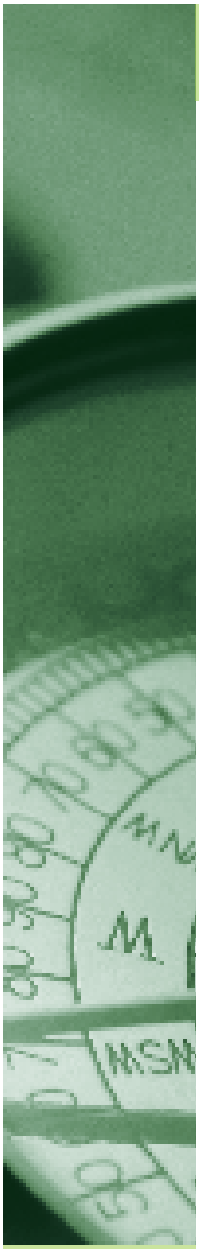
Beyond Basic BHRT Strategies

The Next Step In Patient & Practice Optimization.

The materials contained in this BHRT Training Syllabus were originally presented at
College Pharmacy's annually hosted BHRT Training Symposium June 1-3, 2007 in Denver, Colorado.



Level II BHRT Symposium
Featured Speakers

Level II BHRT Symposium Featured Speakers

George Juetersonke, DO Course Director

George Juetersonke, DO, practices in Colorado Springs, CO. He is Board Certified in Family Practice and has been actively practicing for over 20 years specializing in the treatment of menopause and andropause using BHRT. For five years he served full time on the medical faculty of the University of North Texas Health Science Center where he was an Assistant Professor in the Department of Preventive Medicine. He continues to hold a faculty appointment as Clinical Assistant Professor at the University of North Texas Health Science Center in Fort Worth.

John Crisler, DO

John Crisler, DO, practices in Lansing, MI, where he is president and founder of the AllThingsMale Center for Men's Health. He has distinguished himself in the field of Anti-Aging Medicine by developing two new treatment protocols for Testosterone Replacement Therapy. Commanding a substantial Internet following, Dr. Crisler founded the first Internet Forum on HRT for men in the world moderated by a physician. He now enjoys training fellow physicians in this area of medicine, and is known as a dynamic and informative speaker. Dr. Crisler delivered the very first lecture ever on male hormone replacement therapy before the Michigan Osteopathic Association at their 2004 Annual Convention.

Rebecca Glaser, MD

Rebecca Glaser, MD, has evaluated and treated over two thousand breast cancer patients and over fifteen hundred patients with hormone imbalances, and is currently involved with bio-identical hormone replacement therapy and its impact on healthcare. She continues to treat patients and lectures on 'Bio-identical Hormone Balance and Health' and evidence based age management therapies.

Terry Grossman, MD

Terry Grossman, MD, is the founder and medical director of Frontier Medical Institute in Denver, CO, one of the largest nutritional medicine centers in the country. Dr. Grossman is Board Certified by the American Board of Anti-Aging Medicine and the American Holistic Medical Association and is assistant professor of family practice at the University of Colorado School of Medicine. Dr. Grossman lectures frequently on complementary and age management medicine.

Steven Hotze, MD

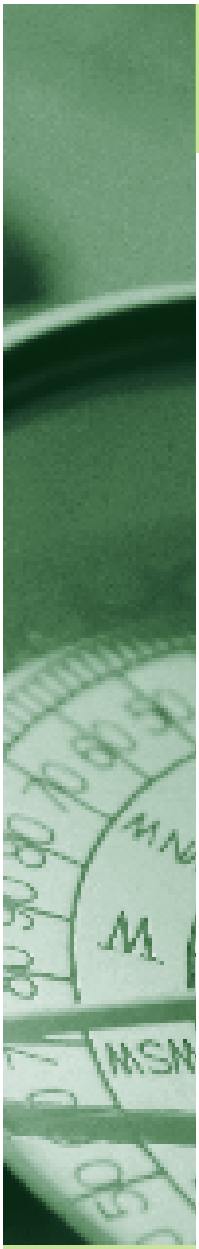
Steven Hotze, MD, is the founder of the Hotze Health and Wellness Center and the American Academy of Biologically Identical Hormone Therapy, in Katy, TX. Dr. Hotze obtained his medical degree in 1976 from the University of Texas Medical School at Houston. He is a Fellow Member of the American Academy of Otolaryngic Allergy, Former President of the Pan American Allergy Society, and the American Academy of Environmental Allergy.

Neil Hirschenbein, MD

Neil Hirschenbein, MD, is Board Certified in Internal Medicine, Gastroenterology, and Age Management Medicine. He has served as Medical Director, Physician Advisor, and Board Member for a variety of clinics and medical groups in the San Diego area. He is a member of the American Nutraceuticals Board of Directors, the Journal of Longevity Medical Board, and the American Board of Holistic Medicine, and a frequent speaker on hormonal therapy, wellness, age management, and nutrition.

Tiffani Schilling, PharmD

Tiffani Schilling, PharmD, is a graduate of the University of Minnesota School of Pharmacy, with over a decade of experience in compounding and women's health care. Trained as an herbalist, Schilling counsels patients on natural and complementary therapies, including bio-identical hormone replacement therapy.



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Update on Bio-Identical Hormone Replacement Therapy

Goals & Review of Current HRT Developments.

Presented by

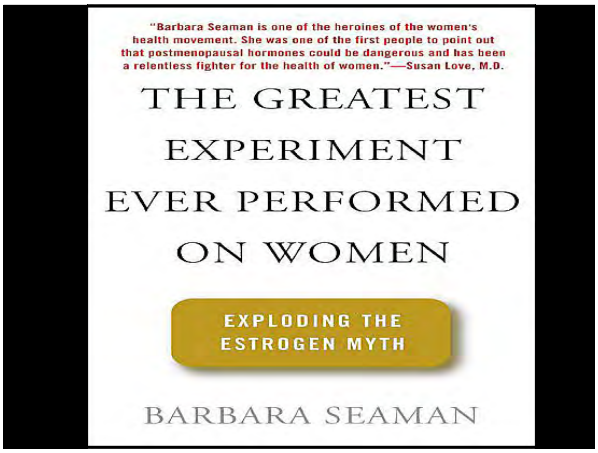
George Juetersonke, DO

Level II BHRT Symposium

1 June 2007

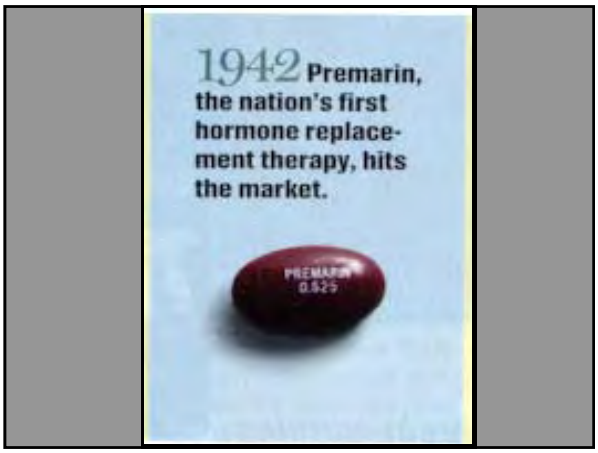
George Juetersonke DO
Adjunct Associate Professor
Midwestern University, College of Health Sciences, IL

Clinical Assistant Professor
University of North Texas Health Science Center, TX



Greatest Experiment Ever Performed on Women

- Imperial Chinese, urine
- 1899 Merck Manual "Climaterica" remedies contained heroin and opium
- Ovariian- dried cow ovaries [Dricovaries? like Premarin?]
- 1928 Germans synthesize estrone
- 1938 British make DES (stilbestrol)



- 1942, pregnant mares urine patented by Ayerst, predecessor to Wyeth, approved by the FDA
- 2001, Premarin 45 million Rx's
  21 million Prempro Rx's

2.04 billion in sales for 2001

Menopause as Disease

- 1952, Estrogen enhances memory
- 1959, JAMA 25 year study
  113 women, estrogen protects bones and improves menopause
  "fear of breast and cervical cancer appears unfounded"

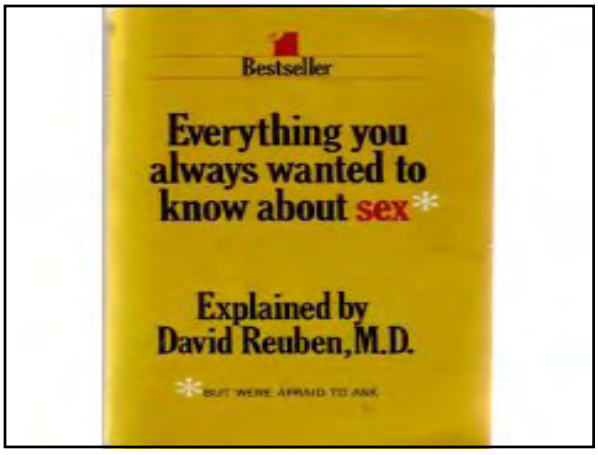
Feminine Forever

- 1962 JAMA, Robert Wilson MD, estrogen reduces breast cancer
- 1966 "cure for the tragedy of menopause..the deficiency disease ...a disease so insidiously blended with chronological aging that there is a tendency for it to be overlooked"
- "all post-menopausal women are castrates"

- "Women will not become dull and unattractive, estrogen makes women adaptable, even tempered, and generally easy to live with... preserves the glow of skin and gloss of hair"
- Response to *Feminine Forever* was stunning
- *Look Magazine*, *Science Digest*

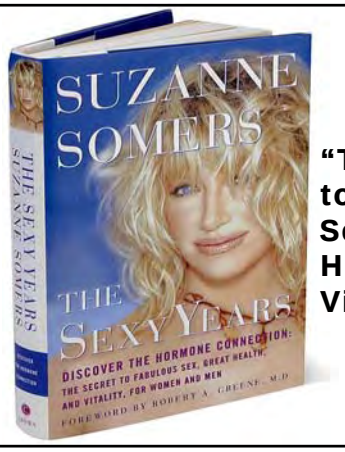
"the book that ends menopause"

- estrogen sales quadruple



Everything You Always Wanted to Know About Sex (best seller)

- David Reuben MD, "Estrogen is a menopausal cure all" 1969
- "Without estrogen a woman gets as close as she can to being a man"
- *Harpers Bazaar*, "estrogen does it all… benefits and safety of ERT has been convincingly demonstrated"



"The Secret to Fabulous Sex, Great Health, and Vitality"

1970

- Medical Journals run Wyeth ads
- "Treat her with Premarin. Keep her on Premarin"
- *All in the Family's* Edith Bunker announces menopause.

