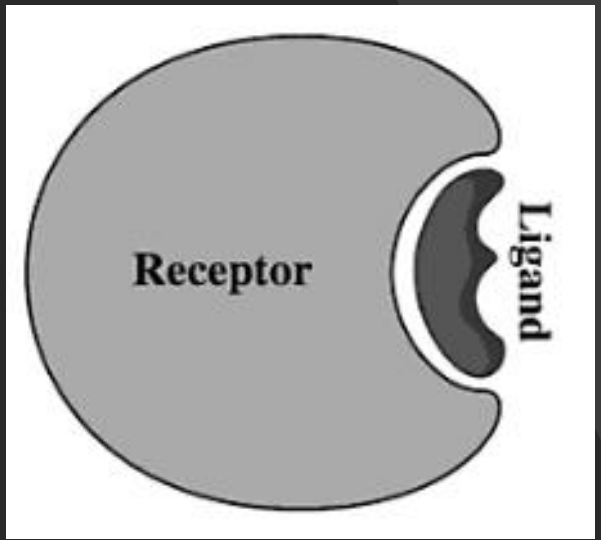
Metals are Metallo-es trogens

- Case History of Premature Ovarian Failure
- 33-year old Indian woman
- Turmeric
- Tested serum (elevated levels indicate present exposure)
- Chelated
- Started to menstruate and became pregnant
- All intakes should test heavy metals I now do serum along with hair analysis
- Serum = exposure now
- Hair analysis, provocation = past exposures

Heavy Metal Exposure

- **---Heavy metals** arsenic, chromium, cobalt, lead and nickel, which are known to be **toxic** and endocrine disruptors, as **contaminants in 22 pesticides.**
- --Found in many fish
- --Heavy metals are persistent environmental pollutants and humans are exposed to them through water, air, food, or industrial settings.
- **---Cigarette smoke through building materials**
- ---Biological buildup in the food chain allows multi-heavy metal pollutants to increase.
- ---Competitive inhibition at the receptor level



Metals and Breast Cancer

- Metalloestrogens are metals that activate the estrogen receptor in the absence of estradiol.
- Metals such as cadmium, calcium, cobalt, copper, nickel, chromium, lead, mercury, and tin.
- **The best studied metallo-estrogen is cadmium, and it is implicated in breast cancer. Estrogen is protective but it 'blocks" it.**
- Many metals are also carcinogens. Cadmium, chromium, and nickel are established human and animal carcinogens, while copper, lead, and mercury are probable carcinogens or co-carcinogen.
- Mammary Gland Biol Neoplasia. 2013 Jan 22. doi: 10.1007/s10911-013-9273-9 Metals and Breast Cancer

Receptor Detox – whose time has come

Receptor Daily Detox supplies the exact nutrients that:

---Allow hormones to exactly dock into receptors and signal for the healthiest duration of time.

---Clears “competitive inhibitors” off receptors in a safe and continuous manner.

--By optimizing receptor functionality, hormones can safely and effectively deliver their signals and overcome resistance.

Terms

- Premenopause – whole life preceding menopause
- Perimenopause is 45 to 55 years of age
- Early menopause is 40 to 45 years - 5% of women
- Normal menopause US 51 years of age
- After 55 years of age about 5% occasionally at 59
- Premature menopause before the age of 40.
- Hormone replacement or else at significant risk of fatal MI.

Menopause - Anti-Mullerian Hormones

- Age of natural menopause often near that of biological mother
- (AMH) anti-muellerian hormone is the best predictive tool.
- AMH, is a substance produced by granulosa cells in ovarian follicles.
- The levels are fairly constant and the **AMH test can be done on any day of a woman's cycle**.
- **AMH blood levels are thought to reflect the size of the remaining egg supply** - or "**ovarian reserve**."
- Women with higher levels of AMH tend to respond better to fertility treatment 1.5 to 4 but this says nothing about egg quality.

Anti-Mullerian Hormone

- Anti-Mullerian hormone (AMH) has emerged as a marker of ovarian reserve and a possible surrogate measure of reproductive aging.
- AMH was a stronger predictor of time to menopause than FSH.

- J Clin Endocrinol Metab. 2012 May; 97(5): 1673–1680. doi:10.1210/jc.2011-3032 **Anti-Mullerian Hormone as a Predictor of Time to Menopause in Late Reproductive Age Women**
- Hum Reprod. 2016 Jul;31(7):1579-87. doi: 10.1093/humrep/dew112**Does anti-Müllerian hormone predict menopause in the general population? Results of a prospective ongoing cohort study.**

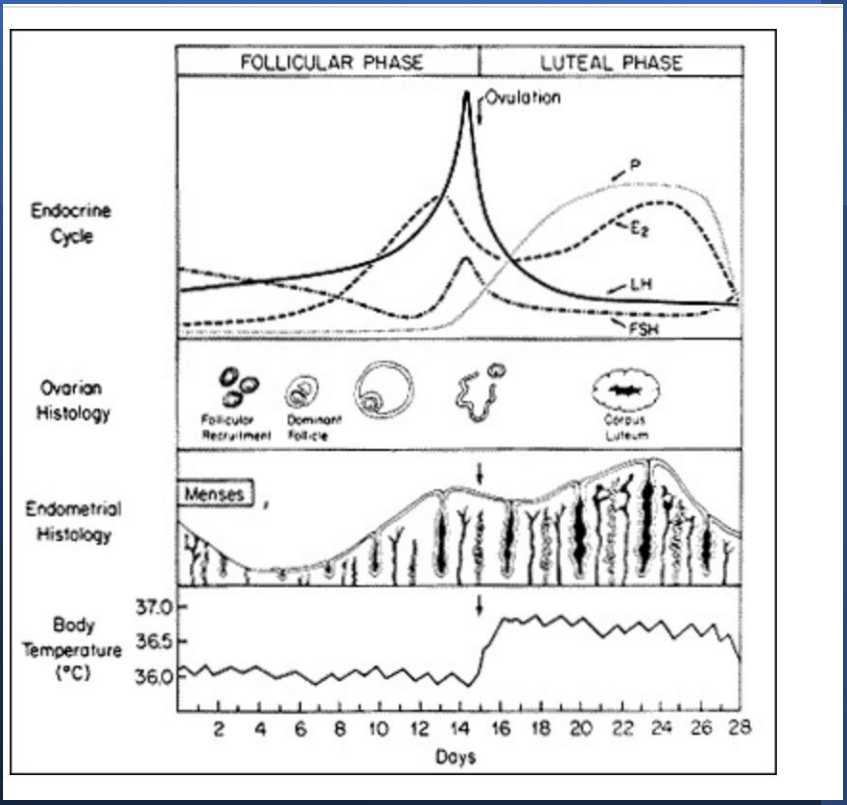
Interpretation	AMH Blood Level
High (often an indicator of PCOS)	Over 3.0 ng/ml
Normal	Over 1.0 ng/ml
Low Normal Range	0.7 – 0.9 ng/ml
Low	0.3 – 0.6 ng/ml
Very Low	Less than 0.3 ng/ml

FSH – Follicle Stimulating Hormone

- FSH normally stimulates ovaries to make eggs
- When no ovulation, it doesn't go down, stays up. Elevated above premenopausal levels.
- **Pre-menopause normal level is less than 10.**
- **Post-menopause 25.8 to 135**: consistently elevated FSH above 30 is diagnostic though rarely needed unless had hysterectomy and if she is on BCPs. Does she still need contraception? FSH can go up and down so can get pregnant.
- **HRT try to get to 35 or below. Goal is to lower it by nutrition and/or HRT.**
- FSH can go up and down for a while so not as set in stone marker.
- When we give hormone replacement we like to monitor the FSH and **see it start to come down closer** to premenopausal levels.

