cortex and testes
- Masculinization effect in men and women

Androstenedione:

- Synthesized and secreted by the ovary
- Substrate for estrogen

Corticotrophin Releasing Hormone (CRH):

- Synthesized and secreted by the hypothalamus
- Simulate ACTH release from anterior pituitary

Cortisol:

- Synthesized and secreted by the adrenal cortex
- Acts as an anti-inflammatory
- Maintains blood sugar levels, blood pressure and muscle strength
- Helps regulate salt and water balance

Epinephrine or Adrenaline:

- Synthesized and secreted by the adrenal medulla
- Fight or flight response
- Increases heart rate
- Increases oxygen and glucose to brain and muscles
- Suppresses non-emergency bodily processes
- Suppresses immune system

Estrogen:

- Predominately synthesized and secreted by the ovaries
- Promotes formation of secondary sex characteristics
- Accelerates height, growth and metabolism
- Burns fat
- Reduces muscle mass
- Increases uterine growth
- Reduces bone resorption
- Increases bone formation

Follicle Stimulating Hormone (FSH):

- Synthesized and secreted by the anterior pituitary
- Stimulates follicular growth in ovaries
- Male: Stimulates spermatogenesis, maturation of seminiferous tubules, and production of androgen binding protein from sertoli cells of testes

Glucagon:

- Synthesized and secreted by the pancreas
- Glycogenolysis and gluconeogenesis in liver
- Increases blood glucose level

Gonadotropin-releasing Hormone (GnRH):

- Synthesized and secreted by the hypothalamus
- Stimulates FSH release from anterior pituitary
- Stimulates LH release from anterior pituitary

Growth Hormone:

- Synthesized and secreted by the anterior pituitary
- Stimulates growth and cell reproduction
- Stimulates insulin-like growth factor 1 release from liver

Growth Hormone Releasing Hormone:

- Synthesized and secreted by the hypothalamus
- Stimulates GH release from anterior pituitary

Inhibin:

- Synthesized and secreted by the ovaries and testes
- Inhibits production of FSH

Insulin:

- Synthesized and secreted by the pancreas
- Regulates intake of glucose, glycogenesis and glycolysis in liver and muscle from blood
- Regulates intake of lipids and synthesis of TG in adipocytes

Luteinizing Hormone (LH):

- Synthesized and secreted by the anterior pituitary
- Stimulates ovulation and formation of corpus luteum
- Stimulates testosterone synthesis

Melatonin:

- Synthesized and secreted by the pineal
- Antioxidant
- Monitors circadian rhythm and induces drowsiness

Norepinephrine or noradrenaline:

- Synthesized and secreted by the adrenal medulla
- Fight or flight response
- Increases skeletal muscle readiness

Progesterone:

- Synthesized and secreted by the ovaries and adrenals
- Supports pregnancy
- Raises epidermal growth factor 1 levels
- Increases core temperature during ovulation
- Relaxes smooth muscle
- Reduces gall bladder activity
- Normalizes blood clotting and vascular tone
- Assists in thyroid function

Testosterone:

- Synthesized and secreted by the testes
- Anabolic growth of muscle mass and strength
- Increased bone density
- Virilization: Maturation of sex organs, deepening of voice, growth of beard and axillary hair

Thyroid Releasing Hormone (TRH):

- Synthesized and secreted by the hypothalamus
- Stimulates TSH release from anterior pituitary

Thyroxine (T4):

- Synthesized and secreted by the thyroid
- Less active than T3
- Stimulates body oxygen and energy consumption increasing basal metabolic rate
- Stimulates RNA polymerase I and II, promoting protein synthesis

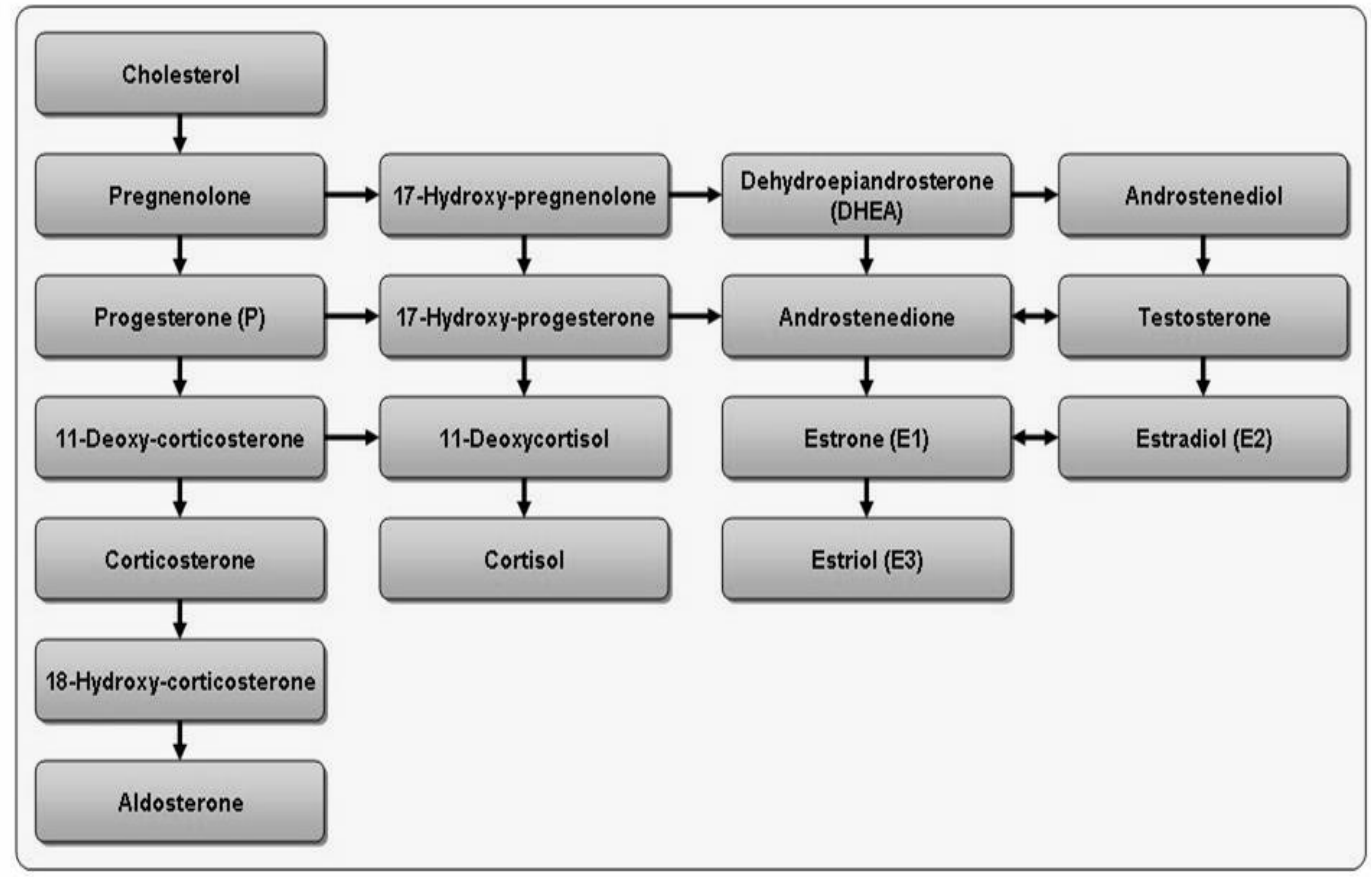
Triiodothyronine (T3):

- Synthesized and secreted by the thyroid and by extra-thyroidal tissue
- More potent than T4
- Stimulates body oxygen and energy consumption increasing basal metabolic rate
- Stimulates RNA polymerase I and II, promoting protein synthesis

Thyroid Stimulating Hormone (TSH):

- Synthesized and secreted by the anterior pituitary
- Stimulates T4 and T3 synthesis and release from thyroid gland

The Hormone Cascade



All hormones originate from cholesterol and the enzyme pathway that is chosen will determine the end product. Pregnenolone, often referred to as the “mother of all hormones”, has the potential to turn into almost any hormone. Depending on the local environment, the enzymes present, and the current bodily demands, certain pathways will be favored over others. For example, the production of sex steroids is favored in the gonads, with particular preference for estrogen synthesis in the ovaries where aromatase levels are in abundance. Interestingly, during times of stress, cortisol synthesis will be favored at the cost of reducing the synthesis and production of sex steroid hormones, highlighting ways in which dynamic demands on the body can sway the hormone cascade into one direction over another.

The Endocrine Organs

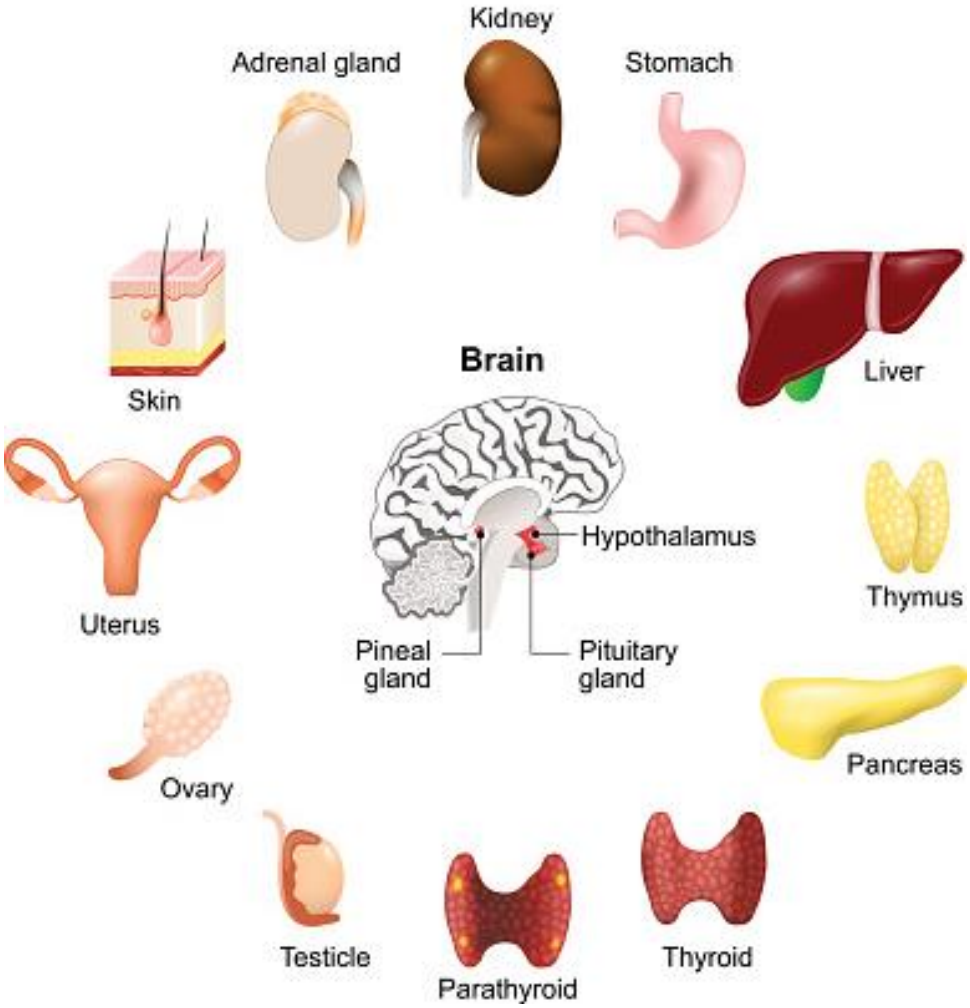


Figure 1. The endocrine organs

Pituitary Function:

- Acts on other target glands or cells influencing growth, metabolism and regeneration

Pineal Function:

- Produces melatonin
- Regulates sleep cycles and normal circadian rhythm
- Associated with premature puberty and hypogonadism

Hypothalamic Function:

- Interface area of the brain and body where electrical signals meet endocrine hormones
- Controls metabolism (energy regulation system), immunity, reproduction, growth, and breakdown of tissue
- Many people refer to the pituitary as the master gland, but the hypothalamus is the real master, it actually controls the secretions of the pituitary gland.