1973

- *Harpers Bazaar* declares:

"There does not seem to be a sexy thing that estrogen can't do…a real package that spruces up your vagina"

30 million Rx's every year, about half of all menopausal women

Wyeth vs Duramed 1990

- Generics release estrogen too fast, ineffective and dangerous
- 1997 FDA says Duramed can't show same rate of absorption
- Wyeth claims generics must have same inactive ingredients
- FDA denies approval of Duramed's product

- Duramed submits *new* drug application
- Performs new clinical trials
- Cenestin approved 2000, marketed as all natural derived from soy but….really is an equine estrogen

Antitrust Lawsuit

- Wyeth prevents health plans and pharmacy benefits mangers from adding Cenestin to formularies with rebates and discounts
- Wyeth begins marketing PremPro, funds HERS

Women's Health Initiative

The 9/11 of HRT?

Beginning of the End ?

Citizen Petition Seeking FDA Actions to Counter Flagrant Violations of the Law by Pharmacies Compounding Bio-Identical HRT Drugs that Endanger Public Health
October 2005

Wyeth's Wealth Vs Women's Health

Filed by Wiley, Rein & Fielding on behalf of Wyeth.

"Wyeth is a leading manufacturer of FDA-approved estrogen-containing hormone therapy drug products and is a leader in women's health. As such Wyeth feels compelled to advise the FDA of the following activities and the potential risk to which American women may be exposed due to insufficient information BHRT compounding pharmacies provide on the risks that accompany their products."

Action Requested

Labeling and Advertising Disclosures

1. BHRT new drug
2. BHRT compounded without FDA requirements
3. Not safe or effective for any use
4. Require above be disclosed

Importance of Thyroid Therapy in Optimizing BHRT.

Thyroid Therapy: Pitfalls and How to Solve Them.

Thyroid Lab Tests: How Useful Are They?

Importance of Treating Adrenal Deficiency in Patients with Both Hypothyroidism & Adrenal Failure.

Presented by

Steven Hotze, MD

Thyroid Therapy: Pitfalls & How To Solve Them

Steven F. Hotze, M.D.
SFH@hotzehwc.com

Level II BHRT Symposium…The Next Step in Patient & Practice Optimization
Denver, Colorado
June 1, 2007

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How to Diagnose Hypothyroidism

1. Clinical History - take a copious history of symptoms
2. Clinical experience - listen to patients and have them describe all of their symptoms
3. Basal Body Temperature
   a. Normal temperature under the arm after sleep 97.8 – 98.2
   b. Use a thermometer to check temperature under the arm before arising in the morning
   c. In women, basal body temperature is most accurate during menses (women's temperature rises at ovulation)

2

4. Thyroid Blood Tests
   a. T3 Uptake (not helpful)
   b. Free T4 index (not helpful)
   c. TSH (thyroid stimulating hormone) (Helpful when elevated above 4.5)
   d. Free Thyroxine (T4) (very helpful) – This measures the amount of unbound thyroxine (thyroxine not bound to protein)
   e. Anti-Thyroid Antibodies (FAMA)
      (1) Anti-microsomal antibodies
      (2) Anti-thyroglobulin antibodies

3

How to Treat Hypothyroidism

1. Armour Thyroid (desiccated porcine thyroid) Supplementation

a. Standardized

b. Contains both T3 and T4 in the same proportions as found in the human body

c. Contains micronutrients from the thyroid gland

d. Desiccated thyroid has been used safely, effectively and inexpensively for approximately 90 years

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e. Start adult patients with good cardiac status on one-half (½) grain/day

(1) Increase by ½ grain increments every 2-3 weeks as indicated until the symptoms of hypothyroidism have resolved

(2) Follow resolution of clinical symptoms

(3) Follow free thyroxine (Free T4) level

(4) Armour Thyroid may be taken in the morning or the dose may be divided between the morning and after lunch in order to boost afternoon energy levels.

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f. Start children between the ages of 6 to puberty on ¼ grain/day

(1) Follow resolution of clinical symptoms

(2) Follow free thyroxine (Free T4) level

(3) Increase incrementally every 2-3 weeks as indicated until the symptoms of hypothyroidism have resolved

6

g. Cautions

(1) Be sure to reevaluate your patients clinically within 6-8 weeks of their initiating thyroid supplementation. Draw a repeat Free T4 at this visit.

(2) I would not recommend treating any patient with known or probable coronary artery disease.

(3) In individuals above 60 years old who have good cardiovascular status based upon a negative stress EKG, I recommend starting them on ¼ grain and increasing it incrementally every 3 weeks as indicated

7

(4) Patients with Adrenal Fatigue

i) Occasionally, patients with Adrenal Fatigue are unable to tolerate even the smallest amount of natural thyroid hormone supplementation. These patients commonly have adrenal fatigue and should be started on low doses of natural cortisol for several weeks before trying to reintroduce thyroid supplementation. Adrenal Fatigue is commonly seen in patients who have Autoimmune Thyroiditis.

8

2. Slow Release T3 (SRT3) Supplementation

a. This is the active, intracellular thyroid hormone.

b. Compounded to be the identical molecule produced by the body

c. Released gradually over 12 hours for maximum benefit

d. Try this in combination with Armour Thyroid for patients whose symptoms fail to resolve using Armour Thyroid alone.

d. Start adult patient on 6.25 mcg. or 12.5 mcg. every morning in combination with the current dose of Armour Thyroid. This may be increased incrementally in 4 days.

e. Some physicians give this every 12 hours.

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Results & Benefits of Natural Thyroid Hormone Supplementation

1. On the appropriate dose of thyroid supplementation, the symptoms of hypothyroidism should be dramatically decreased or resolved.

10

Side Effects of Excessive Natural Thyroid Hormone Supplementation

1. Shakiness
2. Jitteriness
3. Nervousness, agitation
4. Tachycardia (I ask patients to check their pulse as it should remain below 90 beats per minute at rest)
5. Heart palpitations
6. Worsening of fatigue
7. Insomnia

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Treatment of Excess Thyroid Hormone Supplementation

1. If any of these symptoms occur as the patient increases their thyroid supplementation, then they should immediately stop all thyroid supplementation for 3-4 days or until the symptoms have resolved. They then can return to the previous dose which caused no symptoms.
2. If by adding T3 in combination with Armour Thyroid causes the above symptoms of excess thyroid, then stop all thyroid medication for 3-4 days or until the symptoms have resolved. They then can restart Armour Thyroid without T3.

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Treatment of Excess Thyroid Hormone Supplementation cont.

3. If palpitations are frequent or tachycardia is clinically significant, then Tenormin (Atenolol) 25 mg., 1-2 initially, will usually relieve these symptoms within two hours. The patient can then take Tenormin 25 mg. every 12 hours as needed to control the tachycardia. This usually resolves within a day.

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Addressing Pitfalls in Evaluation and Treatment of Thyroid: Clinical Pearls

1. Thyroid blood tests do not correlate well with clinical symptoms.
2. The laboratory "normal" range is arbitrarily defined as plus or minus two standard deviations from the mean, encompassing approximately 90-95% of the population.
3. Thyroid hormone blood levels vary significantly from lab to lab.
4. Thyroid hormone blood levels vary significantly during the day.
5. In patients on supplementation, thyroid hormone blood levels vary significantly depending upon when the patient last took their thyroid supplement.

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6. On sufficient Armour Thyroid supplementation needed to resolve symptoms, the TSH level will fall to near 0. Do not be alarmed! Because Armour Thyroid contains 80% T4 and 20% T3, it tends to suppress TSH production to a greater degree than the synthetic T4 supplements, such as Synthroid. A very low TSH in a patient on thyroid supplementation does not mean that the patient is hyperthyroid or is taking excessive amounts of thyroid supplementation. The patient is only hyperthyroid if he or she has symptoms of hyperthyroidism. If the patient receives excessive thyroid supplementation, then they will know it within a day and can completely stop supplementation. Ultimately, they can reduce their dose to the level that produced no symptoms.

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7. Studies have demonstrated that low TSH levels are not associated with bone loss in an individual who is clinically euthyroid. We have performed numerous repeat bone density studies on our patients who take Armour Thyroid and have low TSH levels. Their bone density levels do not reveal any increased bone loss. In fact, many show increased bone mass, which is due to simultaneous progesterone supplementation.

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8. Studies indicate that there is no increased bone loss in individuals whose Free T4 remains within the "normal" range while on thyroid hormone supplementation.
9. Ovarian aging leads to hormonal imbalances in women, which are manifested by progesterone deficiency and estrogen dominance. Estrogen dominance causes the liver to produce high levels of thyroid binding globulin (TBG), which binds thyroid hormones in the blood, leaving less free available thyroid to be assimilated into the cells.