FSH

- FSH can be increased but still regular cycles and not really in perimenopause.
- Is this perimenopause or not?
- Or she may have irregular menstrual cycles and a normal FSH and a non aware practitioner may say you are not in perimenopause.
- Test itself is not as sensitive as it could be.
- **If FSH is above 10 on day 3 – first common measure and clinical sign of reproductive aging and fertility**



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Earlier Menopause on the Rise

- Even a few months makes a difference in a “hard wired” reproductive milestone
- Premature: Between 40 to 45 years of age (surgery, medical treatments one in two women treated for leukemia and Hodgkin’s in past get early, cytotoxic treatments and sometimes they start working again after a period of time, hysterectomy (about 25% of women with uterus removed, will stop having period within 1-2 years).

Women in Menopause Before 30

- If having premature ovarian failure, she is at increased risk of illness, CVD risk in 7 times more, bone loss, colon and ovarian, cancer, cataract, etc.
- Premature menopause spend greater portion of life without protective benefit of endogenous estrogen.
- Mayo Clinic Study showed significant increase risk of fatal MI if had hysterectomy **before 45 years of age** without estrogen replacement.

Premature Ovarian Failure

- Rare cases of premature ovarian failure, put on continuous E and P and several months later FSH comes down and she starts to menstruate again as E itself may activate receptor formation on the follicles.
- An estrogen reboot.
- Oral estriol 2 mg for 10 days to one month.
- So, if breakthrough bleeding, don't just make assumption should adjust dosing, it may be rebooting. So stop for a while and see.
- Estriol short-term therapy modulates within 10 d of administration the neuroendocrine control of the hypothalamus-pituitary unit and induces the recovery of both gonadotropins synthesis and secretion in hypogonadotropic patients with FHA.

- Gynecol Endocrinol. 2016;32(3):253-7. doi: 10.3109/09513590.2015.1118452. **Short-term estriol administration modulates hypothalamo-pituitary function in patients with functional hypothalamic amenorrhea (FHA).**

Perimenopause

- **Perimenopause (menopause transition) often the most symptomatic years**
- Up to 10 years before menopause
- Not ovulating. Ovulation makes progesterone and oxytocin.
- So tend to anxiety and mood dysregulation.
- Give receptor detox for one week at double dose, then regular dose and add balance and protect then third week start progesterone.
- But happening earlier and earlier even reported at some gynecologic conferences to be occurring in some late 20-year-olds.
- ***North American women spend 1/3 to ½ lifespan in postmenopause.***
- So knowing how to protect hormones nutritionally and scriptively is critical to keep these women healthier longer and morbidity a shorter time later in life.

Perimenopause 3 week reboot

- 1st: Give receptor detox for one week at double dose,
- 2nd: Regular dose detox and add balance and protect
- 3rd Start progesterone staying on the above.

Classic Symptoms with Perimenopause

- Change in classic pattern (used to b 28 days and now 26)
- Decline in fertility (due to first half of cycle is shortening)
- Irregular menses, irregular bleeding, clotting
- Vasomotor symptoms (hot flashes happening in younger ladies)
- Vulvovaginal symptoms, dysparunia, lower libido
- Sleep disturbances
- Weight gain especially around middle
- 3 major issues all helped in most by HRT: fatigue, weight gain, insomnia
- All due to hormonal yo/yoing and periods of dropping and insufficiencies

Other Possible Symptoms

- **Other possible symptoms (must rule out real cause and not be too easily swayed by fad health issues of the times i.e., adrenal fatigue, SIBO)**
- OA, Headaches, changes in cognition, urinary frequency, incontinence, depression, anxiety, moodiness, voice changes (deeper rougher) capsulitis (frozen shoulder) dry eye, body aches, fatigue (must do due diligence in differential diagnosis), weight gain, skin changes (collagen declines thus dryness, wrinkling) tooth changes, gum, dry mouth, burning mouth, receding gums, vision, hearing, hair thinning and hair appearing in new places, dental issues increasing.

Aging

- Loss of hormones + inflammation = aging
- **Disease risk increase with aging for multiple diseases**
- CVD bone loss type 2 diabetes cancers stroke OA osteoporosis periodontal disease mood dysregulation obesity and more.
- Hormones address all above issues.

Many of the Issues

- Related to aging and hormonal decline
- Are improved if not put into remission with hormone balancing and replacement through herbs, nutrients and bioidentical hormones
- But gynecologists are not taught the bigger picture of hormones, that they lean on nutrition, digestion and receptor physiology
- Or that with hormone altering chemicals we need to test and address hormones earlier and earlier
- You can fill this niche - even if you can't prescribe.
- And we will be addressing nutritional hormonal intervention too but also if you know hormones and can chyme in on bases and dosages this will go a long way in your practice and community.

What North American Menopause Society (NAMS) is saying **census statement 2020**

- Estrogen is approved for prevention of osteoporosis but not for treatment.
- Neither ET or EPT before 10 years postmenopausal under 60, not increasing risk of heart disease.
- Surgical menopause and no uterus require long term E therapy.
- Average 1 mg estradiol orally .625 premarin .05 patch all equivalent.
- Dosing .4 mg to 1.8 or 2 mg but outliers that need more or less
- Less than average lower risk of blood clots or strokes of these standard dosages.
- Discontinue after 3 to 5 years.

Hormone Replacement Lowers CVD Risk

- Number one cause of premature death in aging women: heart disease.
- Does the use of post-menopausal vaginal estradiol (VE) affect the mortality risk for coronary heart disease (CHD) and stroke?
- **SUMMARY ANSWER:**
- The use of VE reduces the risk for cardiovascular mortality.
- We studied a nationwide cohort in Finland 1994-2009 during which post-menopausal women (n = 195 756) initiated the use of VE (age [mean ± SD] 65.7 ± 10.9 years). Follow-up data gathered 1.4 million women-years and we assessed the mortality risk due to CHD (n= 9656) or stroke (n = 4294).
- RESULTS: In 1000 women using VE for up to 10 years, a maximum of 24 fewer CHD deaths and 18 fewer stroke deaths is likely to occur.

- Hum Reprod. 2016 Apr;31(4):804-9. doi: 10.1093/humrep/dew014. Epub 2016 Feb 13. **Vaginal estradiol use and the risk for cardiovascular mortality.**

Heart Dx vs. Breast Cancer

Heart disease is the leading cause of death for women in the United States, killing 299,578 women in 2017—or about 1 in every 5 female deaths.

2017

2021

an estimated 42,170 women will die from breast cancer in the U.S.

NAMS POSITION STATEMENT - The 2020 **genitourinary syndrome of menopause** position statement of The North American Menopause Society

- Genitourinary syndrome of menopause describes the symptoms and signs resulting from the effect of estrogen deficiency on the female genitourinary tract, including the vagina, labia, urethra, and bladder.
- Vulvovaginal atrophy is a component of GSM
- This syndrome includes genital symptoms of dryness, burning, and irritation; urinary symptoms and conditions of dysuria, urgency, and recurrent urinary tract infections (UTIs); and sexual symptoms of pain and dryness. Physical changes and signs are varied. Women may experience some or all of the symptoms and signs, which must be bothersome for a diagnosis of the syndrome. Other causes of similar signs and symptoms must be ruled out, including vulvovaginal dermatoses, infection, or cancer.

NAMS POSITION STATEMENT - The 2020 **genitourinary syndrome of menopause** position statement of The North American Menopause Society

- These include vaginal lubricants and moisturizers, vaginal estrogens and dehydroepiandrosterone (DHEA), systemic hormone therapy, and the estrogen agonist/antagonist ospemifene. **Long-term studies on the endometrial safety of vaginal estrogen, vaginal DHEA, and ospemifene are lacking**.
- There are insufficient placebo-controlled trials of energy-based therapies, including laser, to draw conclusions on efficacy and safety or to make treatment recommendations.
- Non-hormone therapies available without a prescription provide sufficient relief for most women with mild symptoms.
- Low-dose vaginal estrogens, vaginal DHEA, systemic estrogen therapy, and ospemifene are effective treatments for moderate to severe GSM.
- When low-dose vaginal estrogen or DHEA or ospemifene is administered, a progestogen is not indicated; however, endometrial safety **has not been studied in clinical trials beyond 1 year.** There are insufficient data at present to confirm the safety of vaginal estrogen or DHEA or ospemifene in women with breast cancer; management of GSM should consider the woman's needs and the recommendations of her oncologist.