Thyroid Function:

- Requires iodine to produce triiodothyronine (T3) and thyroxine (T4)
- T3 and T4 are released into the blood stream attached to TBG
- Controls metabolism
- Carbohydrate calories appear to be the primary determinant of T3 levels in adults
- During stress, the body produces more reverse T3 and less T3, and metabolism slows

Adrenal Function:

- Produces three hormones; cortisol, aldosterone and dehydroepiandrosterone
- Plays a major role in how we feel; too little causes adrenal insufficiency and too much causes elevated blood sugar, inflammation, and changes in metabolism
- Two functions; one part focuses on immediate stressors, the other on homeostasis and delayed onset stressors

  Impact of Stress on body:

  - If our body is stressed epinephrine, nor-epinephrine and cortisol are produced in order to protect it
  - When the body is subjected to a fast paced lifestyle, you have perceived stress and adrenals will make too much cortisol
  - This steals from the other sex hormones and can cause imbalances.
  - This type of imbalance can be associated with hypertension, Addison's disease, Cushing's syndrome, congenital adrenal hyperplasia, adrenal fatigue

Pancreatic Function:

- The pancreas has an exocrine function (digestion) and an endocrine function which is involved in storage and retrieval of glucose, amino acids, and triglycerides. It regulates hunger, thirst, sleep, and wakefulness and most involuntary mechanisms including body temperature. It produces insulin and glucagon and is involved in normal glucose and cholesterol control. It is associated with Diabetes.

SECTION II: Female Reproductive System Functions and Imbalances

The female human life cycle can be divided up into five primary stages that are described below:

Stage 1 – Childhood and Adolescence

- The time between childhood and puberty
- Central influences prevent the release of gonadotropin-releasing hormone during childhood
- Stimulation by the adrenal androgens dehydroepiandrosterone and DHEA sulfate result in onset of female secondary sex characteristics several years before puberty

Stage 2 – Premenopause

- The time between female puberty and perimenopause
- The increase in release of gonadotropin-releasing hormone promotes release of pituitary gonadotrophins; follicle stimulating hormone and luteinizing hormone
- Hypothalamus releases gonadotropin-releasing hormone resulting in an increase in estrogen and progesterone production promoting production of several sex hormones; primarily estrogen
- Estrogen stimulates further development of secondary sexual characteristics
- Gonadotropin-releasing hormone stimulates ovarian development and initiates menarche
- Menarche is the beginning of monthly menses; the beginning of a woman's reproductive life

The Menstrual Cycle

The menstrual cycle can be divided into three phases:

- Follicular Phase
- Ovulation
- Luteal Phase

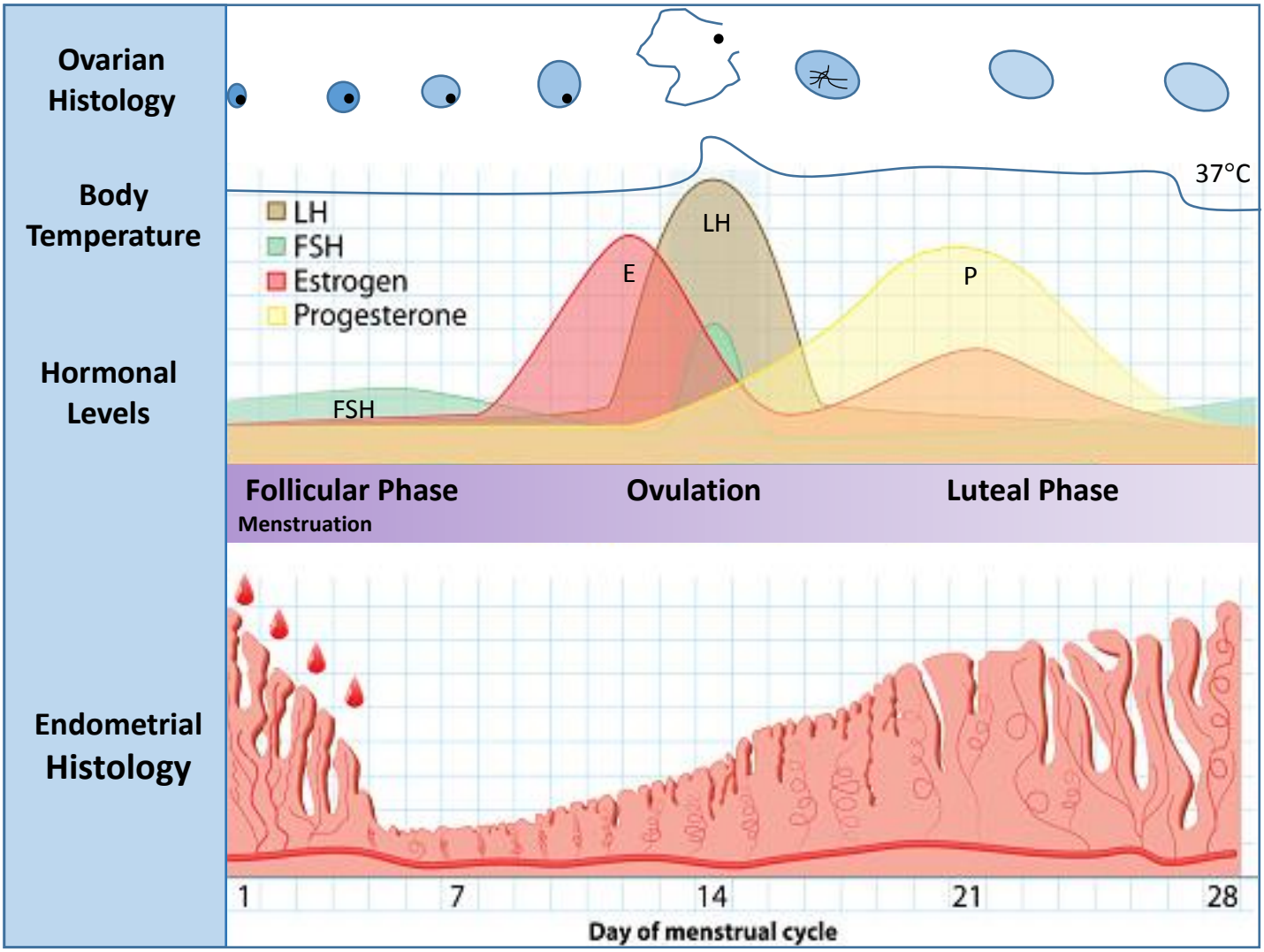


Figure 2. The menstrual cycle

Follicular Phase

- Represents the first half of the menstrual cycle
- Early in the follicular phase, the primary activity is the growth of recruited follicles
- Initially in this phase the cells in the pituitary contain little follicle stimulating hormone and luteinizing hormone due to low gonadotropin-releasing hormone stimulation from the hypothalamus resulting in low estrogen and progesterone production
- Because of low follicle stimulating hormone levels theca cells within the follicle, heavy with luteinizing hormone receptors, produce androgens which are aromatized to estradiol within the granulose cells
- Due to low estrogen levels overall follicle stimulating hormone secretion increases slightly, stimulating growth of recruited follicles
- Circulating luteinizing hormone levels increase slowly, beginning 1 to 2 days after the increase in follicle stimulating hormone.
- Recruited ovarian follicles soon increase production of estradiol which stimulates follicle stimulating hormone and luteinizing hormone synthesis in the pituitary, but inhibits their secretion
- Later in the follicular phase, the follicle is selected for ovulation on approximately day 5 to 7, matures and enlarges reaching 18 to 20 mm before ovulation
- Follicle stimulating hormone is withdrawn from non-maturing follicles leading to their demise
- Levels of follicle stimulating hormone in serum and follicles decrease, but luteinizing hormone levels are less affected.
- Follicle stimulating hormone and luteinizing hormone levels diverge partly because estradiol inhibits follicle stimulating hormone secretion more than luteinizing hormone secretion
- Granulosa cells in the developing follicles produce inhibin further inhibiting follicle stimulating hormone secretion, but not luteinizing hormone secretion
- Continued increases in estradiol eventually induces a luteinizing hormone surge signaling the beginning of the ovulatory phase

Ovulation

- Ovum release occurs
- Estradiol levels usually peak as ovulation begins, and eventually declines
- Stored luteinizing hormone in the pituitary is released due to high estradiol levels in massive amounts; luteinizing hormone surge
- Luteinizing hormone surge lasts between 36 to 48 hours with a much smaller increase in follicle stimulating hormone
- Luteinizing hormone surge is also stimulated by hypothalamic gonadotropin-releasing hormone and progesterone
- Once the luteinizing hormone surge has begun, estradiol levels decrease, but progesterone levels continue to increase
- Approximately 16 to 32 hours after the luteinizing hormone surge, enzymes are released initiating breakdown of follicle wall and release the now mature ovum
- The ovum release signifies the ends the ovulatory phase