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10. All counterfeit hormones, whether in the form of birth control pills or HRT, produce a state of estrogen dominance, adversely affecting the body's ability to assimilate thyroid hormone into the cells.
11. Autoimmune Thyroiditis produces antibodies to the thyroid gland and to thyroid hormones, decreasing assimilation of thyroid hormones into the cells.
12. Routine laboratory studies of thyroid hormone levels measure thyroid hormones bound to protein, which are inactive. Over 97% of all thyroid hormone is bound to protein.

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13. Free T4 measures unbound thyroid hormone.
14. T4 is the prohormone and must be assimilated by the cells and converted to the active hormone, T3, which increases metabolism.
15. Testosterone, progesterone and cortisol all enhance the intracellular conversion of T4 to T3. The hormones work synergistically and by using them in combination, the patient will require less thyroid hormone supplementation.
16. I have seen a few (less than five) patients with symptoms of hypothyroidism, who had apathetic hyperthyroidism, diagnosed by elevated Free T4 and a TSH near 0.

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17. Always obtain a resting EKG before starting an adult on thyroid supplementation. If the clinical history or the EKG suggests a cardiac problem, then obtain a stress EKG before starting the patient on thyroid supplementation.
18. Selenium is a trace mineral which enhances the intracellular conversion of T4 to T3. Selenium is very low in the American diet. Selenium 200 mcg. BID can be beneficial in improving intracellular thyroid hormone function.

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Other Thyroid Medications

1. Levothyroxine (e.g. Synthroid)
   a. Not recommended
   b. Contains only T4
   c. Clinically less effective
   d. Has been under investigation by Food & Drug Administration since 1997
      i) Action: Notice Re: Levothyroxine Sodium
      Significant stability and potency problems
      Failure to maintain potency through expiration date
      Dosage strength various from lot to lot
      Lack of stability and consistent potency poses serious health consequences

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FDA allows 3 years to obtain approved new drug applications (Federal Register: August 14, 1997 Volume 62, Number 157)

ii) FDA issues guidelines for phase-down of Levothyroxine Sodium in July, 2001 because there has been no improvement. All distribution of this product scheduled to gradually cease by August, 2003 unless FDA approval secured.

iii) FDA subsequently approved Synthroid in July, 2002.

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2. Cytomel
   a. Contains only T3 (T3 is short acting, peaking in 2-3 hours)
   b. Liothyronine – slow release T3 (SRT3) lasts 12 hours

3. Conversion of synthetic thyroid hormones to natural desiccated thyroid hormone
   a. Levothyroxine (e.g. Synthroid)
      (1) .05 mg. equivalency- approximately ¾ - 1 grain (45 - 60 mg.) Armour Thyroid

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b. Cytomel (T3)
   (1) 25 mcg. equivalency- approximately 1 grain (60 mg.) Armour Thyroid

c. When converting from Synthroid to Armour Thyroid, err on giving a lesser amount than the equivalent dose because Armour Thyroid is more active. You can always incrementally increase Armour Thyroid

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Contact Information:

Steven F. Hotze, M.D.
Hotze Health & Wellness Center
20214 Braidwood, #215
Katy, Texas 77450
www.hotzehwc.com
281.698.8679

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Thyroid Lab Tests: How Useful Are They?

Steven F. Hotze, M.D.
SFH@hotzehwc.com
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1

Thyroid function tests cannot be clinically correlated with symptoms of hypothyroidism. The issue is not just about thyroid hormone production, which laboratories attempt to measure, but more importantly it's ultimately about thyroid hormone utilization at the cellular level, which can only be measured by clinical symptoms.

2

Thyroid function tests' normal ranges are established by determining the mean plus or minus 2 standard deviations of the last thousand patients. This allows for 95% of the population to fall within the normal lab value range. As the population ages the mean invariably falls as does the laboratory normal range.

3

A. Thyroid Stimulating Hormone (TSH) – can be useful if out of range
   1. TSH is a pituitary hormone, not a thyroid hormone.
   2. TSH should not be used as the sole predictor of thyroid function or the effectiveness of thyroid treatment.
   3. When elevated above 3.0, TSH is a laboratory indicator of hypothyroidism.
   4. There is little or no clinical correlation between the TSH and a patient's symptoms in hypothyroidism.

4

5. TSH measures the setpoint for thyroid production in the pituitary gland, not the cellular side of utilization of thyroid hormone.
6. Very low TSH is to be expected when a proper, symptom-relieving dosage of desiccated thyroid extracts is used.
7. The TSH range reflects the pituitary setpoint for thyroid production needed to stimulate the release of what would be a normal thyroid hormone blood level.
8. The TSH setpoint for thyroid production is not related to the cellular utilization of thyroid hormone.
9. Aging and environmental factors may lower the pituitary setpoint for TSH.

5

B. **Free Thyroxine (Free T4) – excellent baseline measurement**
   1. T4 is the inactive pro-hormone which must be converted intracellularly to the active T3 hormone.
   2. Only 0.03% of the T4 is free and unbound to proteins in the blood, i.e. thyroxine-binding globulin, prealbumin and albumin, in the blood.
   3. Free T4 measures only the unbound thyroid pro-hormone which is available to be assimilated into cells.
   4. Free T4 is useful to monitor thyroid hormone levels in the blood but will not necessarily correlate with the symptoms of a patient, or the resolution of symptoms.
   5. Free T4 does not monitor intracellular thyroid hormone levels or function.

6

C. Total Thyroxine (Total T4) – no longer of real value

1. Total T4 measures T4 bound to proteins, i.e., thyroxine binding globulin, prealbumin and albumin.
2. 97.73% of T4 is bound to protein and unavailable for assimilation into the cells.

D. **Free Thyroxine Index (Free T4 Index) – little or no value**

1. Free T4 Index is a mathematical measurement which is of little or no value.

7

E. Free Tri-iodothyronine (Free T3) – not extremely helpful because of short half life

1. Free T3 measures the unbound active thyroid hormone which is available to be assimilated into cells.

F. Reverse T3 – may be helpful in patients who do not respond to initial therapy

1. Reverse T3 blocks the receptors for T3, inhibiting proper metabolism. This may occur in fasting states and during illness.
2. This test may be useful in patients who do not respond to desiccated thyroid extract as an indicator of when to consider prescribing T3.

8

G. Thyroid Antibodies – excellent baseline measurement

1. Anti-microsomal, anti-thyroglobulin and anti-thyroid peridoxase (TPO) antibody tests are readily available.
2. The presence of these antibodies indicates autoimmune thyroiditis.

9

H. Basal Body Temperature (BBT) test – excellent indicator of metabolic rate
   1. Performed by the patient using a mercury thermometer before arising in the morning.
   2. Basal body temperatures lower than 98.2 demonstrate decreased metabolism, which points toward hypothyroidism.
   3. If the patient's temperature is consistently below 98.6 during the day, then this is also indicative of decreased metabolism which points towards hypothyroidism.

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Contact Information:

Steven F. Hotze, M.D.
Hotze Health & Wellness Center
20214 Braidwood, #215
Katy, Texas 77450
www.hotzehwc.com
281.698.8679

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Importance of Treating Adrenal Deficiency in Patients with both Hypothyroidism and Adrenal Insufficiency

Steven F. Hotze, M.D.
SFH@hotzehwc.com

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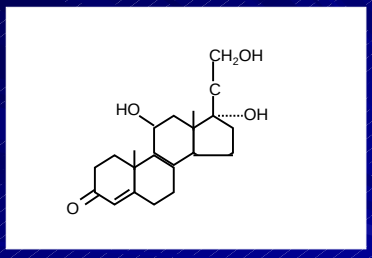
1

Introduction

A. Cortisol (Compound F)

1. Produced by adrenal cortex in the zona fasciculata
2. Predominant glucocorticoid in humans
3. Average daily production – 25 – 30 mg./day
4. Synthesized from Cholesterol via Pregnenolone
5. 21-carbon steroid
6. Also know as hydrocortisone

2



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7. 90% bound to corticosteroid-binding globulin (CBG)
   a. Cortisol Binding Globulin (CBG) is produced by the liver and is increased by estrogens
8. 10% unbound, free
   a. Biologically active fraction of Cortisol
9. Cortisol constitutes 80% of the 17-hydroxy corticoids in plasma
   a. 20% consists of Cortisone and 11-deoxycortisol
10. Hypothalamus-Pituitary – Adrenal Axis
    a. Release of cortisol controlled by diurnal rhythm of ACTH secreted by pituitary gland
    b. ACTH regulated by Corticotropin Releasing Hormone (CRH) from the hypothalamus

4

B. History of Cortisol

1. Discovered by Dr. Edward C. Kendall at Mayo Clinic 1931 –
2. Compound F
3. Nine (9) grams manufactured by Merck in 1948
4. First clinical trials February, 1948 – Dr. Philip S. Hench, Mayo Clinic
5. Rheumatoid arthritis patient

5

C. Actions of Cortisol at Physiologic levels

1. Binds intracellularly to DNA influencing the production of proteins, usually enzymes

6

D. Effects of Cortisol at Physiologic levels

1. Adaptation to stress
2. Anti-inflammatory actions
3. Stimulation of Gluconeogenesis in the liver
4. Promotes protein synthesis at physiologic levels
5. Maintenance of normal blood pressure and cardiac output
6. Maintenance of water and electrolyte balance
7. Promotes immune response
8. Regulates growth
9. Regulates reproduction
10. Enhancement of thyroid function at cellular level
    a. enhances conversion of T4, the inactive pro-hormone, to T3, the active intracellular thyroid hormone
    b. increases intracellular receptor activity for T3

7

E. Adrenal Fatigue (Adrenal Insufficiency)– the decreased production of Cortisol

F. Causes of Adrenal Fatigue

1. Environmental stress
2. Emotional stress
3. Physical stress
4. Inflammation
5. Infections
6. Autoimmune disorders
7. Allergies
8. Illness
9. Hypothyroidism
10. Estrogen Dominance
11. Female Hormone Imbalances, most pronounced in the last half of a woman's menstrual life