- Menopause: The Journal of The North American Menopause Society Vol. 27, No. 9, pp. 976-992DOI: 10.1097/GME.0000000000001609ß2020 by The North American Menopause Society

Finnish Study

Breast Cancer Risk in Postmenopausal

Women Using Estrogen-Only Therapy

Heli Lyytinen, MD, Eero Pukkala, PhD, and Olavi Ylikorkala, MD

VOL. 108, NO. 6, DECEMBER 2006 Am College of OBSTETRICS & GYNECOLOGY

Less Heart Disease

- We evaluated the risk of death caused by coronary heart disease (CHD), stroke, or any disease among users of estradiol-based HT regimens in a nationwide study in Finland.
- **CONCLUSIONS:**
- In absolute terms, the risk reductions mean 19 fewer CHD deaths and 7 fewer stroke deaths per 1,000 women using any HT for at least 10 years.
- Menopause. 2015 Sep;22(9):976-83. doi: 10.1097/GME.0000000000000450. **Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality.**
- Breast Cancer Risk in Postmenopausal Women Using Estrogen Therapy Only ACOBGYN VOL. 108, NO. 6, DECEMBER 2006

Increased Risk When Stop

- We evaluated the risk of cardiac or stroke death after the discontinuation of HT. 332 202 Finnish women discontinuing HT between 1994 and 2009 (data from National Reimbursement register) were followed up from the discontinuation date to death due to cardiac cause (n = 3177) or stroke (n = 1952), or to the end of 2009. The deaths, retrieved from the national Cause of Death Register, were compared with the expected number of deaths in the age-standardized background population. In a subanalysis we also compared HT stoppers with HT users.
- **RESULTS:**
- Within the first post treatment year, the risk of cardiac death was significantly elevated whereas follow-up for longer than 1 year was accompanied with a reduction.
- The risk of stroke death in the first posttreatment year was increased (1.63; 1.47-1.79), but follow-up for longer than 1 year was accompanied with a reduced risk (0.89; 0.85-0.94). The cardiac (2.30; 2.12-2.50) and stroke (2.52; 2.28-2.77) death risk elevations were even higher when compared with HT users.
- **In women who discontinued HT at age younger than 60 years, but not in women aged 60 years or older, the cardiac mortality risk was elevated** (1.94; 1.51-2.48).
- **CONCLUSIONS:**
- Increased cardiovascular death risks question the safety of annual HT discontinuation practice to evaluate whether a woman could manage without HT.
- **Staying on hormone replacement is safer than going off.**

- J Clin Endocrinol Metab. 2015 Dec;100(12):4588-94. doi: 10.1210/jc.2015-1864. **Increased Cardiovascular Mortality Risk in Women Discontinuing Postmenopausal Hormone Therapy.**
- Reproductive endocrinology: Don't be so quick to stop hormone-replacement therapy.

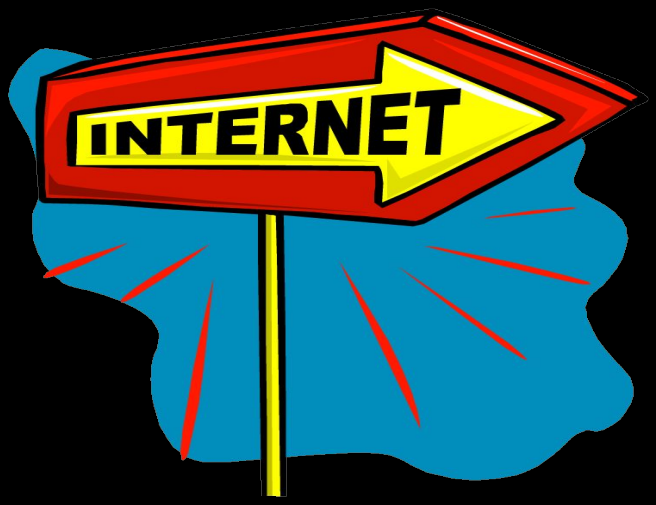
Lobo R. Nat Rev Endocrinol. 2016 Jan;12(1):11-3. doi: 10.1038/nrendo.2015.195. Epub 2015 Nov 20. PMID: 26585665 No abstract available.

Most Doctors and Patients

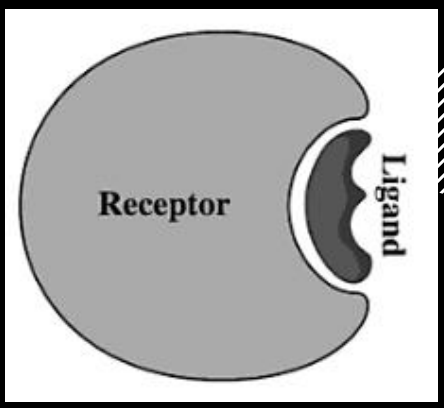
- Think hormones are about sexy and reproductive things
- That we should be concerned about at times; pregnancy, peri and post menopause or andropause
- And only for symptoms for short period of time like hot flashes
- But hormones are main signaling molecules in the body

“It’s all about signals, Jerry” – George Costanza

Hormonal Internet System



Getting Cellular Mail



- Has nothing to do with the blood levels
- Has nothing to do with saliva levels
- Has nothing to do with urine levels
- It has to do with "**Receptor Functionality**"
- One cell sends email to another cell that gets to open it if there is optimal "receptor functionality"

Hormones – Biggest Rabbit Hole in Medicine

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Why

- Hormones are more than sexy or reproductive signals
- Estrogen, progesterone & testosterone control many aspects of cellular growth and homeostasis in most all tissues
- Maintain normal brain function: modulators of mood, cognition, pain, etc.
- Maintain gut health: gut wall permeability, gut immunity, gut nervous system, and help hold protective nutrients in gut wall.
- Maintain renal health.
- Maintain immune system: estrogen boosts immunity, linked to why less females get COVID and less severe cases of Covid, T is immunomodulator.

Mol Cell Endocrinol. 2018 Apr 15;465:61-72. doi: 10.1016/j.mce.2017.11.011. **Sex steroids and the kidney: role in renal calcium and phosphate handling.**

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Hormones – Delivery Modes

- Oral, topical, mucosal, troche, pellet, IM, IV.
- Transdermal or mucosal are safer than oral
- Sublingual is not the same as transdermal and we don't know what stroke risk is as some is swallowed.
- Use of hormones should not be discontinued just because of age.
- Nurses Health Study
- 30-55 yr observational studies
- Hormones and heart dx
- 40-50% reduction in the number of heart attacks

- Oral – coagulation factors + pro-inflammatory metabolites; 1st hepatic pass
- Topical – least amount of cardiac issues even safe with coagulation issues i.e., Factor V Leiden
- Sublingual – no data and still swallowing some so still oral
- Mucosal on vagina/labial best safety profile
- Patch – "even" delivery but estradiol without estriol but sometimes add to other delivery modes.
- Pellet – easy, but highs and lows and need wash out time, some women scar
- If liver or GB disease do not give oral or sublingual

- Start with Receptor Detox and Balance
- Then add foundational nutritional support doses for declining estradiol levels:
- · Vitamin A: 10,000 - 40,000 IU daily
- · Boron: 3-9 mg daily
- Zinc balanced with copper: 30-60 mg balanced with 2-4 mg copper, if copper deficient
- For 3 months
- Giving glandulars
- Herbs like Vitex stimulate progesterone but won't help if progesterone insufficiency or resistance is part of the issue
- Or if low estrogen is part of the issue

Two Paths Hormonal vs Nutritional To Boost Estrogen

Links

- Dr. Berkson's Best Health Radio

- Drlindseyberkson.com
- Drlindseyberkson.com/membership

Hormone Replacement or Balancing

- Fatigue
- Reduces weight gain
- Wrinkles, thinness of skin, age spots
- Improves mood (anxiety, depression, overwhelm)
- Increases insulin sensitivity
- Protects kidneys, lungs, brain and gut lining
- Upregulates adhesive proteins in gut wall
- Strengthens bones
- Reduces risk of type 2 diabetes, Alzheimer's
- REDUCES RISK OF BREAST CANCER

- Hormones need to be addressed as aging to deal with many of the issues of aging.