Luteal Phase

- The remaining dominant follicle minus the ovum is transformed into a corpus luteum
- Progesterone is produced by the corpus luteum
- The corpus luteum secretes primarily progesterone in increasing quantities, peaking at about 25 mg / day for 6 to 8 days after ovulation
- Progesterone stimulates development of the secretory endometrium necessary for embryonic implantation
- Progesterone is thermogenic, resulting in an average increase in basal body temperature of 0.5° C for the duration of phase
- Progesterone acts centrally and within the ovary to suppress new follicle growth
- Because levels of circulating estradiol, progesterone, and inhibin are high during most of the luteal phase, follicle stimulating hormone and luteinizing hormone levels decrease and progesterone levels decrease late in this phase
- In the case of pregnancy, the corpus luteum regresses and human chorionic gonadotropin maintains luteal function
- In the absence of conception, the corpus luteum regresses resulting in a decrease in estradiol, progesterone, and inhibin
- The decrease in estrogen and progesterone production decreases in the development of the lining of the uterus
- The hormone drop also increases gonadotropin-releasing hormone pulses, thus increasing follicle stimulating hormone which signals the start of a new cycle and recruitment of new follicles

Stage 3 – Perimenopause

- The time between premenopause and menopause; referred to as menopause transition.
- Ovaries demonstrate a decreased response to follicle stimulating hormone and luteinizing hormone with age resulting in a shorter follicular phase; shorter and more irregular menstrual cycles and fewer ovulations
- Fewer ovulations cause substantial decreases in progesterone synthesis due to a decrease in follicle response and maturation, and corpus luteum generation
- Decreases in progesterone result in excess or dominance of estrogen activities
- Over time, follicular estradiol production and ovarian production of inhibin decreases to a threshold that no longer suppresses release of pituitary secretion of follicle stimulating hormone and luteinizing hormone
- Extra-gonadal synthesis of estrogen, predominantly estrone, via androgen conversion is increased
- Changes prior to, and during perimenopause include:
    - Most good quality follicles are gone
    - Hormone production from remaining ovum is decreased
    - Number of ovarian follicles decreases due to atresia
    - Inhibin B levels fall
    - Follicle stimulating hormone levels rise; response to stimulate remaining follicles to respond
    - Menstrual cycles are characterized by erratic hormone production and irregular cycle frequency, increasing estrogen and declining progesterone (i.e., estrogen dominance)
    - Over time, cycles become more irregular as remaining follicles respond poorly to follicle stimulating hormone
- During perimenopause the following symptoms are observed:
    - Lighter bleeding
    - Heavier bleeding
    - Bleeding lasting for < 2 days or for > 4 days
    - Cycle length < 7 days or > 28 days
    - Skipped menstrual periods
    - No changes at all

Stage 4 – Menopause

- End of the female's reproductive life
- Ovaries are unable to elicit a response to pituitary gonadotrophin stimulation
- Physiologic menopause is determined when menses have been absent for one year
- Premature ovarian failure is cessation of periods before age, but can be transient
- Note: Induced menopause can be due to medicine, usually chemotherapy or surgery

Hormone-specific changes related to menopause include:

Estrogen:

- Estrogen levels do not necessarily undergo a rapid drop immediately after menopause due to the fact that most women in North America are exposed to a lot of estrogen; water supply, commercially raised meat, poultry, seafood, pesticides, plasticizers, other chemicals
- Nutritional problems promote estrogen overload; increased consumption of refined carbohydrates leads to high insulin, and decreased whole food intake leads to nutritional deficiencies
- Environmental factors contribute to changes in the female lifecycle in the following manner:
    - Increased breast cancer
    - Earlier onset of breast cancer
    - Earlier onset of puberty
    - Higher average BMI

Progesterone:

- Progesterone drops drastically, often starting in the early 40's
- Most women in North America are stressed which further drains progesterone from increased adrenal stressors

Testosterone and DHEA:

- Testosterone and DHEA usually stay normal unless there is co-existing adrenal disease

Stage 5 – Postmenopause

- Begins 12 months after the female's last menstrual period
- Ovarian failure has occurred and sex hormone responsive tissues often display impaired activity

Evaluating the Risks of Female Hormone Restoration Therapy

A decade and half ago, the Writing Group for the Women's Health Initiative (WHI) published a randomized control trial on the "risks and benefits of estrogen plus progestin in healthy postmenopausal women" (WHI, 2002). Prior to this study, there were numerous observational reports claiming the protective effects of menopause hormone restoration therapy in terms of cardiovascular disease and mortality. Given these reports, the WHI wanted to explore these benefits further. To do so, over 16,000 postmenopausal women with an intact uterus aged 50 to 79, were randomly assigned to one of two conditions; conjugated equine estrogens (CEE), 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, or placebo control. Contrary to expectations, at the 5.2 year follow-up, the data and safety monitoring board stopped the trial due to increased risks of breast cancer, cardiovascular disease, stroke, and venous thromboembolism for participants receiving CEE and progestin.

In response to the WHI's 2002 findings, there was a rapid decline in the use of conventional menopause hormone restoration therapy and a rapid rise in the use of bioidentical hormones. With such a substantial shift in consumer demands in response to these unexpected findings, there has been much interest in delineating further the effects of menopause hormone restoration therapy on women's health. Although much remains to be determined, much of the research over the past decade reports that route of estrogen administration and synthetic versus bioidentical progesterone are major determinants as per the risks associated with hormones restoration therapy. These factors are explored in detail in the following required supplementary readings:

REFER TO SUPPLEMENTARY READING 1

Evidence-Based Medicine: Mohammed, K. et al. (2015). Oral vs. transdermal and vascular events: A systematic review and meta-analysis. *Journal of Clinical Endocrinology and Metabolism, 100,* 4012–4020.

**Competency specific to this reading will be assessed at the end*

CASE ASSESSMENT BASED ON READING 1

Amelia is a 47-year old lawyer who works in the city. She loves her job, but admits to occasionally smoking between court sessions to relieve some of the stress. She comes to the clinic complaining about frequent hot flashes and night sweats in addition to bouts of insomnia. After measuring her hormone levels, it is confirmed that she is perimenopausal. However, Amelia is concerned about initiating hormone replacement therapy (HRT) and the possible complications that may arise in association with her pre-existing hypertension.

What treatment regimen would you recommend?

Feedback:

A combination of estrogen and progestin hormone replacement therapy (HRT) is an effective form of treatment for the symptoms of estrogen deficiency in perimenopausal women. The precise regimen, dose, and route of administration can be tailored to suit individual needs and preferences, while minimizing certain risks.

Unlike orally administered hormones that must first be metabolized by the liver before entering systemic circulation, transdermal HRT avoids first-pass metabolism, contributing to a decreased risk of vascular complications. Amelia, who has pre-existing hypertension, is a good candidate for transdermal HRT. This route is the treatment of choice for a variety of medical conditions, such as diabetes, hypertension, and obesity as it is associated with lower thromboembolic and cardiovascular risks. Moreover, symptoms can be properly managed by adjusting the dose accordingly.

In addition to HRT, Amelia may benefit from some lifestyle changes such as regular physical exercise, relaxation techniques, and smoking cessation.

REFER TO SUPPLEMENTARY READING 2

Evidence-Based Medicine: Asi, N. (2016). Progesterone vs. synthetic progestins and the risk of breast cancer: A systematic review and meta-analysis. *Systemic Reviews, 5, 121*

**Competency specific to this reading will be assessed*

CASE ASSESSMENT BASED ON READING 2

Francine is a 53-year old menopausal woman who began combined oral estrogen and progestin HRT and has experienced tremendous relief in her vasomotor symptoms. However, she returns frantically to your office one year later after learning that her sister was diagnosed with breast cancer. She read online that HRT increases risk of breast cancer and wants to know if there is anything else that you can prescribe her.

What would you suggest?

Feedback:

The combination of estrogen with a progestogen is typical of HRT in women with an intact uterus to prevent endometrial hyperplasia and cancer. Various synthetic progestins are commonly used in HRT, however, they have a different chemical structure and pharmacokinetics than endogenous progesterone. Alternatively, micronized progesterone is a bioidentical hormone with a molecular structure identical to progesterone produced by the ovaries.

Although Francine may have read online that HRT increases the risk of breast cancer, the risk depends more heavily on the type of HRT used. Risk of breast cancer varies between regimens and is more strongly associated with the use of progestins, with some variations of progestins exhibiting greater risks than others. Contrarily, progesterone in combination with estrogen has not been shown to increase the risk of breast cancer. It would therefore be recommended for Francine to switch the type of HRT from synthetic progestin to micronized progesterone.

SECTION III: Male Reproductive System Functions

The male human reproductive life cycle can be divided up into four primary stages that are described below:

Stage 1 – Pre-pubescence

- The time from birth to adrenarche
- Central influences prevent the release of GnRH during childhood
- Testosterone levels remain low until puberty
- The pituitary hormones LH and FSH remain low or undetectable throughout pre-pubescence

Stage 2 – Adrenarche

- Begins approximately two years prior to puberty
- Adrenal androgen's dehydroepiandrosterone (DHEA) and DHEA sulfate begin to manifest male secondary sex characteristics, but not spermatogenesis, several years before puberty
- Testes are unable to elicit a response to pituitary gonadotrophin stimulation

Stage 3 – Puberty

- Beginning of male reproductive life
- Hypothalamus releases gonadotropin-releasing hormone to the pituitary gland
- Gonadotropin-releasing hormone causes the pituitary gland to produce gonadotropins; follicle-stimulating hormone and luteinizing hormone
- Luteinizing hormone triggers production of testosterone from cholesterol in the testes
- Testosterone production process continues until the testosterone level becomes too high; then the pituitary slows the release of luteinizing hormone to slow testosterone production
- Follicle-stimulating hormone is similarly involved in the increase and decrease in sperm production
- Secretion of follicle-stimulating hormone and luteinizing hormone initially increase during sleep, but later increase throughout the 24-hour period
- Under the influence of testosterone, the male genitalia enlarge and cells in the testes begin the process of spermatogenesis

Stage 4 – Andropause

- Beginning of the end of the male's virility, but not necessarily fertility
- Hypothalamic secretion of gonadotropin-releasing hormone and the response of the testes to follicle-stimulating hormone and luteinizing hormone diminish with age resulting in lower testosterone production
- SHBG levels increase with aging, causing an even greater decline in serum free and bio-available testosterone
- Extra-gonadal synthesis of testosterone increases, but can rarely meet active needs
- Decreases in lean body weight and increases in visceral adipose can increase estrogen synthesis via the aromatization of androgens
- Follicle-stimulating hormone and luteinizing hormone levels tend to remain the same or higher

CASE ASSESSMENT BASED ON SECTION III

Henry, a 39-year old male patient, is experiencing mild erectile dysfunction (ED), a lower sex drive than before, and a lack of energy. On top of that, he has begun to put on excess weight. He is newly single and dating, but his symptoms are giving him anxiety. Although he is not yet ready to settle, he hopes to have kids in the future. He presents himself to you seeking treatment.