8

G. Symptoms & Signs of Adrenal Fatigue

1. Fatigue and lethargy
2. Intolerance to stress
3. Recurrent infections and illnesses
4. Hypoglycemia
5. Depressed moods
6. Decreased mental function
7. Low Blood Pressure
8. Salt Cravings
9. Diarrhea
10. Arthralgias/Arthritis
11. Myalgias
12. Cold Extremities
13. Allergic Disorders
14. Eczema
15. Hair Loss
16. Syncopal Episodes

9

H. Diagnosis

1. Clinical History – questions the patient and listen
2. Serum Cortisol – (Protein bound Cortisol – 92%)
3. Free Cortisol – (Unbound Cortisol – 8%)
4. Cortosyn (ACTH) Stimulation Test
5. Adrenal Stress Index – Salivary Test
6. Broda Barnes 24 Hour Urine Test
7. In the face of so called normal blood tests, a patient with symptoms of adrenal fatigue deserves a therapeutic trial of a physiologic dose of cortisol

10

I. Initial use of Cortisol in the late 1940s, early 1950s

1. Pharmacological doses – 100mg. – 300mg./day – then the patient was tapered
   a. Side effects – Cushingoid Symptoms
      1) Fluid Retention
      2) Depressed Immune System
      3) Weight Gain
      4) Gastrointestinal pain
      5) Osteoporosis
      6) Hypertension
      7) Hyperglycemia

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2. Synthesis of Cortisol Analogs
   a. Prednisone
   b. Prednisolone
   c. Dexamethasone
   d. Methylprednisolone

3. Physiologic Doses (Sub-replacement doses) of Cortisol William McK. Jefferies, M.D.
   a. 371 patients studied representing 773 years of treatment

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b. Disorders treated –
   (1) Hypothyroidism
   (2) Gonadal Dysfunction
   (3) Infertility
   (4) Hirsutism
   (5) Hyperthyroidism
   (6) Rheumatoid Arthritis
   (7) Essential Hypotension
   (8) Diabetes Mellitus
   (9) Allergies
   (10) Asthma
   (11) Postural Hypotension
   (12) Alopecia Areata
   (13) Acne

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c. Treatment as recommended by Dr. William McK. Jefferies
   (1) Oral Cortisol (Cortef) 2.5 mg. to 5 mg. qid total daily dose – 10 mg. – 20 mg.
      (a) Cortisol's half life is 1 ½ - 2 hours

d. Studies by Dr. William McK. Jefferies
   (1) 24 Hour Urinary 17- Ketosteroids (17-KS) decrease when Cortisol given
      (a) Cortisol 20 mg./day – 50% decrease in Urinary 17-KS indicating a 50% absorption rate
      (b) Cortisol 10 mg./day – 25% decrease in urinary 17-KS again indicating a 50% absorption rate

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   (2) Measurement of urinary Cortisol metabolites
   (3) Corticotropin (ACTH) Stimulation Test
      (a) Normal response with respect to production of 17-KS and Cortisol metabolites as measured in the urine.
   (4) Metapyrone Test
      (a) Metapyrone inhibits the production of Cortisol.
      (b) There was an increase in the excretion of urinary 17-KS.
         1) If sub-replacement doses of Cortisol completely suppressed adrenocortical function, then this increase would not have occurred.

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e. These urinary studies of patients on Cortisol (Cortef) indicate that there is no summation effect of the exogenous and endogenous Cortisol.
   (1) Low dose replacement Cortisol causes a compensatory decrease in Adrenocorticotropic Hormone (ACTH) from the pituitary gland and a subsequent decrease in endogenous Cortisol production.
   (2) No impairment of the hypothalamic-pituitary-adrenal response mechanism occurs.

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f. Results
   (1) Significant resolution of symptoms
   (2) No signs or symptoms of hypercorticism

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J. Treatment of Adrenal Fatigue at Hotze Health & Wellness Center
   1. Physiologic (sub-replacement) dose – Cortisol Slow Release (SR) Capsules - .625 mg – children, 1.25 mg – women, 2.5 mg - men
      a. This is micronized Cortisol produced by a compound pharmacy which is 80-90% absorbed. Micronized Cortisol is put into a Methocel E4M 12 Hour time released base. This provides zero order pharmacokinetics. This allows for a steady state release of the hormone into the system. It is absorbed by the lymphatics and the small capillary beds of the small intestines, thus bypassing the liver.

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b. Take one (1) capsule (Cortisol SR .625 mg, 1.25 mg., 2.5 mg) in the morning with breakfast for 2 weeks, then increase to two (2) capsules in the morning with breakfast.

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K. Original Study December 1, 1998 – February 16, 1999

1. 186 patients were studied
2. 149 (80%) of these patients were diagnosed with Adrenal Fatigue
3. 94 (63%) females diagnosed with Adrenal Fatigue
4. 55 (37%) males diagnosed with Adrenal Fatigue

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L. Short Term Treatment Results

1. 82 (55%) patients responded to our questionnaire
2. 62 (76%) patients responded who were taking Cortisol supplementation
3. The average serum Cortisol level was 8.2 ug/dl
4. Gender Composition of Study – 62 Patients
   a. 40 (65%) females
   b. 22 (35%) males
5. Average age of Patients
   a. 45 years old – females
   b. 41 years old - males

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6. Average length of treatment
   a. 2.1 months
7. 38 (61%) established patients in this study
8. 24 (39%) NPAL (first time patients) in this study
9. 39 (98%) female patients in this study on both female hormone and thyroid hormone supplementation
10. 19 (86%) male patients in this study on both male hormone and thyroid hormone supplementation

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11. Age Composition of Patients in Study

No. of Pts.	Age in Years
1	<10
3	10-19
3	20-29
13	30-39
23	40-49
16	50-59
7	60-69
1	>70

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12. Comparison of New Patients vs. Established Patients - Symptomatic response to treatment (presenting symptoms for each patient differed – not all patients had each of the following symptoms)

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Percentage of Improvement and/or Resolution of Symptoms of Patients in Study Taking Cortisol

Symptom	New Patients		Established Patients	
Allergy Symptoms	82%	(18/22)	44%	(15/34)
Asthma	80%	(4/5)	50%	(6/12)
Recurrent Infections	67%	(10/15)	64%	(16/25)
Fatigue	91%	(20/22)	74%	(26/35)
Loss of Appetite	33%	(3/9)	24%	(5/21)
Weight Loss	62%	(8/13)	17%	(5/30)
Abdominal Pain	100%	(2/2)	17%	(2/12)
Diarrhea	100%	(7/7)	33%	(3/10)
Low Blood Pressure	100%	(3/3)	0%	(0/5)

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Anxiety	77%	(10/13)	48%	(11/23)
Depressed Moods	86%	(12/14)	62%	(16/26)
Irritability	82%	(14/17)	59%	(16/27)
Restlessness	83%	(10/12)	56%	(14/25)
Hair Loss	71%	(5/7)	31%	(4/13)
Joint Pain	91%	(10/11)	67%	(14/21)
Muscle Pain	80%	(8/10)	61%	(11/18)
Muscle Strength	69%	(9/13)	36%	(5/14)
Low Libido	60%	(9/15)	37%	(10/27)

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M. Conclusion

The results demonstrate that natural cortisol supplementation, when indicated in patients with allergic disorders, provides significant improvement in the patient's overall health, well-being and energy level.

An overwhelming number of patients, who were treated for their allergies in combination with natural cortisol supplementation, when indicated, reported a marked improvement in their original symptoms.

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N. Clinical Pearls

1. The adrenal gland and adrenal hormones are essential for general adaptation to the environment.
2. There is a difference between physiologic doses of cortisol and pharmacologic doses.
3. Pharmacologic doses of cortisol cause adverse effects.
4. Animal studies and clinical experience indicate that physiologic doses of cortisol are essential for life. In adrenalectomized animals, any stress in the environment would lead to the death of the animals.
5. Adrenal stress decreases cortisol production as the adrenal gland fatigues.
6. Cortisol enhances the conversion of T4 to T3.

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7. Physiologic doses of cortisol are safe.
8. A healthy individual in his 20, in his prime, will produce 25-30 mg. of cortisol daily under normal circumstances. Stress will increase the production of cortisol.
9. Synthetic analogs to cortisol, drug company counterfeits, are four times as potent mg for mg.
10. Prednisone 5 mg. is equal to Cortisol 20mg.
11. William Mck. Jeffries, M.D. recommends a total initial daily dose of 10 to 20mg of cortisol, prescribed as Cortef, and given in divided doses, before meals and one at bedtime. (Example – Cortisol 5mg., i ac and hs.)

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12. When under stress or when illness develops, cortisol should be doubled until symptoms have been gone for five days. Then the cortisol can be tapered back to the original dose over several days.
13. Pharmacologic doses of cortisol prior to being exposed to a bacterial or viral illness will depress the immunity.
14. Physiologic doses may be given for treatment of recurrent miscarriages and should be continued throughout the entire pregnancy.
15. Physiologic doses of cortisol during pregnancy do not increase the incidence of congenital defects.

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16. The hormones work together synergistically and have permissive effects.
17. At physiologic doses cortisol enhances immunity, stimulating the production of immunoglobulins.
18. Pharmacologic doses of cortisol, doses great than the physiologic dose, decrease immunity.
19. Cortisol aids in the peripheral utilization of thyroid hormone.
20. Hypoglycemia is caused by low level of cortisol.
21. Physiologic doses of cortisol enhance the conversion of T4 to T3.

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22. Physiologic doses of cortisol enhance the nuclear receptor uptake of T3.
23. Influenza virus adversely affect the HPA axis by inhibiting the production of CRF from the hypothalamus and ACTH from the pituitary. Therefore, the production of cortisol is prevented by the flu virus.
24. Cortisol doses should be doubled when an individual contracts the flu.
25. Physiologic doses of cortisol may be given to diabetics without worsening the blood glucose level.