ANTI-AGING SPECIALIST

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Estrogen Window

- Most complete benefits given in first 10 years.
- Does not mean that giving in 70's, 80's or 90's is out of the question.
- Timing of estrogen is everything, the earlier the better the longer the benefit years to come even with 5 years of replacement.
- Preexisting condition of endothelium matters as to how it will respond to estrogen.
- Careful for women who already have heart disease so must do cardiac work up. Start low. Go slow.
- If have a uterus and on estrogen need to do vaginal US to rule out proliferation (endometrial stripe should be 5 mm or less)
- PEPI trial first study to show bioidentical progesterone adequate to prevent endometrial thickening if give E. Bioidentical progesterone boosts HDL but NOT with progestins.

•Dear Dr. Berkson,

•I want to say THANK YOU for your help at the Biotics seminar in Tysons, VA!

•I'm the woman who came up to you and told you about the terrible headaches I had been getting with my periods each month ever since the birth of my first son - 9 years ago.

•The headaches were so bad that during my period, I would literally throw up from the pain multiple times each day, with absolutely no relief. Although I'm very natural minded (eat all organic foods, grass-fed free ranch meat, no sugar, only complex carbs, take supplemental nutrients, etc), out of desperation, 4.5 years ago I tried various "mainstream" doctors who gave me various medications, but had very poor results - including ending up in the hospital one time from a reaction to the medications.

•That event was so scary, that afterward I chose to just endure the intense pain and "lose" those days of my life each month while we continued to search for a solution to this problem.

•I calculated that I would spend approximately 40 days out of each year in extreme pain and vomiting. It would turn on like a switch, and off like a switch. I could literally be fine in the morning, and in terrible, terrible pain later in the day, which would then continue - without any relief (day and night) - for 2 to 4 days at a time. Sometimes it would even happen during ovulation too.

•I had my period this past week, and added in the vitamins/nutrients you mentioned at the seminar (Zinc, Iodine, B6 with B-complex back up, Vit A, Boron, and increased fish oils).

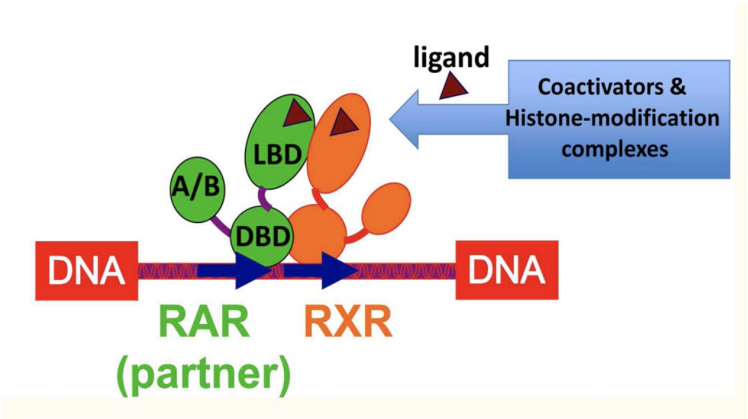
• I sailed through my period with NO PAIN!!!!

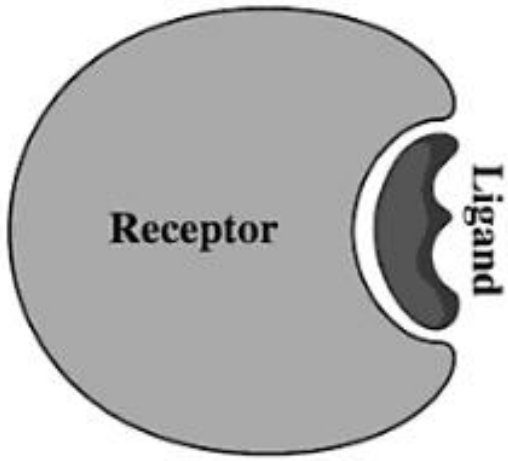
• I am so very, very grateful. I have been sitting here at my computer typing and re-typing, trying to figure out how to express how relieved I am to be able to look at the days ahead with hope. I can honestly say that I simply don't know how to say it.

•Thank you, thank you, thank you!

Sex steroid signaling requires vitamin A

- Chem Rev. 2014 Jan 8; 114(1): 233–254.
- **Retinoic Acid Actions Through Mammalian Nuclear Receptors**





Menorrhagia

Vitamin A is a co-factor of 3 beta-dehydrogenase in steroidogenesis and deficiencies of this **vitamin** may result in impaired enzyme activity.

The level of endogenous 17 beta-oestradiol appears to be elevated with **vitamin** A therapy, and **menorrhagia** was alleviated in more than 92% of patients.

Vitamin A

PABA

Vitamin A in the treatment of menorrhagia. S Afr Med J. 1977 Feb 12;51(7):191-3. PMID: 847567

You can have a decrease in hormonal signaling due to:

- Decrease in hormone
- Decrease in critical nutrients at binding domains, vitamin a, magnesium, zinc, iodine, B vitamins.
- Blockage of hormone docking due to **competitive inhibition**
- **In today's toxic world lots of issues with hormones due to this.**
- Or due to hormonal resistance
- You can be resistant to any hormone not just insulin and thyroid, such as progesterone and leptin.

- Br J Obstet Gynaecol. 1998 Mar;105(3):345-51.
- **Progesterone resistance in women who have had breast cancer.**
- Journal of Biomedical Science 2014, 21:2

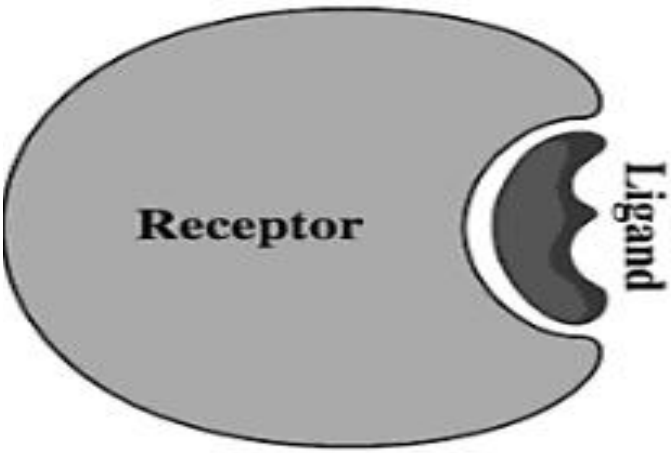
http://www.jbiomedsci.com/content/21/1/2

- **Endometrial progesterone resistance and PCOS**

"It's Complicated"
Hormones are much more complicated than just testing levels (saliva, blood, urine or by dowsing rod)