How would you proceed?

Feedback:

Proper labs should be drawn to determine the underlying cause of his symptoms. It would be beneficial to measure total testosterone levels in addition to determining the amount of bound/inactive testosterone and free/unbound testosterone in the bloodstream. Other measured hormone levels typically include DHEA, FSH, LH, and estradiol.

Ideal HRT produces and maintains physiologic serum concentrations, while minimizing the risks of adverse effects. There are different variations of synthetic testosterone, doses, and routes of administration that can be adapted to suit the patient's needs, each with a unique set of properties and method of action. High doses of testosterone are associated with increased aggression, depression, and infertility. It is important to be mindful of the fact that Henry wishes to have kids one day when determining his treatment dose.

SECTION IV: Adrenal System Functions and Dysfunctions

This section of the self-study briefly addresses adrenal functions and dysfunctions. It is intended to afford the reader the opportunity to understand established relationships between organ system functions and related hormone levels; they being either too low or too high. A significantly greater level of detail, the inter-relationship between systems and specific hormones, and treatment options will be addressed in the live component of this practice-based activity.

The Physiological Stress Response

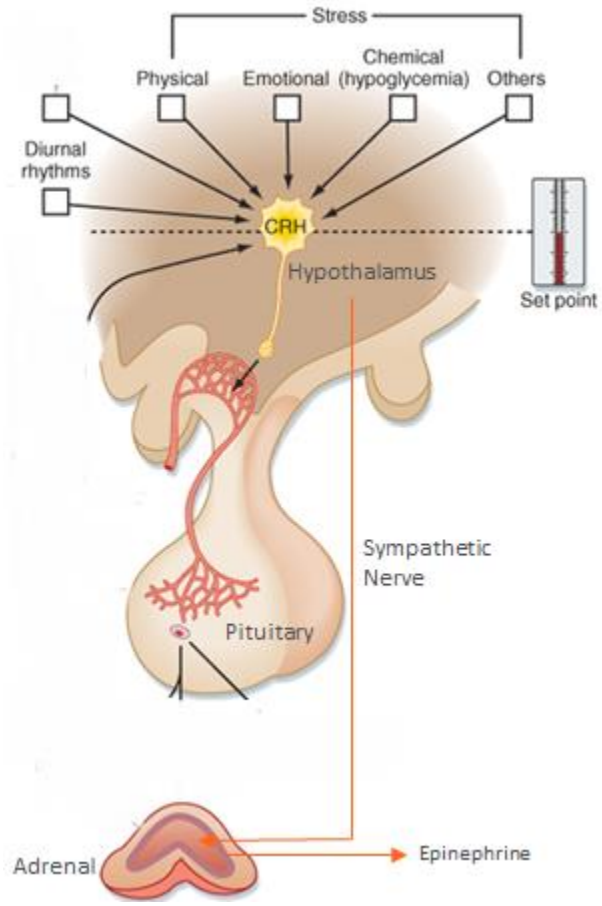


Figure 3. The Sympathetic-Adrenal-Medullary (SAM) Axis

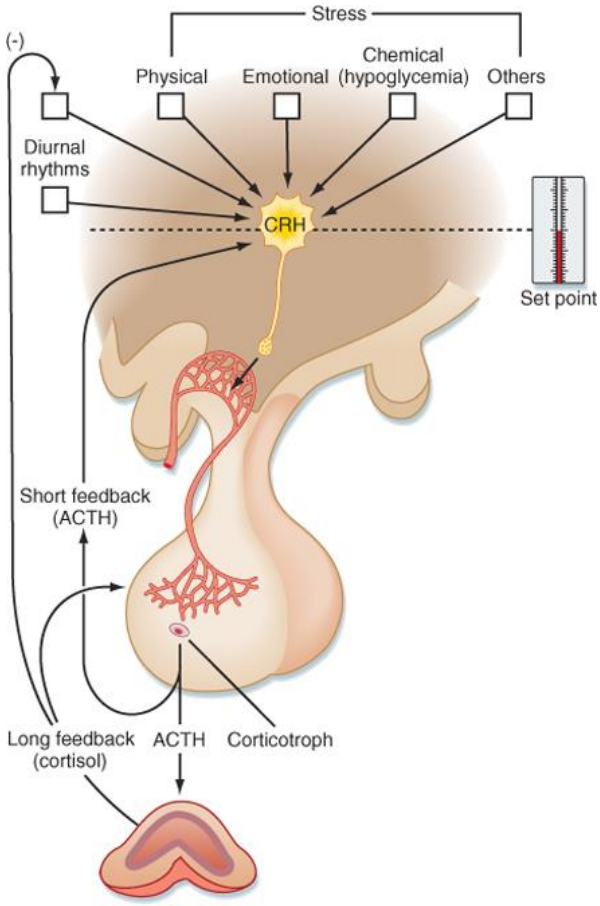


Figure 4. The Hypothalamic-Pituitary-Adrenal (HPA) Axis

The stress response is a necessary and adaptive physiological response system that mobilizes the body to respond to intrinsic and extrinsic stressors (Melmed et al., 2015; Tsigos & Chousos, 2002). This intricate and well-coordinated system is necessary for ensuring survival of the species (i.e., food intake, sexual reproduction, maternity/paternity behavior, avoidance of danger and threat, among much more) and is initiated and maintained by two systems:

- Sympathetic-adrenal-medullary (SAM) axis: Fast and quick response system
- Hypothalamic-pituitary-adrenal (HPA) axis: Slow and longer lasting response system

General Adaptation Model

Coined by Hans Selye in 1936 the General Adaptation Syndrome model outline three stages of the stress response (Selye, 2013):

Stage 1 – Alarm Reaction:

- The *alarm reaction* stage refers to the body's initial reaction to a perceived stressor, as interpreted by the hypothalamus, which is responsible for integrating intrinsic (e.g., deviations in homeostatic set points) and extrinsic (e.g., external threats) information. When a stress is perceived, the hypothalamus rapidly initiates and coordinates the stress response through the activation of the SAM and HPA axes.

- The **SAM axis** is the rapid and quick response system responsible for 'fight or flight' (e.g., why you jump/startle when there is a loud noise). In this system, the hypothalamus activates descending sympathetic efferent nerve fibers, which innervate peripheral organs to stimulate changes adapted for stress (e.g., pupil dilation, increased HR, increased BP, etc.). These adaptive responses are further potentiated with the sympathetic activation of the adrenal medulla, which causes the secretion of epinephrine/norepinephrine that further stimulate peripheral organs (Tsigos & Chousos, 2002).

- The **HPA axis** is the slower, but longer lasting response system that predominately functions to mobilize energy storages (i.e., fat reserves, protein reserves, and carbohydrate reserves) that provide fuel to keep up with the demands on the body during a stressful situation. This is achieved through the coordinated chain of communications between the hypothalamus, pituitary, and adrenal cortex that ultimately results in pronounced secretion of glucocorticoids (e.g., cortisol – the 'stress' hormone) (Tsigos & Shousos, 2002).

- Together, this stage of the stress response is characterized by significant increases in the synthesis and secretion of epinephrine/norepinephrine and cortisol. This shift in hormone synthesis is paired with drops in testosterone and DHEA levels.

Stage 2 – Resistance:

- During the *resistance* stage sympathetic arousal (i.e., SAM axis) subsides.

- HPA axis activity is maintained, cortisol levels remain elevated, and DHEA levels continue to drop. During this stage the body remains in a state of arousal as an adaptation to deal with potential lingering threats.

- Under adaptive circumstances, HPA activity is maintained acutely and shut down by cortisol negative feedback onto the hypothalamus and pituitary. Failure to shut down HPA activity results in chronic arousal that can lead to a state of exhaustion.

Stage 3 – Exhaustion:

- The *exhaustion* stage of the stress response is a maladaptive response characterized by chronic activation of the HPA axis. Chronic activation of the HPA axis ensues with repeated exposure to stressors and mechanistic failures to shut down this system.

- The sustained elevated cortisol levels over time can:
    - Destroy healthy muscle and bone
    - Slow down healing and normal cell regeneration
    - Impair digestion
    - Interfere with healthy endocrine function
    - Weaken the immune system
    - Compromise metabolism and add more weight around the middle

Cortisol

Cortisol, produced by the adrenal gland, can dominate many endocrine activities by virtue of its broad scope of activities. Examples of this broad scope include:

- Maintenance of blood pressure through aldosterone production (Toda, Nakanishi, & Tanabe, 2013)
- Maintenance of blood glucose levels during periods of stress by inducing gluconeogenesis and glycogenolysis (Cryer, Davis, & Shamoon, 2003)
- Reduction in bone mineralization (Henneicke, Gasparini, Brennan-Speranza, Zhou. & Seibel, 2014)
- Suppression of immune system (Henneicke et al., 2014)

Low cortisol levels are associated with (Phillips, Ginty, & Hughes, 2013):

- End stage adrenal disease
- Adrenal hyperplasia
- Anovulation
- Luteal phase defects
- Drug induced adrenal suppression
- Hypothyroidism

High cortisol levels are associated with:

- Early stage adrenal stress
- Hypoglycemia
- Hypertension
- Hypothyroidism
- Pituitary adenoma
- Pregnancy

High cortisol can cause a generalized resistance to hormone receptors resulting in the need to use more hormones to create the desired effect (Park & Ahima, 2015; Westphal, 1986). The hormones affected are:

- Insulin
- Thyroid
- Progesterone
- Testosterone
- Estrogen

High levels of cortisol in the brain can decrease estrogen's effect on cells in the central nervous system. This explains that when a woman encounters a high amount of stressful activity her cortisol raises which often causes a hot flash even though estrogen levels may be normal. Subsequently, the patient is treated with estrogen unnecessarily which often results in estrogen dominant-related symptoms.

Therefore, moderating cortisol release is imperative to effective hormone restoration. Having an excess amount of cortisol can inhibit many hormone activities.

Adrenal Dysfunctions

Chronic Stress

The body was designed with the adaptive stress response. The premise was that you would encounter some kind of stressor, usually life or death, and you would have the physiologic response to stress. The stress would be limited, and would usually be followed by a period of rest and recovery. For example, if you were a pioneer living in the frontier you could have encountered a wild animal. At that time, your body would get an adrenaline rush and would respond as detailed Stage 1 of the general adaptation model. The stress would pass – either the animal would kill you or you would escape – and usually life went on as normal in the frontier. You were sleeping a normal amount since there was no electricity, you would have been cooking all of your food and eating good quality foods, and you would be exercising doing the hard manual work that was common during that time period.