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Contact Information:

Steven F. Hotze, M.D.
Hotze Health & Wellness Center
20214 Braidwood, #215
Katy, Texas 77450
www.hotzehwc.com
281.698.8679

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Optimizing Testosterone Replacement Therapy for Men: A Recipe for Success

Presented by

John Crisler, DO

TESTOSTERONE REPLACEMENT THERAPY

-A RECIPE FOR SUCCESS-

--John Crisler, DO
Lansing, MI USA
MSU-COM

"Everything You Always Wanted to Know About TRT But Didn't Have Time to Ask"

WHAT IS TESTOSTERONE REPLACEMENT THERAPY?

TRT: Restoration of Testosterone to HEALTHY physiological levels.

TRT is NOT:

- Total T>normal range
- Steroids
- Viagra

SCREENING FOR HYPOGONADISM

WHAT ARE THE SYMPTOMS OF LOW TESTOSTERONE?

- TAT Syndrome
- Fatigue
- USTA Syndrome
- Loss of muscle mass
- Fat gain
- Poor recovery
- Pain/Inflammation
- Irritability
- Depression
- Decreased memory
- Loss of Libido
- Erectile Dysfunction

ADAM Questionnaire

1. Do you have a decrease in sex drive?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased enjoyment of life?

ADAM Questionnaire (con't)

6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Has it been more difficult to maintain your erection throughout sexual intercourse?
9. Are you falling asleep after dinner?
10. Has your work performance deteriorated recently?

INITIAL LAB WORK

INITIAL HYPOGONADISM PANEL

- Total Testosterone
- Bioavailable/Free T
- SHBG
- DHT
- FSH
- LH
- Estradiol
- Total Estrogens
- Prolactin
- Cortisol
- Thyroid Panel (TSH, FT4, FT3)
- Comp Metabolic Panel
- CBC
- Lipid Panel
- PSA (if over 40)
- Progesterone

MEASURES OF TESTOSTERONE

- Total Testosterone—all that is produced (300-1000ng/dL)
- Free Testosterone—all that is unbound (2-4%) (80-300pg/dL)
  --Equilibrium Dialysis, NOT RIA!
- Bioavailable Testosterone—Gold Standard "Free and Loosely/Weakly Bound" (120-600ng/dL)

"Laboratory reference values for testosterone vary widely, and are established without clinical considerations."

Lazarou S, et al. Harvard Medical School, Division of Urology, Beth Israel Deaconess Medical Center

T SAMPLE PREPARATION (SERUM)

- Refrigerated, no additive serum preferred (red-top)
- Heparanized serum less acceptable (green-top)
- NO Serum Separator Tubes (SST)

IMPORTANT ABOUT ESTROGEN TESTING

- Total Estrogens is not a valid assay for adult males
- Estradiol MUST be by “ultrasensitive” or “Extraction Method” assay
- Gold standard is 24 hour urine, esp w/ TD’s
- Be extra mindful of SHBG level

Sample Matrixes

- BLOOD
  --most common
  --Total, Free, Bioavailable
  --”snap shot” only
  --plain Red Top Tube for T’s, no SST’s
- SALIVA
  --only suitable for Cortisol
- URINE
  --best of all, esp. w/ TD’s
  --Free levels provided, no SHBG needed
  --limited assay types, but incl. metabolites
  --only 24 hour collections
  --be careful of contamination
  --better assess 5-AR activity

COMMON SENSE

IN ORDER TO TEST THE LEVEL OF A DRUG, YOU MUST TAKE THE DRUG, ON SCHEDULE!!!

COMMON SENSE

HAVE PATIENT DRAW AT SAME TIME OF DAY EACH TIME.
ESPECIALLY WITH TRANSDERMALS (PK's)!

COMMON SENSE

1. NEVER SMOKE IN BED!

2. ALWAYS WEAR PAJAMAS

DHT

- Most responsible for All Things Male
- 5-AR'd from T
- Unfairly deemed "evil hormone"
- NOT responsible for prostate morbidity
- 30-85ng/dL
- Serum assay valid?
- Avoid finasteride

Estradiol

- Major player amongst estrogens
- Total Estrogens is NOT valid assay for males
- MUST be monitored during TRT
- Masks benefits of TRT
- Adjunctive cause of serious illness
- Numerous benefits for health, so…
- Must not be driven too low
- (10-50pg/mL) maintain mid-range (mid-range SHBG)
- May rise over time

Luteinizing Hormone (LH)

- Produced by pituitary
- Stimulates T production
- Pulsatile production
- Short half-life
- Acute phase reactant
- Must be careful in its interpretation
- Possible Gn-secreting tumor

Follicle Stimulating Hormone (FSH)

- Produced by pituitary
- Spermatogenesis
- 180-240 minute half-life
- Inhibited largely by estrogen
- Better measure of gonadotrophin output?
- Possible FSH-secreting tumor

Prolactin

- Significant cause of hypogonadism
- May signal tumor presence
- Health benefits
- Must be maintained within normal range
- Ref Range (3.0-18.0 ng/mL)
- >300= tumor
- Elevated by eating, sex (<30)

HYPERPROLACTINEMIA CAUSES

- Pituitary tumor
- Stalk compression
- Primary hypothyroidism
- Chronic renal failure
- Cirrhosis
- Opiates
- Tri-cyclics
- D2 antagonists
- Metoclopramide
- Verapamil
- Chest wall trauma

Cortisol

- "Stress hormone"
- Cause of secondary hypogonadism
- Healthful benefits
- Must be maintained within normal range
- If elevated: Tx'd with Phosphatidylserine (PS) (300mg QD)
- If depressed: Tx'd with Hydrocortisone PO

OTHER CONSIDERATIONS

- SHBG
  --MUST have to interpret hormone assays
  --Total T is only useful as screening tool
  --tends to rise with elevating estrogen
  --higher SHBG=>lower Free, Bio levels
  --preferentially binds androgens over estrogens
  --"estrogen dominance"
  --lower SHBG=> higher free, Bio T levels
  --so can mean E problems at low [E]
  --system set to half/half (hormone/SHBG)
  --variable affinities across population?

SHBG (con't)

SHBG is raised by thyroid, estrogen, lignans, and progesterone.
SHBG is lowered by insulin, testosterone, DHT, growth hormone, DHEA, and other androgens.

SHBG (con't)

- High-normal:
  --"Estrogen dominance" via preferential binding of androgens over estrogens
  --Tx with low dose Danazol troche
- Low-normal range:
  --high Bioavailable Testosterone, but…
  --also high Bioavailable Estrogens

SHBG (con't)

Please keep in mind that SHBG is often unreliable. It is best to rely upon assay performed at same lab as Testosterone Group (Total T, Free T, Bio T).

PROGESTERONE FOR MEN

- Feminizing effects (incl. gyno)
- Elevates SHBG
- Estrogen antagonism increases effects
- Can cause lower abdominal "pooch"
- Can cause impotence
- "Puts plaque in the arteries, and wrinkles in the penis"

T/E ratio

- Measure of system performance
  --ratio does have importance, but…
  --absolute values of hormones are important
  --cannot elevate E without consequence as long as T is proportionately high
- Used to explain pathophysiology
  --low T→ higher proportionate E →morbidity
- NOT to be used as treatment goal

LABS (con't)

- Thyroid Panel (TSH, FT4, FT3)
- CBC
- Comprehensive Metabolic Panel
- Lipid Profile
- PSA (if over 40)

FOLLOW-UP LABS

- Total T
- Bio T
- LH/FSH (especially with transdermal)
- FSH—to back up LH interpretation of HPTA status
- SHBG
- Estradiol
- Total Estrogens
- DHT (?)
- CBC
- Comp. Metabolic Panel
- PSA (if over 40)

FOLLOW UP LABS (con't)

- Initial F/U at 3 weeks with TD (transdermal)
  --stable serum T levels quickly attained
  --logistical consideration
- Initial F/U at 6 weeks with IM
  --takes that long to equilibrate
  --interpret by PK's of T ester (48-72 hour peak)
  --cypionate/enanthate t1/2 5-8 days
- F/U at 4 weeks S/P dosage change or estrogen control

FOLLOW-UP LABS (con't)

- Once dose is titrated:
  --q 6 months or yearly
  --Include PSA
  --Perform Digital Rectal Exam (DRE)

TESTOSTERONE DELIVERY SYSTEMS

- Gels and Creams
- Patches
- Implantable Pellets
- IM
- Orals

Gels and Creams

- Ease of application
- May be more convenient—OR NOT!
- Stable across week, not day
- "Pulsing" may be benefit
- Quickly attains stable serum levels
- Boosts DHT
- May elevate estrogens
- Risk of accidental transferal
- Be mindful of application method
- Avoid antecubital fossa—looks like AAS
- EXTREMELY variable absorption…
- Especially with hypothyroidism

Gels and Creams (con't)

- "Big House" products
  --MUCH more expensive
  --support physician education ("The Cause")
  --covered by insurance
  --vouchers/sample
  --1%
- Compounded gels/creams
  --various bases
  --1%, 5%, 10, 20%
  --higher conc. → < E, DHT conversion
  --soy, yam-based T's
  --ALL T gels/creams are "bioidentical testosterone"
  --creams slow absorption
  --can compound anti-E's into product
  --MUCH less expensive

Testosterone Patches

- Convenient—MAYBE!
- No risk of accidental transfer
- Stable serum androgen levels
- Little DHT boost
- May elevate estrogen
- 2/3's--Contact Dermatitis

Testosterone Injection

- Convenient—MAYBE!
- MUST be injected weekly
- Stable across day, not week
- Ease of dose titration
- Injection risks
- The Gold Standard

NEEDLE SIZES

- Glutes: 22ga 1 ½"
- Thighs: 25ga 1"