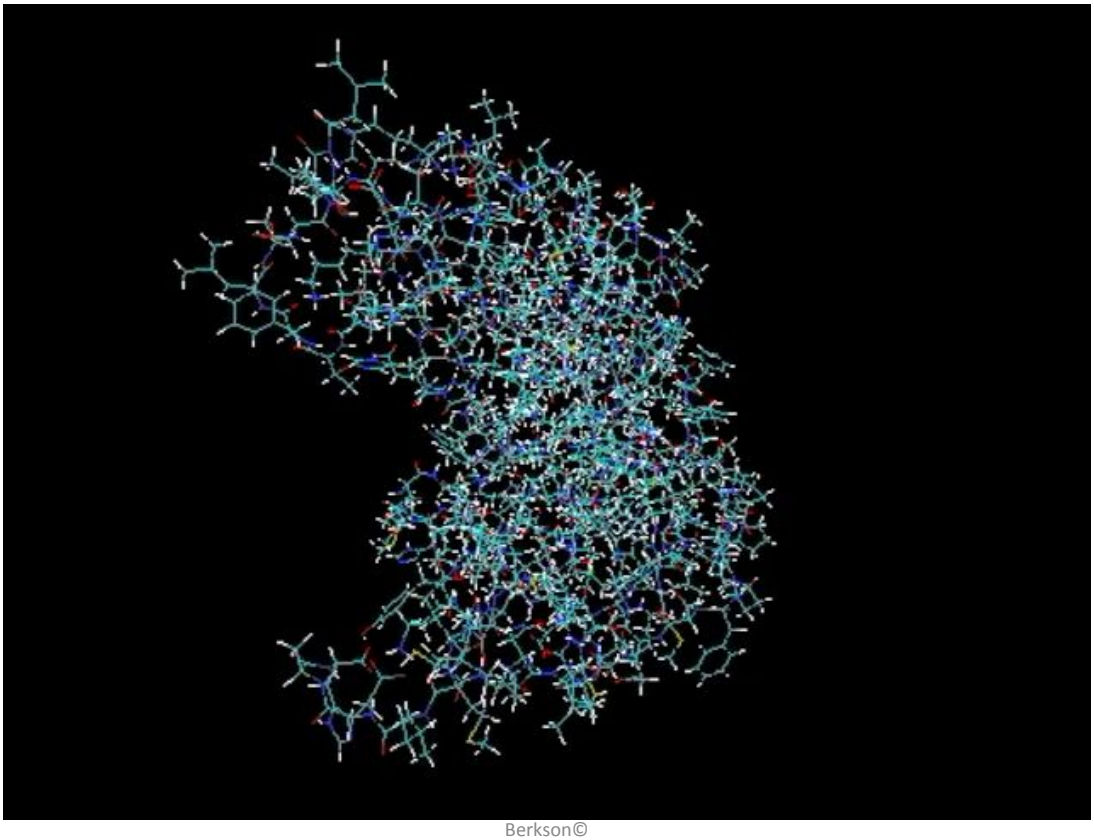
Hormones - Signalers

Receptor Domain



Hormone Cascade

- **Ligand** (hormones that DELIVER signals
- **Receptors** – proteins in the shape of satellite dishes that RECEIVE signals
- Hormones (ligands)
- Signal Receptor
- Receptor signals genes
- Genes tell cells what to do
- Operate most of body
- Brain, gut, kidneys, skin, etc.



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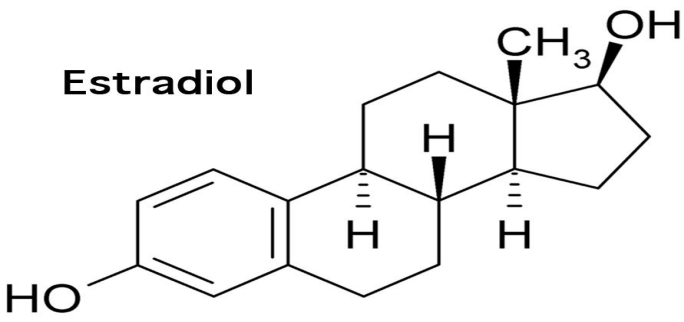
Example Estrogen (estradiol)



Esophagus | Kidney | Brain

Bone | Mitochondria energy | DNA histone epigenetics

T & B cells, Treg cells (immune cells) | Estrogen is not just a sexy or reproductive hormone

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First to exist was the receptor

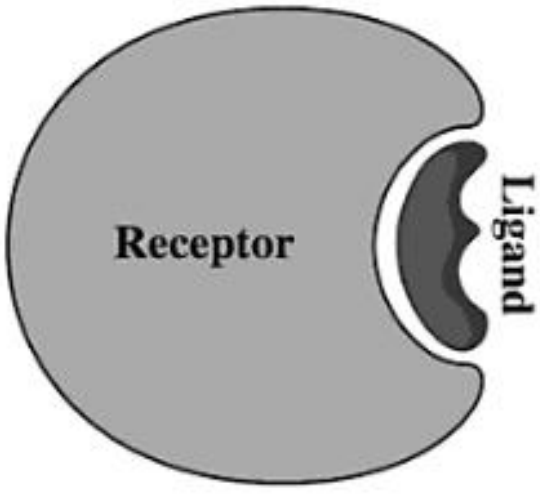
Hormone

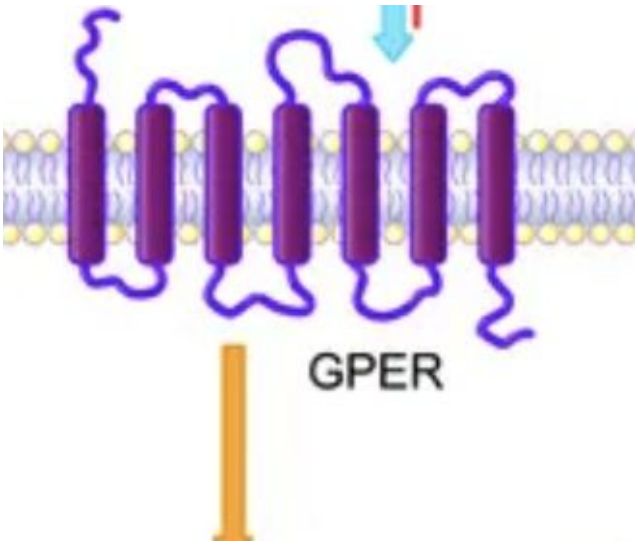
- Estrogen has the most receptors, up to 12 so far
- Progesterone has 2 receptors, A + B
- Testosterone has a bit more
- It is the balance of the receptors in tissues that dictates the action of hormones more than the hormones themselves
- The receptors deliver the message to the genes to tell cells what to do

Receptor

- Every hormone has several receptors
- Estrogen is the oldest so she has the most receptors
- ER alpha ER beta G protein couples estrogen receptor ER gamma ER delta ER X and more
- Signals to different receptors have different actions
- Many estrogenic compounds ie breakdown products of estrogen have different actions

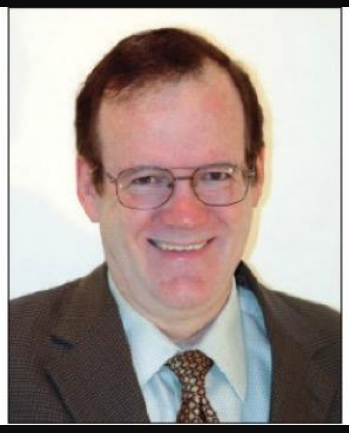
Genomic & Non-genomic Signaling





Sex Steroids Bind to Nuclear Receptors

- Nuclear receptors are a family of ligand-regulated transcription factors that are activated by steroid hormones, such as estrogen and progesterone, and various other lipid-soluble signals, including retinoic acid, oxysterols, and thyroid hormone.
- Nuclear receptors are inactivated until signaled by lipid-soluble signals (e.g., steroid hormones) that cross the plasma membrane.
- Once activated, most function as t**ranscription factors** to control gene expression for numerous biological processes.
- These are the nutrients as is found in Receptor Detox.
- But they can also act on cell surface membrane. Cold Spring Harb Perspect Biol. 2013 Mar; 5(3): a016709.
- doi: 10.1101/cshperspect.a016709 **Signaling by Nuclear Receptors**



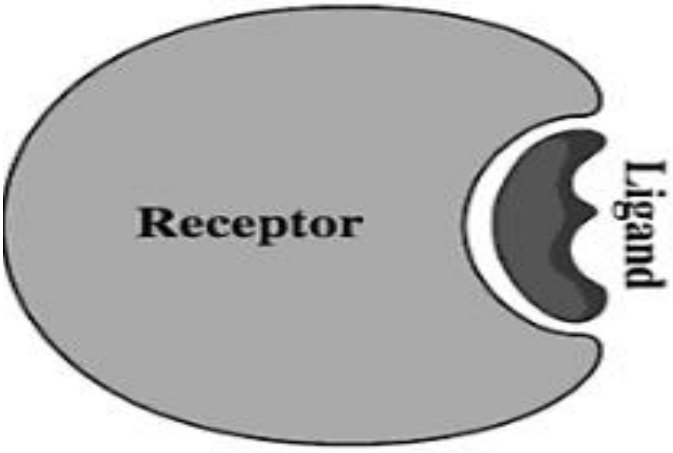
He Who Jumps Up and Down in the Window

- Sometimes hormones signaling a receptor can give one action, like before getting breast cancer, and may have a different reaction once have disease like having breast cancer.
- So hormones are not set in stone.
- They are flexible.