Fast forward now to present day. We live in a 24/7 era. We have 24-hour pharmacies and stores, shift work and processed food. Many people are sedentary. Our stress is not usually life or death, and it is most likely chronic. So we are bombarded by stress after stress; financial, emotional, physical, nutritional, and rarely have we the needed time for rest and restoration. So many people pass from Stage 1 through to Stage 3 of stress. The adrenal gland is not designed to keep up with that kind of chronic stress hormone production. It is even less able to without proper sleep and nutrition, which is common in modernized societies. Consequently, many individuals develop low adrenal function.

Adrenal Fatigue

While Addison's disease (i.e., hypo-adrenal function) and Cushing's disease (i.e., hyper-adrenal function) are well established and well recognized disorders, the remaining spectrum of adrenal dysfunctions remain largely overlooked (Guilliams & Edwards, 2010). This is particularly the case with adrenal fatigue. Adrenal fatigue is defined as a subclinical condition/phenomenon characterized by insufficient secretion of adrenal hormones (Allen, 2013). Stated otherwise, adrenal fatigue describes the spectrum of adrenal insufficiency that cannot be diagnosed as Addison's disease. By virtue of this concept, adrenal fatigue dispels the notion that adrenal dysfunctions can only be defined by one of two extremes (*refer to figure 10)*. Indeed, the idea that pathology falls along a continuum that is not constrained by extreme cut-offs is becoming increasingly recognized in many fields of medicine, endocrinology included. That being said, despite prevailing symptoms (e.g., fatigue, cognitive deficit, hormonal imbalance, inability to cope with stress, insulin resistance, recurrent infection, reduced libido, sleep disturbance, suppressed immune system, weakness, etc.) current blood tests are often unable to detect small declines in adrenal function (Allen, 2013; Guilliams & Edwards, 2010). Moreover, there are a plethora of different hormonal combinations that can be present with measuring cortisol four times a day, rendering this condition difficult to ascertain via serum measures alone. Consequently, patients are often left untreated or misdiagnosed with alternative conditions including depression, chronic fatigue syndrome, or fibromyalgia.

Although the mechanisms of action of adrenal fatigue remains unknown, the predominant theory argues that symptoms of adrenal fatigue emerge when the adrenal glands are unable to keep up with the demands of chronic stress. As previously reviewed, when a stress is perceived the hypothalamus initiates a chain of commands that eventually results in the secretion of adrenal cortical hormones, most notably, cortisol (Tsigos & Chousos. 2002). In the short-term, the heightened release of cortisol is a highly adaptive response that prepares the body to deal with the perceived threat. Failure to shut down this response in times of chronic stress, however, can result in sustained cortisol release that leads to an array of maladaptive physiological responses, including hyperglycemia, insulin resistance, and diabetes (Lee et al, 2013); immunosuppression (Dhabhar, 2009); hypertension, atherosclerosis, and cardiovascular disease (McEwan, 2004); increased risk for mental illness (McEwan, 2004); among much more. According to current theories, after a variable period of time (i.e., years) the adrenal glands are unable to keep up with the chronic secretion of cortisol imposed by chronic hyperactivation of the HPA axis (Guilliams & Edwards, 2010). Consequently, cortisol stores deplete inducing symptoms of hypocortisolism (i.e., adrenal fatigue).

REFER TO SUPPLEMENTARY READING 3

For a detailed clinical evaluation of the influence of chronic stress on HPA axis activity and overall health refer to the following required supplementary reading:

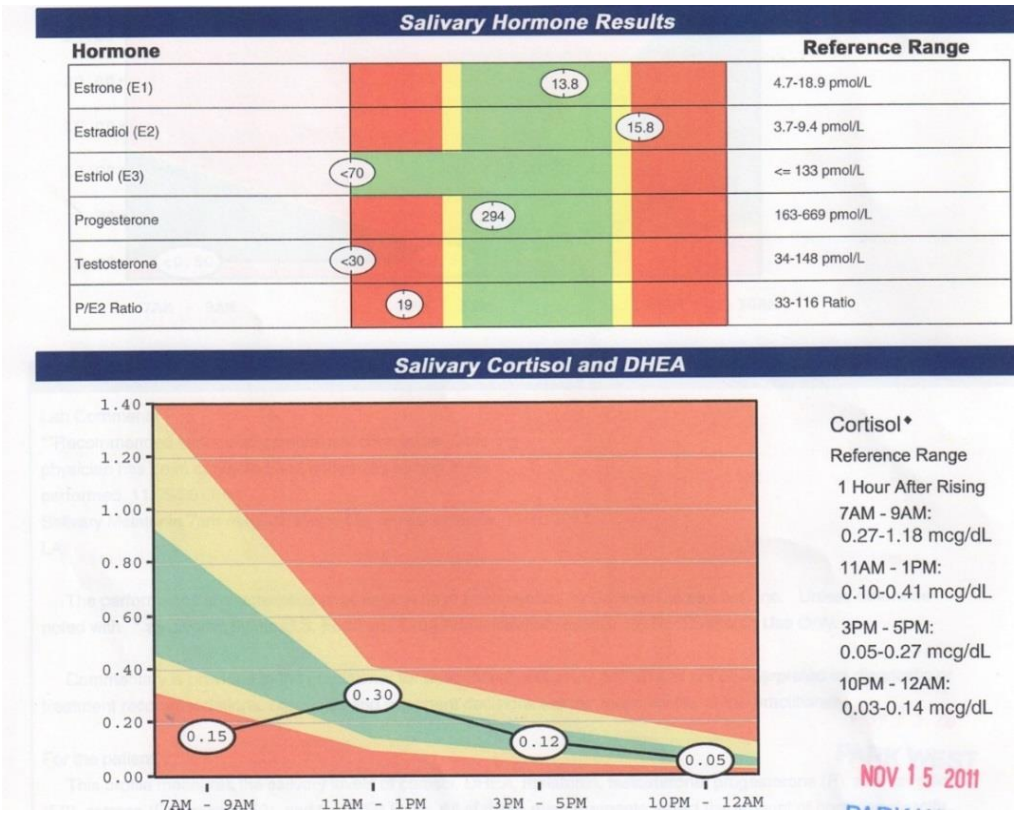
Evidence-Based Medicine: Guilliams, T.G. & Edwards, L. (2010). Chronic stress and the HPA axis: Clinical assessment and therapeutic considerations. *The Standard: A Review of Natural & Nutraceutical Therapies for Clinical Practice, 9.*

**Competency specific to this reading will be assessed*

CASE ASSESSMENT BASED ON READING 3

Monica is a 35-year old working mother of 4 children ages 10 and under. She is a free-lance editor and is able to work at home. Her main complaint is fatigue and lack of motivation. She has been very scattered and unable to concentrate on her work at home, constantly getting up to do laundry or dishes in the middle of working on a book. She complains of disrupted sleep, morning fatigue, mood swings, and breast tenderness.

The following are her most recent test results:



What treatment regimen would you recommend?

_____

_____

Feedback:

Monica's salivary hormone results indicate a low progesterone to estrogen ratio. A common first-line treatment for high estrogen levels is oral contraceptives, however, in this case, pursuing that line of treatment would provide the patient with synthetic hormones without addressing the underlying adrenal issues. Instead, cyclic progesterone would be useful in mitigating this hormone imbalance. In addition, vitamin B complex would be helpful in enabling the liver to more effectively metabolize estrogens. Vitamin B complex also supports adrenal function by serving as a co-factor in several enzymatic pathways in the adrenal cascade.

Monica's salivary cortisol and DHEA results reveal that she experiences low cortisol levels in the mornings. In adrenal fatigue, progesterone and pregnenolone levels may become reduced. Therefore, pregnenolone can be supplemented to help increase her morning energy, with some patients reporting an increase in mental clarity as well. Additionally, adrenal adaptogens can be selected based on her specific cortisol curve to help regulate cortisol and energy levels.

SECTION V: Thyroid System Functions and Dysfunctions

The Hypothalamic-Pituitary-Thyroid (HPT) Axis

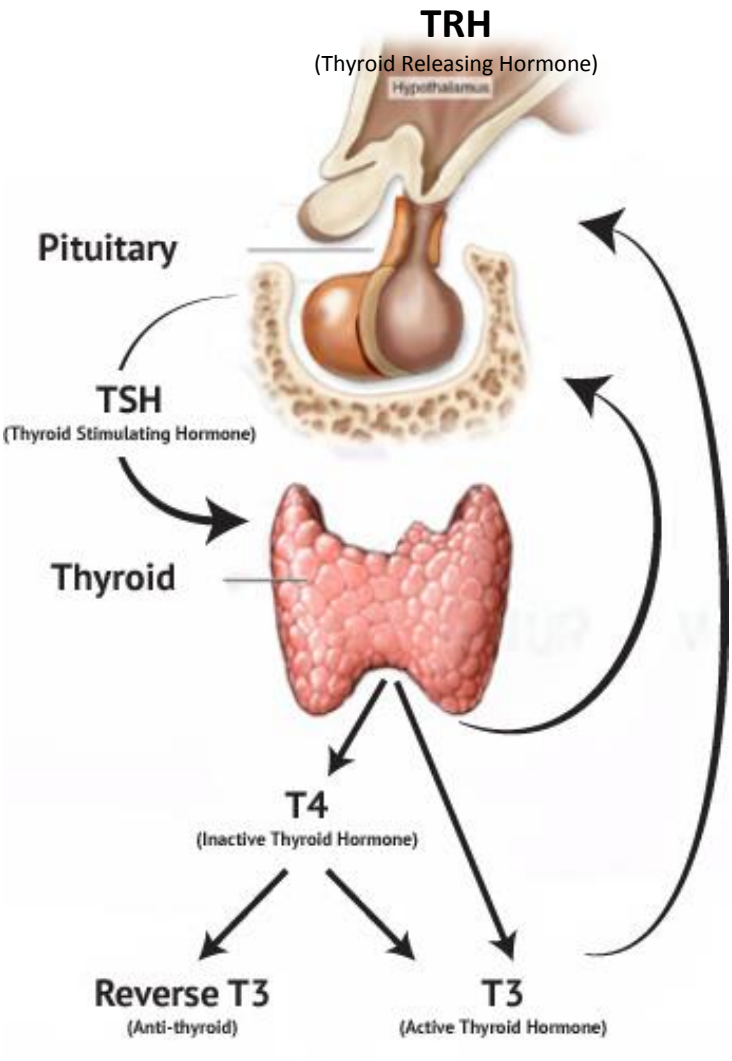


Figure 5. Hypothalamic-Pituitary-Thyroid axis

The **hypothalamic-pituitary-thyroid** (HPT) axis plays an integral role in maintaining metabolic homeostasis through a cascade of hormone signals and negative feedback loops.