Oral Delivery Systems

- Testosterone undecoanate
  --not available in the US
- Mucoadhesive patch
  --buccal delivery system
  --produces very stable serum levels
  --many find them difficult to tolerate
  --useful in limited population:
  (hirsute, obese and opposed to IM)

IMPLANTABLE PELLETS

- Stable serum androgen levels (benefit?)
- For adventurers
- Less rise in estrogens
- Risk of surgical procedure
- Cost of surgical procedure
- Titration difficulties

OTHER MEDICATIONS:

- HCG
  --LH analog
  --traditional treatment-of-choice for 2nd low T
  --not just "fertility drug"
  --best use is adjunctive to TRT
  --does not produce subjective benefits of T delivery
- SERM's
  --elevates T, but…
  --does not bring subjective benefits of TRT
  --for testing, purposes of HPTA intactness
  --HPTA recovery "PCT"
  --"rescue" Tx for gynocomastia
  --possible issues with respect to brain function

SERM's (con't)

- Clomiphene
  --racemic mixture (antagonist AND agonist)
  --enclomiphene+zuclomiphene
  --may bring untoward visual effects
  --may bring untoward emotional effects
- Tamoxifen
  --pure estrogen antagonism
  --great for "nipple issues"
- Raloxifen
  --great estrogen antagonism
  --MUCH more expensive
- Others (more to come)

CONTRAINDICATIONS TO TRT:

- Prostate CA
- Breast CA
- Untreated prolactinoma

RELATIVE CONTRAINDICATIONS:

- PSA >4.0 or accel>0.75
- H/H> 18/55
- Sleep Apnea
- Cardiac, Hepatic, Renal Dz

DRUG INTERACTIONS:

- Diabetic Medications
- Propranolol
- Oxyphenbutazone

The Meat and Potatoes of TRT

INITIAL DOSAGES

- Transdermal gels/creams
  5mgs (delivered) QD

- Testosterone Cypionate IM:
  100mg QW
  --split weekly dose for those with anxiety issues?

DHT ISSUES

- DHT is not “evil hormone”!
- May rise with androgen acceleration, then baseline
- May rise more in senior patients
- If elevated too far, switch to test cyp IM
- Serum DHT questionable validity
  (use metabolite ratios on urinary labs)
- Not in favor of finasteride
  --growing body of patients who now suffer permanent hypogonadism/ED from it

ESTROGEN ISSUES

- Do not Tx until post F/U labs
  --E2 may actually DROP with TRT
  --insight into body’s response

- Maintain E2 at mid-range
  --with mid-range SHBG

ANASTROZOLE

- Aromatase (“Estrogen synthase”) Inhibitor
- Competitive Inhibitor
- #1 use of this med in world: Male TRT
- Other AI’s available
- Concerns with Endocrine pathway disruption (as with finasteride)
- 0.25mg QOD, 0.5mgQ3D
- 5 day t1/2
- “Frontload” (double initial dose)
- Titrate from there
- SHBG will likely drop (be mindful of consequences)

CRISLER HCG PROTOCOL

- 250IU twice per week SC (starting dose)
- NEVER more than 500IU QD
  (or elevate estrogens, progesterone)
- Transdermal T patients:
  --every third day
- Test cyp IM patients:
  --T-2/T-1 prior to IM injection
  --Fri/Sat c/ Sun IM is nice!

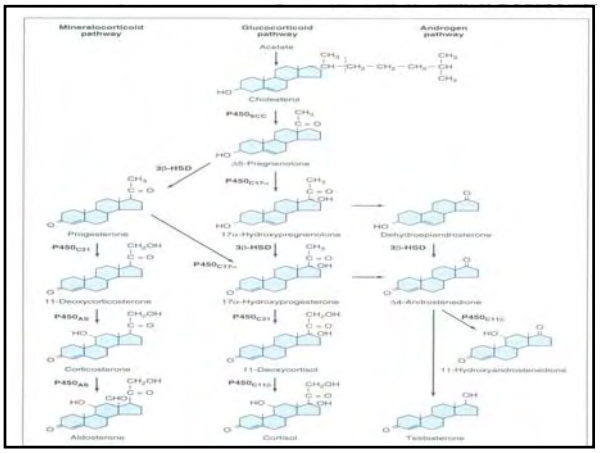
CRISLER HCG PROTOCOL (con't)

- Evens out serum androgen levels by t1/2 of cypionate ester
- Prevents testicular atrophy
- Stimulates all three CHOL pathways
- Abundant boost in libido/sense of well being

LOW DOSE HUMAN CHORIONIC GONADOTROPIN MAINTAINS INTRATESTICULAR TESTOSTERONE IN NORMAL MEN WITH TESTOSTERONE INDUCED GONADOTROPIN SUPPRESSION.

Coviello AD, et al. 1: J Clin Endocrinol Metab. 2005 Feb 15

In HPTA-suppressed adult males, ITT was 7% below baseline at 250IU HCG QOD, and 26% greater than baseline at 500IU HCG QOD.



RESTORING PATHWAYS

- HCG
  --IM: start at 250IU SC Days5/6
  --TD: start at 200IU SC QOD
  --never more than 500IU
- DHEA
  --25mg BID
  --100mg QD can elevate E1
- Pregnenolone
  --50mg TD QD in a cream

Rescue from “Nipple Issues”

- Burning, itching, swelling, FREAKING
- Occurs with mere changes in hormone levels, even within physiological range, so…
- DO NOT treat in first month (get F/U labs)
- 40mg QD tamoxifen until gone, then taper --cut dose ½ Q5D
- Prefer tamoxifen over clomiphene
- Cannot assay estrogens on SERM-class drugs!
- Hold GhRT (magnifies E fx)
- Gyno may be caused by progesterones

NO TRT “CYCLING”

- Historically “borrowed” from AAS use.
- No evidence of benefit
- Does not do what is claimed
- Leaves substantial periods of letdown
- The body thrives on regularity

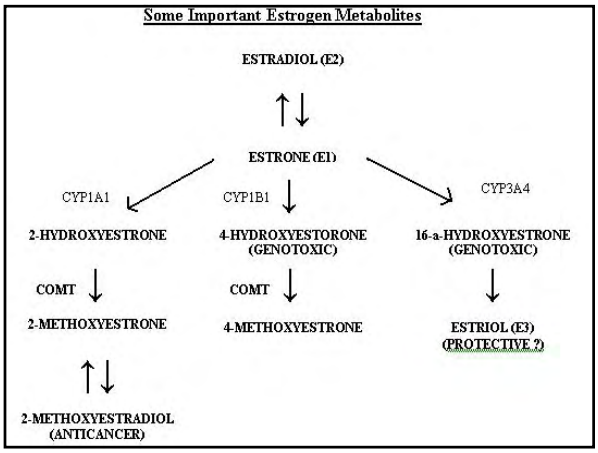
WHAT IS THE FUTURE OF TRT?

- Elevating T to healthy, happy levels
- Estrogen metabolism
- Actions at the androgen, estrogen receptors
- Restoring endocrine pathways

THE GOAL?

"The ultimate goal of TRT medicine is to optimize health and happiness in our patients, which means producing an environment where we have elevated testosterone to sufficient levels, with the body responding as if it is unaware of the exogenous manipulations."

--John Crisler, DO



Testosterone Boosting the Female Libido

Presented by

George Juetersonke, DO

Female Androgen Insufficiency FAI

George J Juetersonke DO

Clinical Assistant Professor, University of North Texas Health Science Center, TX

Adjunct Associate Professor, Midwestern University College of Health Sciences, IL

Definition of Androgen Insufficiency

A pattern of **clinical symptoms** in the presence of **decreased testosterone** (at or below the lowest quartile of the reference range for women 20 – 40 years old) and **normal estrogen status.**

Bachmann G, et al. *Fertil Steril.* 2002;77:660-665.

What Are the Signs and Symptoms of Androgen Insufficiency?

- Diminished well-being
- Unexplained fatigue
- Decreased sexual desire
- Thinning and loss of pubic hair

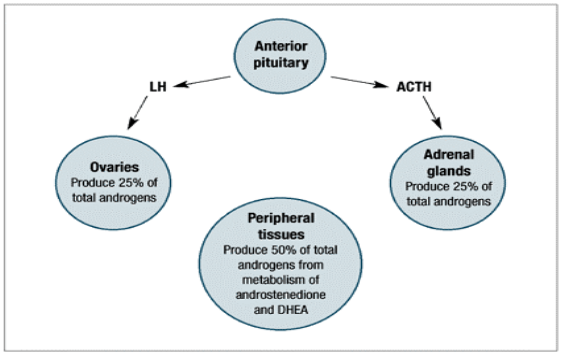
Bachmann G, et al. *Fertil Steril.* 2002;77:660-665.

Legitimate?

1. Symptoms are individual
2. No correlation with estrogen
3. Aging causes decrease in T
4. Alterations in mood and well-being hard to quantify

FIGURE 1. Female androgen production

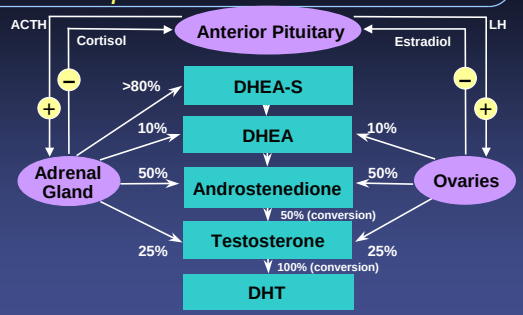
FA Production



LH = luteinizing hormone; ACTH = adrenocorticotropic hormone; DHEA = dehydroepiandrosterone.