- J Steroid Biochem Mol Biol. 2000 Nov 30;74(5):279-85.**Molecular mechanisms of estrogen action: selective ligands and receptor pharmacology.**
- Katzenellenbogen BS[1], Montano MM, Ediger TR, Sun J, Ekena K, Lazennec G, Martini PG, McInerney EM, Delage-Mourroux R, Weis K, Katzenellenbogen JA.

Receptor Functionality

Inactive **Receptor when hormone can successfully bind it becomes ACTIVATED to deliver its message to genes.**



Is where the hormone rubber meets the hormone road.

Receptor Functionality

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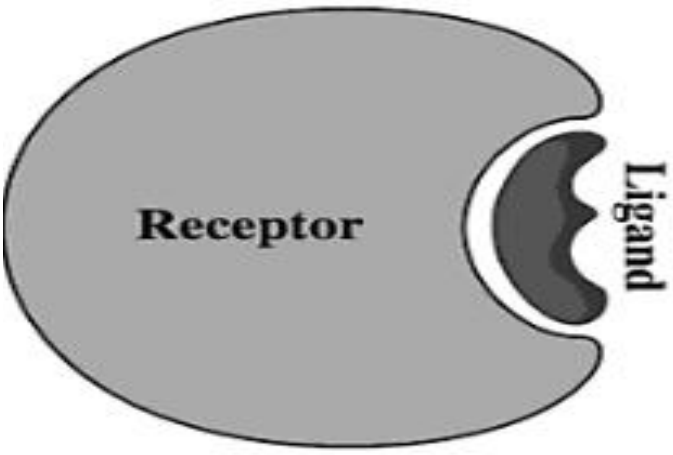
Nuclear Receptor: 3 Parts

- Receptor
- Ligand (or anti-ligand)
- **Co-regulatory proteins** (where what you eat and what you are exposed to - comes to play and competitive inhibitors)

- Recent Prog Horm Res. 2000;55:163-93; discussion 194-5. **Estrogen receptors: selective ligands, partners, and distinctive pharmacology.**

Receptor Functionality Nutrients



Nutrient Bowl – co-regulatory transcription factors

- Zinc (fingers)
- Vitamin B6
- Magnesium
- Iodine
- Vitamin A

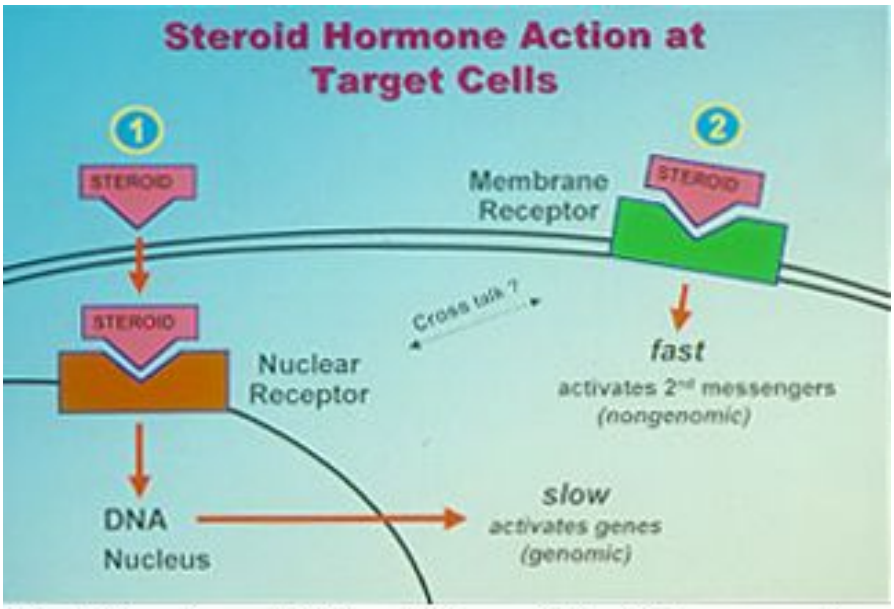
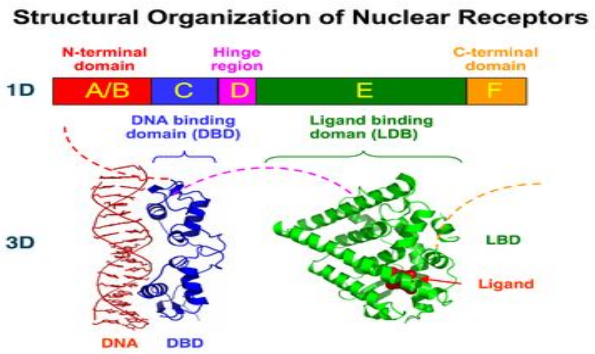


Fig 1. Receptor-mediated mechanisms of steroid hormone action

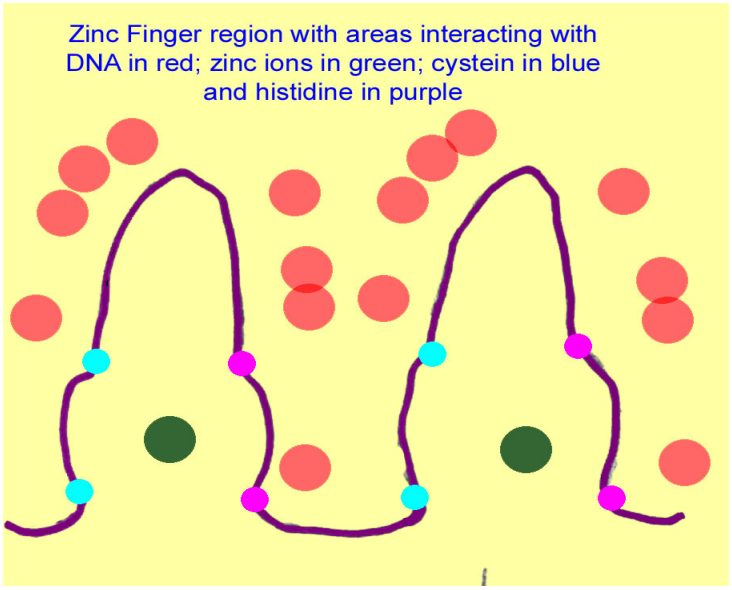
Binding Domain – "It's all about that…



Zinc finger

- Part of C domain of steroid receptors
- Best characterized domain of steroid receptors is C domain
- Zinc finger creates a SHAPE that can insert into a specific base pair of DNA
- Essential part of SHBG
- Inhibits aromatase
- Low zinc linked to hormonal issues
- Not responding to endogenous or exogenous hormones
- Leads to low T and high E
- Symptoms of low zinc: easily ill, chronic diarrhea, poor wound healing, ringing in the ears, feet smell, white spots on nails

Zinc Fingers



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Activators + Suppressors

- Activators – nutrients, fungi like candida, phytoestrogens
- Suppressors – heavy metals, competing pesticides, endocrine disruptors, nutrients - hormone altering chemicals, medications like tamoxifen, abd many unknown/

- J Agric Food Chem. 2003 Dec 17;51(26):7632-5.
- **Phytoestrogens modulate binding response of estrogen receptors alpha and beta to the estrogen response element.**
- J Musculoskel Neuron Interact 2003; 3(4):357-362 Overview of estrogen action in osteoblasts: Role of the ligand, the receptor, and the co-regulators

Duration of Signal - Vitamin B6

- Involved in the clearance of estradiol (and other hormones like cortisol) from nuclear receptors
- B6 deficiency > Estrogen dominance (sluggish removal from receptor)
- Estrogen supplementation including birth control pills; increased need for B6
- Sugar increases need for B6, many chemicals do even flaxseeds

- Am J Obstet Gynecol. 1976 Aug 15;125(8):1063-9.
- **Effect of oral contraceptives on nutrients. III. Vitamins B6, B12, and folic acid.**
- Biochem Pharmacol. 1976 Nov 1;25(21):2411-3.
- **In vitro trials to counteract the inhibitory effect of beta-oestradiol and ethynyloestradiol on the B6-dependent kynurenine aminotransferase enzyme.**