At the beginning or center of this cascade is thyroid-releasing hormone (TRH), which is released by the hypothalamus where it travels to the pituitary to stimulate the secretion of thyroid stimulating hormone (TSH). TSH then travels to the thyroid gland to stimulate the release of thyroid hormones, thyroxine (T4) and triiodothyronine (T3) (Biondi & Wartofsky, 2012; Shroeder & Privalsky, 2016).

T4 is exclusively synthesized (iodine required) and secreted by the thyroid gland. T4 is considered a prohormone where it is taken up by extra-thyroidal tissue to be converted into active T3 or inactive reverse T3 (rT3). Under certain stressors (e.g., pregnancy, caloric restriction, emotional stress, chronic illness), T4 metabolism favors the synthesis of rT3. In circulation, T4 (and T3) binds to thyroxine-binding globulin (TBG) with an affinity that is 20-folds higher than the affinity of T3 to TBG (Biondi & Wartofsky, 2012; Koulouri et al., 2013).

T3 is predominately synthesized in extra-thyroidal tissue (80% is secreted by extra-thyroidal tissue and 20% is secreted by the thyroid). T3 is considerably more active than T4 with a 10- to 20-fold greater affinity to thyroid receptors (TR) than that of T4. T3 availability, however, depends highly on deiodinase activity, which is responsible for converting T4 into T3. Deiodinase Type 1 is responsible for peripheral conversion and Deiodinase Type 2 is responsible for hypothalamic and pituitary conversion. (Biondi & Wartofsky, 2012; Koulouri et al., 2013).

There is an inverse relationship between TRH/TSH and T3/T4. **TRH** and **TSH** control systemic availability of T3 and T4, and T3 and T4 ultimately regulate TRH and TSH levels through negative feedback loops

- T4 and T3 levels decrease, TRH and TSH increase
- T4 and T3 levels increase, TRH and TSH decrease

Thyroid Dysfunction

Decreased Thyroid:

Like the adrenal gland the thyroid has activities that encompass virtually all of the other endocrine glands. All cells in the body have thyroid receptors. When thyroid levels are low, often a person feels very poorly.

- Decreased thyroid hormone activity in the presence of normal thyroid hormone levels can be caused by low or high cortisol levels; both hormones are needed for optimal energy and metabolic activity.
- Symptoms of progesterone deficiency and hypothyroidism can be very similar. Progesterone is anabolic (burns fat) and thermogenic (increases temperature) so that a deficiency causes weight gain and low temperature.
- Progesterone can improve thyroid activity by improving or eliminating estrogen dominance (Bertoni, 2015). Excess estrogen can increase thyroid binding globulin synthesis thus binding thyroid hormone and decreasing its activities.
- Synthetic progestins decrease thyroid hormone function. Progestin blocks progesterone receptors and prevents biomimetic progesterone from modulating its normal activity such as decreasing estrogen dominance. Common monographs for synthetic progestins list fatigue and loss of energy as common side effects.

Factors that Disrupt T4 to T3 Conversion

Nutrient Deficiencies	Medications	Other Factors
Selenium(Lin et al., 2014)	Glucocorticoids(Greenen, 2016)	Aging(Donda & Lemarchand-Beraud, 1989)
Chromium(Larson & Berry, 1995)	Beta-Blockers(Greenen, 2016)	Alcohol(McGregor, 2015)
Iron(Prasad, 2013)	Oral Contraceptives / HRT(Awad, 2015)	Smoking(McGregor, 2015)
Copper(Larson & Berry, 1995)	SSRIs(Greenen, 2016)	Diabetes(Hashizume, 2013)
Zinc(Maxwell & Volpe, 2007)	Opiates(Ilias et al., 2001)	Growth hormone deficiency(Burman et al., 1996)
Iodine(Larson & Berry, 1995)	Amiodarone(Greenen, 2016)	Low Adrenal function(Wilson, 2015)
Vitamin A(Larson & Berry, 1995)	Chemotherapy(Geffner et al., 1975)	Mercury(Wilson, 2015)
Vitamins B2, B6, B12(Stokstad et al., 1980)	Lithium(Greenen, 2016)	Pesticides(Campos & Freire, 2016)
Vitamin D(Alrefaie & Awad, 2015)	Lithium(Thut & Cheng, 2013)	Stress; excessive cortisol(McGregor, 2015)
		Surgery or Radiation(Hajioun et al., 2014)
		Weight loss(Agnihothri, 2014)
		Liver and kidney disease(Lim, 2001)
		Weight loss(Agnihothri, 2014)
		Liver and kidney disease(Lim, 2001)

Hypothyroidism

Characterized by:

- Lack of production of T4 and T3
- Thyroid function decreased with age
- Could be due to lack of components that make up thyroid hormone; Iodine and tyrosine deficiency
- Could be due to poor recovery following acute stress
- Basal body temperature will be low on five consecutive mornings

Adrenal fatigue; most common features:

- Early morning fatigue
- Diurnal energy pattern
- Hypoglycemia symptoms greatly increased with stress

Factors that Increase T4 to T3 Conversion	
Selenium, Zinc, Chromium, Potassium, Iodine, Iron, Vitamins A, B2, E	Insulin, Glucagon
Growth Hormone	Tyrosine
Testosterone, Melatonin	High protein diet

Functional Hypometabolism (Functional Hypothyroidism)

In this case, thyroid levels are optimal in values and relationship to each other, but symptoms persist. Thyroid receptors are not responding to optimal thyroid level and target tissues of the body have reduced responsiveness to thyroid hormone.

Causation related to Hypo-metabolism:

- Low range of Vitamin D
- Impaired T3 transport
- Low ferritin; optimal level is 90-110
- Chronic low cortisol
- High rT3 and High TPO
- Autoimmune antibodies

Causation related to Functional Hypo-metabolism:

- Genetic abnormalities of the thyroid hormone receptor
- Autoimmune or toxic damage to the thyroid hormone receptor
- Competitive binding to receptor by pollutants, food additives
- Excessive competitor to T3:
    - Progesterone, Vitamin D, Omega 3 Fatty Acids
    - Excess of any can block signaling of the others
- Excess Cortisol:
    - Inhibits T4 to T3 conversion
    - Suppresses TSH
    - Decreases thyroid receptor responsiveness
- Low Cortisol:
    - Decreases thyroid receptor responsiveness
    - May inhibit T4 to T3 conversion
    - Transport across the membrane is energy dependent & modified by cortisol
    - Cortisol regulates T3 receptor density
    - May have to give cortisol to make thyroid supplementation work properly

Why Functional Hypothyroidism is often Undiagnosed

- Most clinicians only check the TSH.
    a. While this is the accepted standard for screening for disease, it often misses imbalances and only reflects pituitary production of TSH.
    b. The TSH "normal range" is wide.
    c. The American Association of Clinical Endocrinologists (AACE) recommends a tighter range than most labs recommend:
        a) "Until November 2002, doctors had relied on a normal TSH level ranging from 0.5 to 5.0 to diagnose and treat patients with a thyroid disorder who tested outside the boundaries of that range. Now AACE encourages doctors to consider treatment for patients who test outside the boundaries of a narrower margin based on a target TSH level of 0.3 to 3.0. AACE believes the new range will result in proper diagnosis for millions of Americans who suffer from a mild thyroid disorder, but have gone untreated until now."
        b) Most clinicians are still going by the labs normal range
    d. If cortisol is low, it will inhibit the release of TSH from the pituitary, this will be *falsely low.*
    e. If the TSH is the only lab ordered, the balance of the thyroid will be missed.
- Many clinicians only check TSH and T4:
    a. Often free hormone levels are not ordered. This goes back to our rule of Free vs. Bound.
    b. In functional hypothyroidism, often the problem is conversion from T4 to T3.
    c. Unless a free T3 is ordered, the problem will go undiagnosed.

Personalized Treatment Opportunities for Hypothyroidism

For the past 5 decades levothyroxine (L-T4) has been the recommended lifelong treatment for hypothyroidism. Despite its long standing at the first-line therapeutic, many patient's symptoms are inadequately treated with L-T4 and personalized options are becoming increasingly warranted. To explore further customized opportunities in the treatment of hypothyroidism, particularly in regards to combination T3 and T4 therapy, refer to the required supplementary reading:

REFER TO SUPPLEMENTARY READING 4

<u>Evidence-Based Medicine</u>: Biondi, B., & Wartofsky, L. (2012). Combination treatment with T4 and T3: toward personalized replacement therapy in hypothyroidism?. *The Journal of Clinical Endocrinology & Metabolism*, *97*(7), 2256-2271.

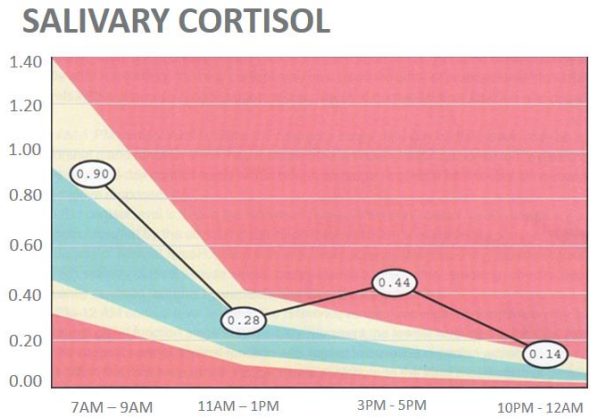
**Competency specific to this reading will be assessed*

CASE ASSESSMENT BASED ON READING 4

Tracy is a 40-year-old female who had been diagnosed with an underactive thyroid when she was pregnant with her third child. Her main complaints were fatigue, weight gain, and sleep disturbance. Her PCP who was managing her thyroid kept telling her that it was fine as her TSH was 2.12 uIU/L, which was in the middle of the normal range.

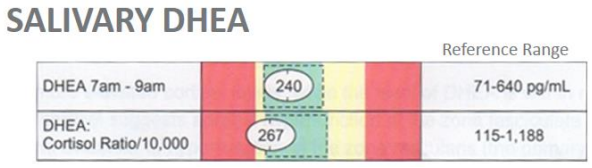
She comes to you seeking a second opinion. She is currently taking levothyroxine 75 µg. She does admit to some stress as her husband got laid off 4 months ago and she was staying home with their 3 kids. She has started working at a restaurant in the evenings to make extra money.