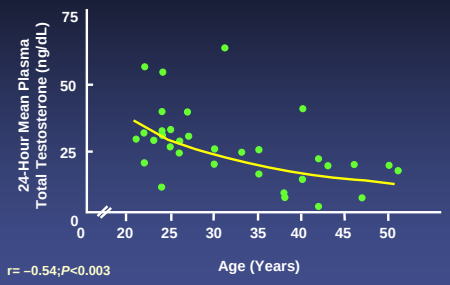
FA production

Androgen Dynamics in Premenopausal Women



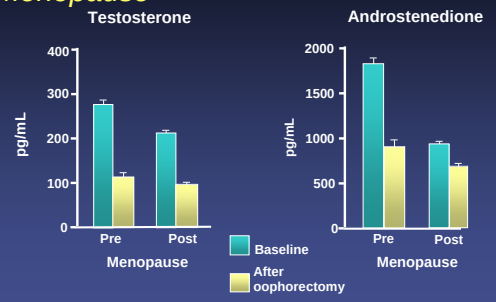
Buster JE, et al. In: Lobo RA, ed. *Treatment of the Postmenopausal Woman: Basic and Clinical Aspects*. 2nd edition. Philadelphia, Pa: Lippincott, Williams & Wilkins; 1999:142.

Total Testosterone Levels in Women Decrease With Age



Zumoff B, et al. *J Clin Endocrinol Metab.* 1995;80:1429-1430.

Testosterone and Androstenedione Before and After Surgical Menopause



Judd HL, et al. *Am J Obstet Gynecol.* 1974;118:793-798.

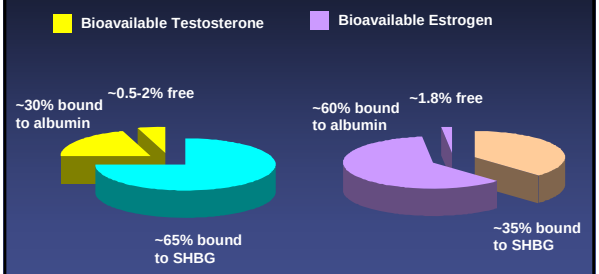
Relationship Between Estrogen and Androgens

Sex Hormone-Binding Globulin

- SHBG is the carrier protein for estrogen and testosterone
  - SHBG-bound fraction is unavailable for biological activity
- Production regulated by estrogen-testosterone balance
  - Estrogen stimulates SHBG production
  - Testosterone decreases SHBG synthesis

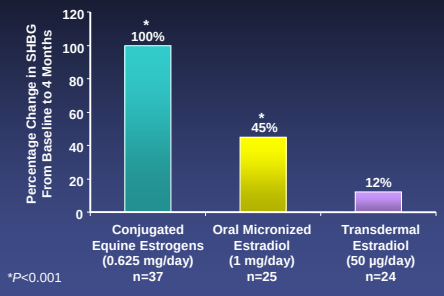
Selby C. *Ann Clin Biochem*. 1990;27:532-541.

Testosterone and Estrogen Circulation in the Body



Simon JA. *Fert Steril*. 2002;77:S77-S82.
Demers LM. In: Redmond, G, ed. *Androgenic Disorders*. Raven Press, New York, NY; 1995:21-34.

Effect of Estrogen Therapy on SHBG in Menopause



*P<0.001

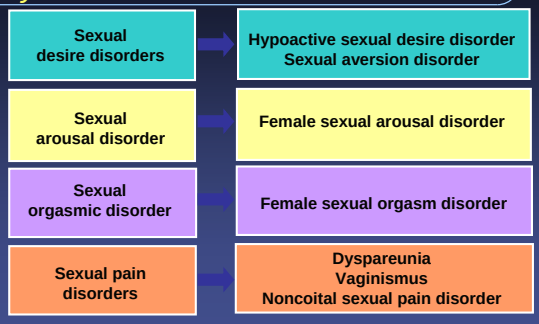
Nachtigall LE, et al. *Menopause*. 2000;7:243-250.

Impact of Oral Contraceptives on Sex Hormone-Binding Globulin and Androgen Levels

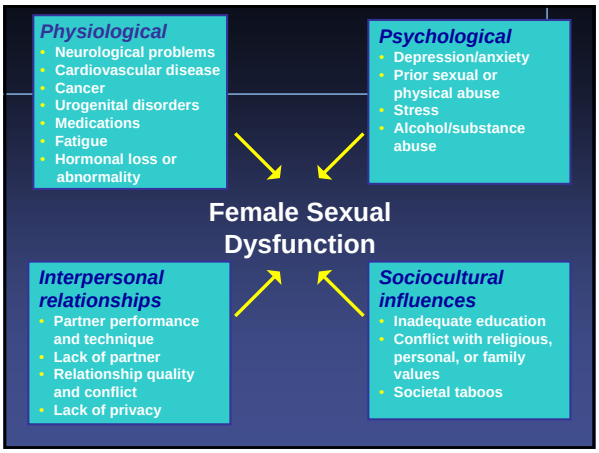
- *62 Current SHBG 4x Never users*
- *39 Past SHBG 2X Never users 6 to 12 months after discontinuing BCP*
- *23 Never users*

Panzer et al The Journal of Sexual Medicine, January 2006;3:p.104-113

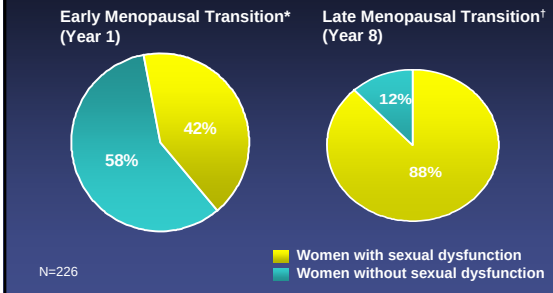
Categories of Female Sexual Dysfunction



Basson R, et al. *J Urol.* 2000;163:888-893.


Physiological
• Neurological problems
• Cardiovascular disease
• Cancer
• Urogenital disorders
• Medications
• Fatigue
• Hormonal loss or abnormality
Psychological
• Depression/anxiety
• Prior sexual or physical abuse
• Stress
• Alcohol/substance abuse
Female Sexual Dysfunction
Interpersonal relationships
• Partner performance and technique
• Lack of partner
• Relationship quality and conflict
• Lack of privacy
Sociocultural influences
• Inadequate education
• Conflict with religious, personal, or family values
• Societal taboos

Sexual Dysfunction and the Menopausal Transition

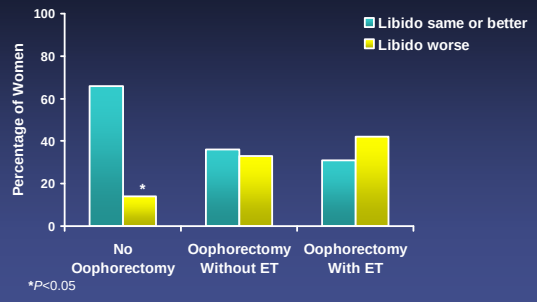


N=226

*Mean age=49.1 ± 2.25 years; †mean age=57.1 ± 2.35 years

Dennerstein L, et al. *Fertil Steril*. 2002;77:S42-S48.

Sexuality After Hysterectomy With and Without Estrogen Therapy (ET)



**P*<0.05

Nathorst-Boos J, et al. *J Psychosom Obstet Gynaecol*. 1993;14:283-293.

Causes of Low Testosterone in Women

- **Normal aging**
- **Conditions that alter testosterone production**
  - **Oophorectomy**
  - **Ovarian failure**
  - **Adrenal insufficiency**
  - **Hypopituitarism**
  - **Chronic illness**
- **Pharmacotherapy**
  - **Corticosteroids**
  - **Estrogen therapy including BCP**

Medications FSD

- Antihistamines
- Anticonvulsants
- Metronidazole
- Metoclopramide
- Antihypertensives
- Antiandrogens (cimetidine, spironolactone)
- Anticholinergics
- Oral contraceptives

Medications FSD

- Antidepressants
- Sedatives
- Alcohol
- Hypnotics
- Antiestrogen
  Tamoxifen
  raloxifene
  leuprolide

Rationale for Testosterone Therapy

- Testosterone levels in women decline with aging
  - Women in their 40s have approximately one-half the level of women in their 20s
- Women who undergo oophorectomy experience dramatic decreases in the level of testosterone
  - Level of testosterone decreases to one half of those prior to surgery

Zumoff B, et al. *J Clin Endocrinol Metab*. 1995;80:1429-1430.
Judd HL, et al. *J Clin Endocrinol Metab*. 1974;39:1020-1024.

Rationale for Testosterone Therapy (cont'd)

- **Testosterone has been linked to sexual desire and coital frequency in menopausal women**
- **Accumulating data indicate that testosterone therapy increases sexual function, including sexual desire, in postmenopausal women**

McCoy NL, et al. *Maturitas*. 1985;7:203-210.
Shifren JL, et al. *N Engl J Med*. 2000;343:682-688.
Lobo RA, et al. *Fertil Steril*. 2003;79:1341-1352.

Oral Estrogen and Testosterone Patch: Effect on Sexual Function

Author (Year)	Population (N)	Treatment (Dose)	Outcome (at 24 Weeks)
Braunstein (2003)	SM, HSDD (N=447)	T patch (150, 300, 450 mcg/d) Placebo patch	↑ Desire ↑ Activity
Davis (2003)	SM, HSDD (N=77)	T patch (300 mcg/d) Placebo patch	↑ Desire ↑ Activity

SM=surgically menopausal; HSDD=hypoactive sexual desire disorder; T=testosterone

Braunstein GD, et al. In: Program and abstracts of the 14th annual meeting of the North American Menopause Society; September 17-20, 2003; Miami Beach, Fla. Abstract 60.
Davis S, et al. *Fertil Steril*. 2003;80(suppl 3):76.