B6 – critical for hydroxsteroid dehydrogenase enzymes

High B6

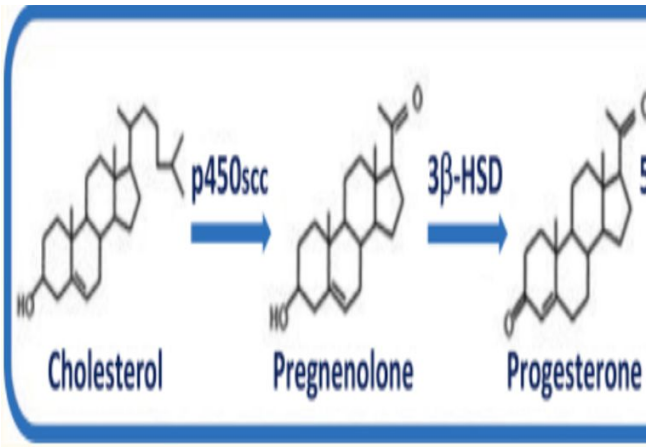
Suppresses Signaling

Insufficient B6

Prolonged Signaling

Just Right B6

Just right signaling



- **3 beta hydroxysteroid dehydrogenase**
- **Co-factor is NAD (niacin and vitamin B6)**

B6 deficiency linked to longer estradiol (and other hormones like T and cortisol) signaling

- 1. In vitro, pyridoxal phosphate extracts steroid-hormone receptors from tight nuclear binding (Cidlowski & Thanassi, 1981); in vitamin B6-deficient rats there is increased and prolonged nuclear accumulation of oestradiol in the uterus and testosterone in the prostate, associated with enhanced biological responsiveness of these target tissues to steroid hormone action (Symes et al. 1984; Bowden et al. 1986). 2. Slices of uterus from vitamin B6-deficient rats accumulated more [3H]oestradiol than did tissue from repleted animals. Acute repletion with vitamin B6 (0.5-1 h before killing) further increased the uptake of the steroid. 3. Isolated hepatocytes from vitamin B6-deficient rats accumulated more [3H]dexamethasone than did cells from repleted animals. Pre-incubation of the hepatocytes with pyridoxal phosphate resulted in a further increase in the uptake of the steroid. 4. The results suggest that in addition to the putative role of pyridoxal phosphate in releasing steroid-hormone-receptor complexes from tight nuclear binding (Cidlowski & Thanassi, 1981), vitamin B6 deficiency may also increase the concentration of steroid-hormone receptors or enzymes and other steroid-binding proteins in target tissues.

- Effects of vitamin B6 deficiency and repletion on the uptake of steroid hormones into uterus slices and isolated liver cells of rats. Br J Nutr. 1989 May;61(3):619-28. doi: 10.1079/bjn19890149. PMID: 2758016.

B6 & Zinc deficiencies decrease estrogen signals – more complex than hormone levels

- A deficiency of vitamin B6 has been reported to enhance oestrogen responsiveness of the uterus in rats whereas zinc deficiency provokes a syndrome suggestive of a diminution in oestrogen sensitivity. In this study [3H]oestrogen uptake by the uterus was increased in rats deficient in either nutrient and the differences were additive in the dually deficient animals. The total number of oestrogen receptors per g tissue was unaffected by either nutrient but the proportion of the receptors recovered from the nuclear fraction increased from about 6 to 74% when both nutrients were withheld. The results are consistent with the hypothesis that both zinc and pyridoxal phosphate play important metabolic roles in end-organ responsiveness to oestrogen.

- Effect of zinc and/or pyridoxine deficiency upon oestrogen retention and oestrogen receptor distribution in the rat uterus. J Steroid Biochem. 1987 Mar;26(3):303-8. doi: 10.1016/0022-4731(87)90093-8. PMID: 3586647.

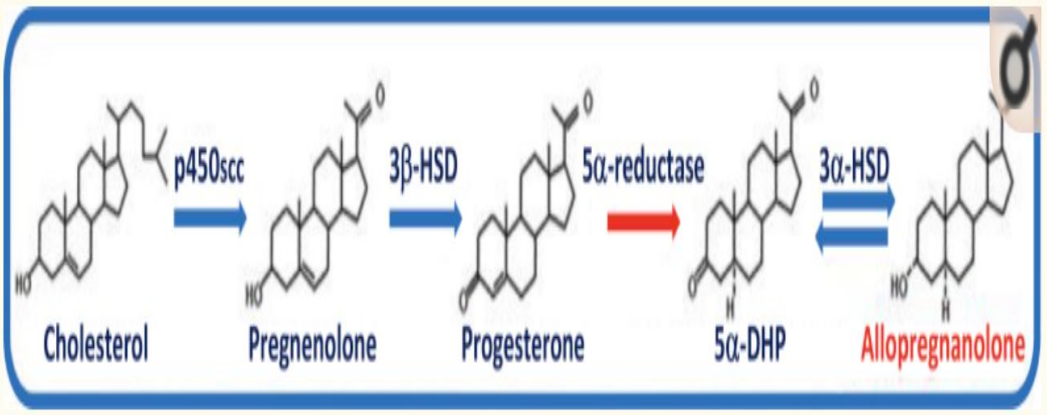
Vitamin B6 Insufficiency

- **Makes sex steroids bind to their receptors stronger, longer**
- **Even make more receptors**
- **Helps it bind**
- But if insufficient, ”holds” it there
- Velcroes cortisol to its receptor

- We found that the binding activity of nuclear extract prepared from the liver of vitamin B6-deficient rats was far greater than that of the control rats, indicating that the DNA-binding activity of glucocorticoid receptor was enhanced by vitamin B6 deficiency.
- Pyridoxal 5'-phosphate modulates expression of cytosolic aspartate aminotransferase gene by inactivation of glucocorticoid receptor. J Nutr Sci Vitaminol (Tokyo). 1995 Jun;41(3):363-75. doi: 10.3177/jnsv.41.363. PMID: 7472680.

Vitamin B6

- Dictates timing of E, T and cortisol on receptors
- Too little B6 and too long of signal. Excess E, T, and C signals.
- Too much and tamp down signals.
- It is part of orchestration of “Duration of Steroid Signaling”
- Blocks LPS entry into body!
- Supports **3 beta hydroxysteroid dehydrogenase** –
- Co-factor is NAD (niacin)
- J Cell Mol Med. 2020 Mar; 24(5): 3139–3148. **Vitamin B6 inhibits macrophage activation to prevent lipopolysaccharide-induced acute pneumonia in mice**



- **3 beta hydroxysteroid dehydrogenase** –
- Co-factor is NAD (niacin)

- **3 alpha hydroxysteroid dehydrogenase** –
- In target tissue regulates how steroid hormones occupy their receptors
- effected by other steroids too such as Er beta, progesterone and T

Structure and function of 3 alpha-hydroxysteroid dehydrogenase. Steroids. 1997 Jan;62(1):101-11. doi: 10.1016/s0039-128x(96)00167-5. PMID: 9029723.

Allopregnanolone: From molecular pathophysiology to therapeutics. A historical perspective Neurobiol Stress. 2020 May; 12: 100215.doi: 10.1016/j.ynstr.2020.100215

B's

- Niacin and vitamin B-6 have complementary functions, with both vitamins helping to support your metabolism especially NAD.
- Niacin helps make up a part of NAD, a chemical your cells use to make mitochondrial energy.
- Vitamin B-6 also helps derive energy from nutrients.
- Vitamin B-6 metabolizes protein from your diet
- And helps break down stored carbohydrates into glucose, the fuel your cells need to function.

Hormones need B6

With both products daily you get the perfect support of B6.