The following are her most recent test results:



Reference Ranges:

- 7AM – 9AM: 0.27-1.18 µg/dL
- 11AM – 1PM: 0.10-0.41 µg/dL
- 3PM – 5PM: 0.05-0.27 µg/dL
- 10PM-12AM: 0.03-0.14 µg/dL



Hormone	Result	Reference Range	Units
TSH	2.5	0.45 – 4.5	uIU/mL
Free T4	1.3	0.82 – 1.77	ng/dL
Free T3	1.9	2.0 – 4.4	pg/dL
TPO	Negative	0 – 34	uIU/L

What are some alternative treatment regimens that you could suggest?

Feedback:

The salivary cortisol results reveal a peak in cortisol levels in the evening between 3 p.m. to 5 p.m. This is common in working moms and most likely corresponds to the time of the day that Tracy begins her evening shift at the restaurant. Tracy's overall high cortisol levels could ultimately affect thyroid function. Her DHEA value could mark the beginning of adrenal issues as well.

The results of her serum thyroid test show that Tracy's TSH value is in the middle of the normal range. However, high levels of cortisol can inhibit the release of TSH from the pituitary gland, so the TSH value obtained could potentially be a false normal. As expected, the patient's free T4 level is in the middle of the normal range as she is currently taking levothyroxine 75 µg. Contrarily, Tracy's T3 level is below the normal range and she has negative TPO antibodies, indicating insufficient conversion of T4 into T3. Ways to address this issue include adding a separate T3 commercial preparation to her current regimen, trying a desiccated thyroid that contains both T4 and T3, or compounding an alternative treatment that has both T4 and T3.

SECTION VI: Hormone Restoration Therapy – Personalized Medicine and Fundamental Principles

Personalized Medicine

With major investments in scientific research and the growing advances in healthcare and diagnostic testing, personalized medicine is on the exponential rise. Now more than ever before, patients are seeking unique therapeutic options that are tailored to their specific needs and requirements. The need for this customized approach is gaining scientific support as empirical reports on genetic and biological markers for specific conditions and disease states continue to accumulate. While there still remains much to be learned on the significance of certain genetic and biological markers, the trend of current findings reveal that individual variations play a profound role in the development, progression, and consequently the treatment of pathology. **Personalized medicine** refers to medical decisions, practices, and interventions that are tailored to an individual patient based in individual pathological markers, symptoms, treatment response, among many other factors. Given that pharmacotherapy contributes significantly to a treatment intervention, customized pharmaceuticals is in growing demand.

According to Chapter <795> of the *United States Pharmacopeia,* **pharmaceutical compounding** refers to the:

> "The preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug-delivery device, or device in accordance with a licensed practitioner's prescription, medication order, or initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice."

Pharmaceutical compounding allows pharmacists and licensed practitioners the flexibility to create a medication that is designed to fit the unique and specific requirements of a practitioner's therapeutic plan for an individual patient. Compounding is the art and science behind customized pharmaceuticals and by these lines, serves as a means to an end for personalized medicine. Among its many possibilities, pharmaceutical compounding allows the one flexibility to:

- Address the challenges and limitations of manufactured products (e.g., discontinued medicine, one-size-fits-all).
- Adjust the dosage strength of a medication.
- Reformulate and modify the dosage form (e.g., developing a transdermal dosage form to replace a solid oral dosage).
- Combine multiple ingredients, thereby simplifying a dosing regimen.
- Exclude certain ingredients to eliminate unwanted side effects and intolerances.

Fundamental Principles and Rules

The following are a series of unique and critical rules that serve as a guide to hormone restoration therapy. This set of fundamental principles is the basis upon which clinical decisions are weighted and opportunities for customization are considered. Strong emphasis and ample study time should be allocated to these rules.

1. Restoration and Balance

The human body maintains homeostasis via an array of mechanisms and restoration and balance are two of its essential functions. The endocrine system is a dynamic arrangement with hormone levels changing regularly depending on the time of day, the time of month, changes in the intrinsic and extrinsic environments, and individual variations among other factors. Moreover, these changes in hormone levels are directly correlated to changes in the number of available receptor sites (Handa, 1994). Receptor sites are sometimes specific to a given hormone and other times they are shared between hormones. In the latter circumstance, one hormone typically has greater or lesser affinity for the receptor site than the other (Klinge, 2001). Furthermore, as the number of hormone molecules received at their respective receptor sites changes, so too does their production capability (Handa, 1994). The hormones and receptor sites combined are in constant flux, undergoing perpetual change. Sometimes the body is unable to restore hormones to their desired levels and consequently it cannot restore a sense of balance. Attempts to maintain homeostatic balance that is offset typically involves the application of a significant exogenous factor…hormone therapy!

The fluctuating cyclical patterns seen in hormonal homeostatic mechanisms, in effect, create moving targets for the clinician (Czeisler, 1998; Fuleihan, 1997). The goal of the clinician and compounding pharmacist are to make appropriate adjustments in treatment as it relates to this moving target until a new balance between the effect of the endogenous and exogenous systems and symptoms lead to the desired physiological effect and clinical outcome. It is this moving target that carries a great deal of weight when a clinician attempts to restore and bring a new sense of balance to the endocrine system on a patient-specific basis.

Unlike many other treatments, hormone restoration and balance is, for the most part, a long-term journey the clinician and pharmacist must take along with their patients. This mere fact lends itself to the study of the long-term effects of your pharmacotherapeutic interventions. Not only are clinicians responsible for the restoration and balance of hormonal levels and system functions, but they must also demonstrate responsibility for the balance that exists between treatment for the prevention of other conditions, such as Alzheimer's Disease (Shao, 2012) and osteoporosis (Torgerson, 2001; Mosekilde, 2000), as well as the cancer-related risk factors associated with long-term hormone therapy. All of which, must be considered in reference to the individual patient's specific needs.

2. Relative versus Absolute

With individual genetic predispositions and individual environmental influences, there tends to be a range of normality for any given hormone (Gray, 1991). Given exogenous and/or endogenous factors, the absolute value of any hormone can fall within, rise above, or fall below its normal range.

Depending on the effects of altered hormonal levels, it may be decided that treatment is required. When reviewing the level of any hormone, the clinician must evaluate the absolute and relative effect of hormones on the homeostatic mechanisms. It is often the interaction and interplay between hormones that determine the physiological effect on the homeostatic mechanism. Both the absolute values and the ratios between specific hormones must undergo review and is a fundamental component of the basis for which therapeutic intervention is determined (Supornsilchai, 2003).

The changes in absolute and relative values of two functional entities undergo a balancing act every minute of every day; a virtual seesaw or teeter-totter. This is what constitutes the homeostatic mechanism. When the homeostatic mechanism fails, it is often deemed necessary to treat this imbalance with exogenous hormones (Rohr, 2002). It must be further recognized that the addition of these exogenous hormones will have a further effect on the homeostatic mechanism, which may also affect the relative and absolute values of yet other hormones within the larger homeostatic mechanism. Despite the fact that we now have numerous moving targets in constant flux, most of them are measurable, nonetheless. These moving targets are the relative and absolute values of hormones in the body.

3. Balance and Relative Sensitivity

As it applies to hormone treatment, until the newly desired homeostasis is reached, frequent monitoring becomes necessary. This is particularly pertinent for hormones whose absolute therapeutic range are narrower. Given the complexity of genetic factors on the overall homeostatic mechanism, attaining and maintaining balance has a varied patient-specific sensitivity. The interaction of genetic factors, lifestyle, diet, among an array of other personal factors, on the homeostatic mechanism is referred to as the patient's relative sensitivity to a given treatment protocol (Andersen et al., 2002).

Adding exogenous hormones to the homeostatic mechanism without recognizing the effect of their metabolites can cause deleterious side effects and render your hormone therapy initiative harmful.

Furthermore, feedback loops within the homeostatic mechanism often leads to decreased sensitivity or ability of the exogenous hormones to achieve their desired physiological effect.

4. Free versus Bound

Free drug is considered to be available to interact with receptors and is thus considered biologically active. **Bound drug** can be divided into two relative categories – bioactive and reservoir. Loosely bound drugs in the plasma can be considered to be biologically active if the bond between the protein molecule and hormone is easily broken. Relative binding affinities can affect the rate of release and thus the degree of biological activity (Tripathi, 2013). Bound drugs are considered reservoir when either the site of binding or the affinity to bind affect the release of the hormone. Hormones that are metabolized to a storage form that require a reverse of this metabolic function prior to their release are difficult to release (Tripathi, 2013).

Hormones are typically stored in tissue; the greater the amount of tissue the larger the hormone depot and the lesser the amount of tissue the smaller the hormone depot. The size of the depot is a significant factor in both immediate treatment protocol establishment and long-term effects (Tripathi, 2013).

Certain hormones have higher affinities to various binding proteins and some binding proteins can be influenced by the amount of hormone present in the body. For example, estrogen and testosterone bind equally at approximately 70% to the binding protein, Sex Hormone Binding Globulin, and DHEA binds to albumin at approximately 80%. Additionally, high body estrogen levels can increase the Sex Hormone Binding Globulin formation thus increasing the binding of testosterone (Tripathi, 2013).

5. Up and Down Regulation

Receptor sites play a critical role in maintaining homeostatic balance. They can be slightly different in their design or have a different range of affinities to hormones due to genetic predisposition. Receptors are regulated by endogenous homeostatic mechanisms to make them more or less available to interact with bioavailable hormones and their metabolites (Briggs & Christie, 2014).

Typically, over time, exogenous hormones and their metabolites cause down regulation of receptor sites or existing active receptor sites are rendered less or non-responsive to the exogenous hormone; referred to as desensitizing or tolerance effects. Once this down regulation takes place, increased dosing will not have the desired effect since the receptors initiating or maintaining receptors is no longer available or capable of this activity (Briggs & Christie, 2014).

Up regulation of receptors or sensitization of receptors can be caused by exogenous hormones if these receptors are dependent upon the availability of the specific exogenous hormone or their metabolites (Briggs & Christie, 2014).

6. Additive, Synergistic, and Antagonistic Activity

- Most hormones work with other hormones to produce additive, antagonistic, or synergistic effects (*refer figure 1)*.
- **Additive activity**: When two or more substances produce a total effect that *equates* to the sum of each substance's individual effect (Moscou and Snipe, 2014).
- **Synergistic activity**: When two or more substances produce a total effect that is *larger* than the sum of each substance's individual effect (Moscou and Snipe, 2014).
- **Antagonistic activity**: When two of more substances produce a total effect that is *less* than the sum of each substance's individual effect (Moscou and Snipe, 2014).

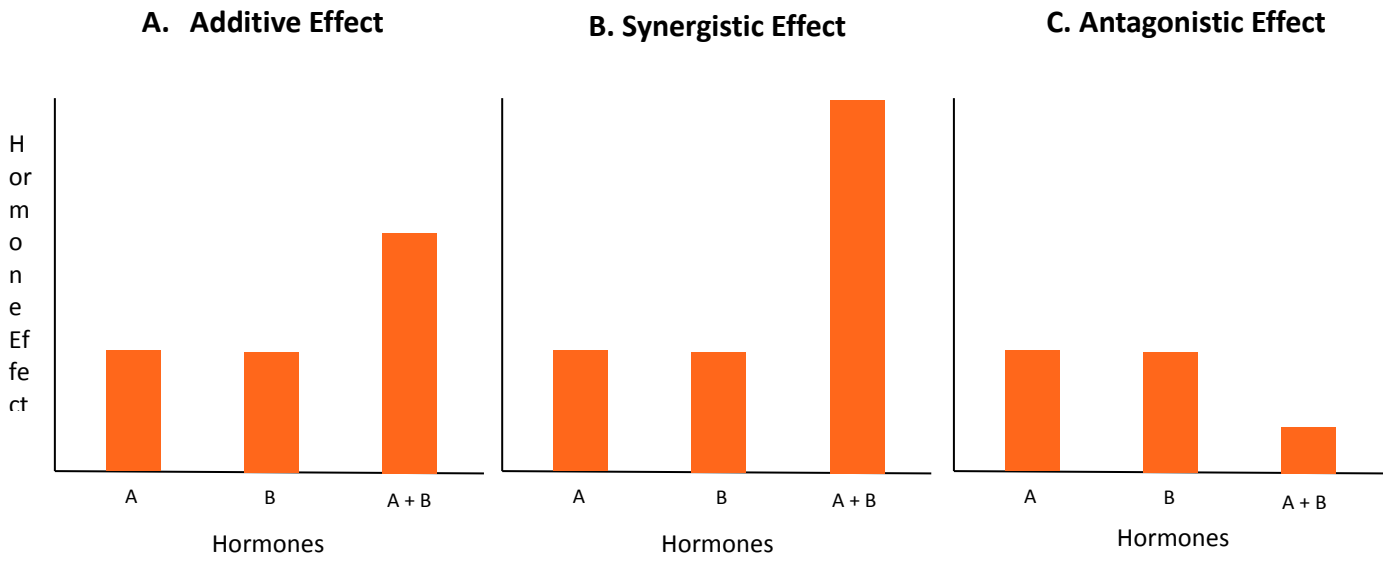


Figure 6, Graphical depiction of additive, synergistic, and antagonistic interactions

7. Pharmacokinetic versus Pharmacodynamic Balance

Consideration must always be given to the principles of pharmacokinetics and pharmacodynamics; what the body does to a drug versus what a drug does to the body. Much of this dynamic interaction can be explored by looking carefully at the absorption, distribution, metabolism, and excretion of a drug.

Absorption directly affects a substance's bioavailability. It is determined by the physical and chemical properties of an active agent and the excipients in a delivery system. Of particular interest is the drug agent's acidity or basicity, ionization, and water or lipid solubility. Unless administered IV, a drug agent must cross several semi-permeable membranes before it reaches the systemic circulation. It is the membrane's bimolecular lipid matrix that determines membrane permeability, which selectively inhibits passage (Meibohm, 2013).

Distribution of drug agents is influenced by their binding capacities to proteins and lipids, blood perfusion into tissue, and cell membrane permeability. The entry rate of a drug into a tissue is dependent upon the rate of blood flow through tissue, tissue density, and partition characteristics between blood and tissue. For poorly perfused tissues distribution is very slow, especially if the tissue has a high affinity for the drug (Meibohm, 2013).

Distribution of drug agents from tissues into the blood stream is directly related to serum protein and tissue binding and is transported partly in solution as free or unbound drug and partly reversibly bound to blood components such as serum proteins and blood cells. Only unbound drug is further available for passive diffusion into tissue sites. 'Lipid loving' drugs often bind to fat resulting in a longer equilibration time, especially if the drug is highly lipophilic. Drug storage in fat initially shortens the drug's effect. However, over time, it will eventually prolong the effects (Meibohm, 2013).

Metabolism takes place primarily in the liver; however other organs such as the intestines, skin, and lung can also metabolize drug agents. Although metabolism most often inactivates drugs, some drug metabolites are pharmacologically active (Meibohm, 2013).

Excretion of most active drugs and their metabolites is as a result of kidney filtration. However, drugs bound to serum proteins will remain in the circulatory system (Meibohm, 2013).

As the pharmacokinetic and pharmacodynamic characteristics of drug agents and the body are explored a complex interplay is realized; that one of these subjects cannot be evaluated without consideration for the other.

8. Cyclic versus Continuous Dosing

This particular topic is philosophical in nature and often controversial. We are going to keep it that way throughout the program. Until such time as long-term studies prove superiority, one approach over the other, there will continue to be a divergence in philosophical guidelines for the treatment of hormone restoration and balance.

The decision to prescribe hormones in a cyclic versus continuous dosing manner is divided and, for the time being, may end up being a personal preference. Long ago when a progestin was added to estrogen therapy, it was always cyclic. The routine was to give estrogen during days 1 - 25 of the calendar and add progestin on days 14 - 25. That would leave day 26 to the end of the month as a hormone free interval. Most women would still have a withdrawal bleed during that time, and some women were very symptomatic with four or more days off estrogen. As a result, the estrogen was prescribed on a continuous basis, but the progestin was still given the same way. After some research studies confirmed that there was no increased risk of endometrial hyperplasia with continuous dosing, the dosage of progestin was decreased and was also given continuously. The lower dose of progestin helped to decrease its side effects, and the continuous dosing eliminated the withdrawal bleed in most women. When the shift toward using more bio-mimetic hormones took place, the practice of continuous dosing was maintained. It is usually recommended to have four hormone free days per month, either all at once, or one day a week, to prevent tolerance at the receptor site. For the patient who continues to have a withdrawal bleed after menopause, it becomes difficult to discern between physiologic and pathologic bleeding (Vlahos et al., 2013).

9. Routes of Delivery and Delivery Systems

In hormone therapy, as is the case with any atypical segment of pharmacotherapy, there exist a number of routes of delivery from which drug agents may be administered. The most common routes of delivery for hormone therapy include **oral**, **rectal**, **vaginal, topical**, and **sublingual**. Each route of delivery has its advantages and disadvantages from too slow or too fast acting, to first pass effect being by-passed or not, to local versus systemic effects, and to the manner in which the drug agent will interact with the body and how the body will react to the presence of the drug agent (Goodman, 2012; Grant & Leone-Bay, 2012; Fantasia & Sutherland, 2014).

With each route of delivery there are numerous delivery systems and respective compositions that will result in intersystem variability as far as rate of absorption is concerned. While the **diffusion coefficient** is of concern when we speak of the route of delivery, it is the **partition coefficient** that need be addressed when a delivery system is selected. Partition coefficient refers to the rate of release of a drug from the delivery system's base and the subsequent rate of absorption of the drug agent through the tissues. Together these rates of diffusion determine serum levels of the drug agent at any instant in time. It is the capture of that same serum level at multiple time intervals that will reveal a critical aspect of the drug agent's bioavailability and corresponding potential for therapeutic effect; its onset and duration (Meibohm, 2013).

Hormones can be classified into a number of categories (Grant & Leone-Bay, 2012):

- **Amine hormones** are small molecules originating from amino acids (e.g., thyroid hormone).
- **Steroid hormones** in all instances are derivatives of the precursor steroid cholesterol (e.g., testosterone and estrogen).
- **Peptide and protein hormones** are the largest and most complex of hormones (e.g., insulin).

Hormones are either lipid-soluble or lipid-insoluble. It is this solubility factor that determines the mechanism by which a hormone molecule acts on its target cell or tissue. Seeing as how drug agents need be in solution to by-pass many tissue barriers, in particular the stratum corneum in the case of transdermal applications, the selection of base components is an important consideration in the design of an appropriate delivery system.

Lipid-soluble hormones more easily penetrate cell membranes and subsequently bind to their target receptors. Lipid-soluble hormones often act on DNA, inhibiting and stimulating the transcription of specific proteins. This hormone-DNA interaction can have effects on the body's overall function for hours and in some cases days. A lipid-insoluble hormone and its inability to penetrate the cell membrane require secondary messengers which translate the outer message and functions though the cell membrane to its secondary target.

10. Monitoring Frequency and Therapeutic Intent

The endocrine system is perhaps one of the more complex systems of human physiology. One single perspective of this system is clear; subsequent to administration of hormones there exist levels of bound and free molecules that are in reservoir and bio-active modes. Each need be monitored for their potential therapeutic and side effect profiles. Rate of tissue perfusion, absorption, distribution, metabolism, excretion, reservoir capacity and the impact of absolute and relative levels of hormones, receptor site affinity, etc… all contribute to a system in perpetual flux. This truly makes hormone therapy a moving target (Meibohm, 2013).

Summary of the Fundamental Principles and Rules of Engagement for Hormone Restoration Therapy	
Fundamental Principle	**Rule of Engagement**
1. Restoration and Balance	Ascribe hormone treatments that restore deficiencies and bring balance to the homeostatic mechanism within the female or male reproductive life cycle.
2. Relative versus Absolute	Concurrently assess absolute hormonal levels, as well as their relative qualifiable and quantifiable relationships to one another.
3. Balance and Relative Sensitivity	Be aware of the innate differences between individuals as it applies to the sensitivity of the relative relationship between any two hormones.
4. Free versus Bound	Qualify and quantify bound and bioavailable hormone levels on an ongoing and consistent basis.
5. Up and Down Regulation	Assess prescribed hormone levels in order to rationalize the potential impact on up and down receptor site regulatory mechanisms.
6. Additive, Synergistic, and Antagonistic Activity	Consider the impact of additive, synergistic, and antagonistic interaction of hormones and their concomitant impact on cellular and tissue proliferation.
7. Pharmacokinetic and Pharmacodynamic Balance	Provide adequate and equitable consideration for the impact of what a drug agent is doing to the body, and what the body is doing to that same drug agent.
8. Cyclic versus Continuous Dosing	Determine the absolute and relative short- and long-term significance of cyclic versus continuous hormone administration.
9. Routes of Delivery and Delivery Systems	Determine the rate of absorption and subsequent bioavailability from known and/or hypothesized partition and diffusion coefficient-related variables.
10. Monitoring Frequency and Therapeutic Intent	Monitor and subsequently adjust treatment protocols to minimize the quantity of hormones delivered, while attempting to maximize therapeutic effect and reduce or avoid completely the potential for long-term side effects.

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