Berkson©

Birth Control Pills

- Int J Vitam Nutr Res. 1996;66(1):46-54. **Early effect of a low dose (30 micrograms) ethinyl estradiol-containing Triphasil on vitamin B6 status. A follow-up study on six menstrual cycles.**

Retinoic Acid – The Bomb that…

- Receptor on every single cell in the body
- Factor
- Transcription factors i.e., for estrogen: retinoic acid (RA) receptor-a (RARa),
- RARa is an estrogen induced gene
- **We now show that RAR alpha is required for efficient estrogen receptor-alpha** (ER)-mediated transcription and cell proliferation. RAR alpha can interact with ER-binding sites, but this occurs in an ER-dependent manner, providing a novel role for RAR alpha that is independent of its classic role.
- Dr Wright has a non-hormone program to induce more estrogen production
- Genes Dev. 2010 Jan 15;24(2):171-82. doi: 10.1101/gad.552910. **Cooperative interaction between retinoic acid receptor-alpha and estrogen receptor in breast cancer.**

Vitamin A — Ain’t Get No Respect

Unappreciated Role of Vitamin A

- Critical for working of estrogen optimally
- Hypovitaminosis A was found to be an important cause of menorrhagia, and a statistically significant difference between the fasting serum vitamin A values of healthy controls and patients with menorrhagia was noted.
- **Vitamin A is a co-factor of 3 beta-dehydrogenase in steroidogenesis and deficiencies of this vitamin may result in impaired enzyme activity**.
- The level of endogenous 17 beta-oestradiol appears to be elevated with vitamin A therapy, and menorrhagia was alleviated in more than 92% of patients
- S Afr Med J. 1977 Feb 12;51(7):191-3.
- **Vitamin A in the treatment of menorrhagia.**

Boron + Vitamin A Help Boost Estrogen Signals

- Boron increases '**bioavailability of estrogen**'
- **Some symptoms of Boron deficiency**are arthritis, brittle bones, carpal tunnel syndrome, degenerative joint disease, hormonal imbalance, loss of libido, memory loss, muscle pain, osteoporosis, receding gum, and weak joint cartilage. Boron deficiency causes greatly increased amounts of calcium and magnesium to be lost with the urine.
- Boron deficiency causes the parathyroid to become overactive and stressed which causes the glands to release too much parathyroid hormone. Excess parathyroid hormones raise the blood level of calcium by releasing calcium from the bones, joints and teeth into the blood stream. This then leads to osteoarthritis and other forms of arthritis, such as rheumatoid arthritis, juvenile arthritis, spondylitis, gout, lupus, osteoporosis, pyorrhea and tooth decay.
- Integr Med (Encinitas). 2015 Aug;14(4):35-48.
- **Nothing Boring About Boron.**
- Biull Eksp Biol Med. 1997 Jul;124(7):111-4.
- **[Effect of boron on the ultrastructure of parathyrocytes and atrial cardiomyocytes].**
- Okajimas Folia Anat Jpn. 1993 Dec;70(5):209-17.
- **Ultrastructure of the parathyroid gland of magnesium-treated golden hamster exposed to a hypergravity environment: a stereological study.**
- **Need boron: taking estrogen but not feeling any different, elevated PTH or calcium, diagnosed with primary hyperparathyroidism not due to vit D insufficiency.**

PABA

- **What is it:** Paraaminobenzoic acid (PABA) is an intermediary in the synthesis of folic acid.
- PABA potentiates the action of hormones: glucocorticoids and estrogens. Historically, PABA was thought to be a member of the B vitamin family.
- **It's history**: In the early 1950's when cortisone was very expensive, it was discovered that adding para-aminobenzoic acid to cortisone slowed down the breakdown of cortisone in the liver allowing the patient to get more benefit from less medication and cost**.**
-

PABA

- **Hormone potentiator**: PABA was found to potentiate the action of glucocorticoids and estrogens

It does so by slowing down the breakdown or degradation of these hormones and many sex steroid hormones so they stay in the blood stream longer.

- Am J Med Sci. 1954 Jan;227(1):80-2. Effect of para-aminobenzoic acid on the metabolism of cortisone in liver tissue.
- PABA and cortisone. Lancet 1951:2;674.

PABA

- **Mechanisms of action** : **PABA slows down the breakdown of hormones in the liver and in the uterus so they hormones can act longer .** PABA is so effective at this that a reduction in the dosage of hormonal therapies might be considered when taking PABA along estrogens or possibly other steroid hormones.
- Ukr Biokhim Zh (1978). 1990 Jan-Feb;62(1):97-101. [Aminobenzoic acid derivatives as specific inhibitors of cyclic nucleotide phosphodiesterase in the rat uterus].
- Nutrtional Medicine Second Edition. Gaby R. Alan Perlberg Publishing Concord, NH. 2017;p 248.
- **More benefits of PABA:**
- —**PABA is a known estrogen potentiator** .
- In an uncontrolled trial, administration of 100 mg of PABA 4 times a day per day for 3 to 7 months to 16 women who had been infertile for at least 5 years resulted in pregnancy in 12 cases (75%).
- The clinical effects of a new B complex factor, para-aminobenzoic acid, on pigmentation and fertility. South Med Surg 1942(March):104:135-139.

PABA Protects Against Ovarian Cancer

- Med Chem. 2006 Feb 9;49(3):1157-64. PABA/NO as an anticancer lead: analogue synthesis, structure revision, solution chemistry, reactivity toward glutathione, and in vitro activity.
- PABA is an immune booster by boosting natural production of interferon.
- Antibiot Khimioter. 1999;44(4):17-20. [Para-aminobenzoic acid--an interferon inducer].
- —PABA protects against stroke so is excellent to take along with estrogens or to keep natural estrogens from clotting.
- Eksp Klin Farmakol. 2000 May-Jun;63(3):40-4. [Antithrombotic activity of para-aminobenzoic acid].
- Thromb Res. 1997 Apr 15;86(2):127-40.p-Aminobenzoic acid, but not its metabolite p-acetamidobenzoic acid, inhibits thrombin induced thromboxane formation in human platelets in a non NSAID like manner.

PABA is a natural and effective anti-inflammatory agent.

- Am J Med Sci. 1954 Jan;227(1):74-9. Long term treatment of rheumatoid arthritis with para-aminobenzoic acid and cortisone acetate.
- Am J Med Sci. 1951 Sep;222(3):243-8. The synergistic action of paraaminobenzoic acid and cortisone in the treatment of rheumatoid arthritis.
- Am J Med Sci. 1954 Jan;227(1):80-2. Effect of para-aminobenzoic acid on the metabolism of cortisone in liver tissue

PABA is a powerful antioxidant and a lipid peroxidase inhibitor, even in the eyes
And an anti-fungal agent!

- .
- Dokl Akad Nauk. 1998 Jul;361(3):419-21. [Para-aminobenzoic acid as an antioxidant].
- Vestn Oftalmol. 1998 Nov-Dec;114(6):39-44. [Comparative assessment of antioxidant activity of para-aminobenzoic acid and emoxipin in retina].
- ——PABA appears to have antifibrotic actions as it has been used successfully to treat excessive fibrotic conditions such as Peyronie's disease, Dupuytren's contracture and in some patients with Scleroderma though these treatments were with the pharmaceutical version of PABA, KPAB.
- As human age, fibrosis can drive adverse modeling of tissues in the heart, kidney and brain. PABA inhibits fibrosis, so PABA promotes healthier heart, brain and renal tissue as we age. It also then appears to increase the use of oxygen especially by the skin.
- Am J Med Sci. 1964 Nov;248:550-61. ANTIFIBROTIC THERAPY WITH POTABA.
- Nutritional Medicine Second Edition Gaby Alan R. Perlberg Press 2017 ps: 612, 701, 846, 644.

You want PABA in a daily protect hormone product, along with A, B6 etc.

- —PABA has been used by some practitioners to treat, at high dosages, Hashimoto's thyroiditis.
- While PABA appears to decrease TPO antibody levels to some extent, additional research is needed. But it is not contraindicated in autoimmune thyroiditis.
- Nutritional Medicine Second Edition Gaby Alan R. Perlberg Publications 2017 p: 1194.

It's all here along with adequate niacin, especially combined with Receptor Detox, to keep the skin healthy & young . Both = 40 mg of niacin/d

More about the estrogen receptors