Oral Estrogen and Testosterone Patch: Effect on Sexual Function

Author (Year)	Population (N)	Treatment (Dose)	Outcome (at 24 Weeks)
Simon (2004)	SM, HSDD (N=562)	T patch (300 mcg/d) Placebo patch	↑ Desire ↑ Activity
Buster (2004)	SM, HSDD (N=533)	T patch (300 mcg/d) Placebo patch	↑ Desire ↑ Activity

SM=surgically menopausal; HSDD=hypoactive sexual desire disorder; T=testosterone

Simon JA, et al. *Obstet Gynecol*. 2004;103(suppl):64S.
Buster J, et al. In: Program and abstracts of the 86th annual meeting of the Endocrine Society; June 16-19, 2004; New Orleans, La. Abstract OR44-6.

Transdermal Testosterone in Premenopausal Women

- Goldstat et al JNAMS 2003:10;5
  - Mean age 39, low libido
  - Rx 10 mg testosterone cream /day
- Improved well being, mood and sexual function
  - Mean testosterone high normal
  - Estradiol unchanged

Potential Side Effects With Testosterone Therapy

- Hirsutism, Acne, Alopecia
- Voice deepening
- Liver toxicity, Lipoproteins
- Clitoromegaly, Nipple tenderness
- Coagulation, hyperglycemia
- Polycythemia
- Endometrium
- Anger, hostility

Side Effects in Studies With Testosterone Therapies

- Few side effects are reported in studies
- Increased doses are associated with
  - Facial hair
  - Acne/oily skin
- Oral preparations
  - Decreases in high-density lipoprotein
    - Not seen with transdermal preparations

Absolute Contraindications

- Pregnancy
- Lactation
- Polycythemia
- Breast cancer ??
- Endometrial Cancer

Relative Contraindications

- Acne
- Hirsutism
- Androgenic Alopecia
- PCOS
- Anger Management disorders

Dimitrakakis, et al Menopause. 11(5):531-535, September/October 2004.

Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy.

238/100,000 women yrs T only

293/100,00 women yrs EP+T

380/100,000 women yrs WHI

521/100,00 women –Million

Combined Estrogen and Testosterone and Risk of Breast Cancer

Arch Intern Med 2006

24 year Nurses Health Study

2.5 fold increase for ET compared to never users

Greater for E

Marginal for EP

study medication Estratest

Estratest is Not Approved by the FDA

- In 1981, Solvay Pharmaceuticals submitted an Abbreviated New Drug Application for Estratest; however, this application is still pending with the FDA—25 years later. Estratest has never been FDA approved.
- Kristen Suthers *Arch Intern Med.* 2007;167:205-206.

Off Label Use

NO FDA approved form of testosterone or DHEA to treat low libido or sexual dysfunction

Informed consent important

Assays for Measuring Testosterone

- Commercial assays for testosterone lack sensitivity and reliability
  - Do not accurately measure low ranges found in women
- Reference range is flawed
- Equilibrium dialysis or equilibrium ultrafiltration
  - "Gold standard" for measuring free testosterone
  - Difficult, time consuming
- Do in AM, middle third of cycle
- Salivary measures highly variable

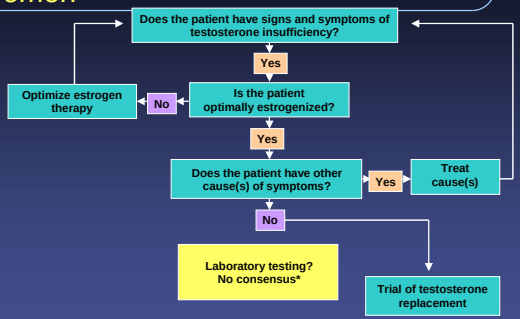
Guay AT. *Fertil Steril.* 2002(suppl 4);77:S83-S88.

Ranges

Total T 45-145 ng/dL

DHEAS 59-452

Assessing Testosterone Status in Women



Adapted from Braunstein GD. *Fertil Steril.* 2002;77(suppl 4):S94-S99.
*Bachmann G, et al. *Fertil Steril.* 2002;77:660-665.

Diagnosis of Female Androgen Deficiency

- Diagnosis established by
  - Symptoms
  - Circumstances
- Tests which may be supportive, but not diagnostic
  - Total testosterone, Free T
  - Sex hormone–binding globulin

Conclusion

- The assessment and treatment of hypoactive sexual desire disorder should consider biological, interpersonal, and psychological factors
  - Symptoms
  - Medical causes
  - Personal issues
  - Relationship quality

Conclusion continued

- Testosterone therapy, (with or without estrogen/progesterone therapy as needed) may be indicated in the following women:
  - Surgical menopause
  - Postmenopausal
  - Decreased libido
  - Diminished sense of well-being
  - Premenopausal

*Testosterone Therapies Available and Under Investigation**

- Oral
  - Methyltestosterone
- Subcutaneous(implant)
  - Testosterone pellets
- Intramuscular
  - Testosterone propionate
  - Testosterone cypionate
  - Testosterone enanthate
- Transdermal
  - Transdermal testosterone patch
  - Testosterone gel
- Sublingual testosterone
- Other
  - Testosterone-vaginal cream

* Not approved by US Food and Drug Administration for use in women.

Formulations

Testosterone gel 1-10 mg/day dose range Provided as

Commercial gel: use 1/10th of male dose provides approximately 5 mg per day dosed once daily

Compounded gel: 0.625-5 mg / 2 ml daily dispense 65 ml

Sublingual tabs total dose split and given twice per day: 0.625-2.25 mg SL BID

Pellets 25-100mg

Men 50 – 200 mg/day gel

DHEA

5-50 mg per day topical or oral
Typical dose 25 mg per day

Diagnosis Codes

- 256.8 or 256.9 Ovarian dysfunction
- 255.9 Adrenal dysfunction
- 259.9 Endocrine disorder
- 627.2 Menopause, 627.3 Atrophic Vaginitis
- 799.81 Libido decreased
- 995.20 Unspecified adverse effect of drug, medicinal and biological substance (due) to correct medicinal substance properly administered
- E932.2 Adverse effect of ovarian hormones and synthetic substitutes

North American Menopause Society

1. Testosterone Tx without E not recommended
2. Lab testing not accurate
3. Lab testing not for diagnosis only for monitoring (methyltestosterone cannot be measured)

4. Salivary testing not reliable
5. Rx T therapy for shortest time possible, safety for more than six months not known
6. Topical preferred but not FDA approved
7. Counsel patients

Strategies for Minimizing Cancer Risks with the HRT Patient

Presented by

Neil Hirschenbein, MD, PhD

HORMONES AND BREAST CANCER

LEVEL II BHRT SYMPOSIUM

June 1-3, 2007

Neil Hirschenbein MD, PhD

HRT after Breast Cancer DX

- Vasomotor symptoms associated with menopause or cancer therapies are increasingly common problem for breast cancer survivors
- Use of menopausal hormone therapy (MHT) for chronic disease risk reduction in any population **cannot be supported**

HRT after Breast Cancer DX

- In breast cancer survivors even local vulvar/vaginal symptoms are best treated by **nonhormone products** since drug absorption with systemic estrogen-like effects reported
- Chlebowski, R. et al. Estrogen deficiency symptom management in breast cancer survivors in the changing context of menopausal hormone therapy. Semin Oncol. 2003, 30(6): 776-88

HRT after Breast Cancer DX

- Breast cancer is the most frequently diagnosed cancer in Canadian women. Many of these women have to face the consequence of premature menopause & prolonged estrogen deprivation.
- Recent studies have demonstrated that not only is HRT associated with an increased risk of developing breast cancer, but it also has been **shown to increase the risk of recurrence in those with a breast cancer history**.

HRT after Breast Cancer DX

- Gainford MC. et al. A practical guide to the management of menopausal symptoms in breast cancer patients. Support Care Cancer. 2005, 13(8): 573-8.

HRT after Breast Cancer DX

- Hormonal replacement has been shown to increase breast cancer incidence as well as **risk of recurrence and no longer should be recommended.**
- Bruno D. et al. Management of postmenopausal symptoms in breast cancer survivors. Semin Oncol. 2006, 33(6):696-707.

HRT after Breast Cancer DX

- Purpose: critically review the literature regarding effects of ERT/HRT on the risk of breast cancer in postmenopausal women, with a focus on risks & benefits in women with a previous dx of breast cancer
- Results: none of the 5 meta-analyses demonstrated a significantly increased risk of developing breast cancer in ever users compared with never users of ERT/HRT

HRT after Breast Cancer DX

- Results: preliminary information does not suggest a major detrimental effect of ERT/HRT in women with a previous diagnosis of breast cancer, but these reports include few women with limited follow-up data
- Roy JA, et al. Hormone replacement therapy in women with breast cancer. J Clin Oncol. 1996 14(3): 997-1006.

HRT after Breast Cancer DX

- Purpose: determine whether ERT alters the development of new or recurrent breast cancer in women previously treated for localized breast cancer
- Methods: potential participants (n=319) in a trial of ERT after breast cancer were observed prospectively for at least 2 years. Of 319 women, 39 given ERT & 280 not given hormones.

HRT after Breast Cancer DX

- Results: one patient in ERT group developed a new lobular ER+ breast cancer 72 months after dx of ductal ER-breast cancer & 27 months after initiation of ERT. In the control group, there were 20 cancer events: 14 patients developed new or recurrent breast cancer at a median time of 139.5 months after dx & 6 patients developed other cancers at a median of 122 months.

HRT after Breast Cancer DX

- Vassilopoulou-Sellin R. et al. Estrogen replacement therapy after localized breast cancer: clinical outcome of 319 women followed prospectively. J Clin Oncol. 1999 17(5): 1482-7.

HRT after Breast Cancer DX

- Method: prospective descriptive study of all breast cancer survivors who requested ERT because of intractable menopausal symptoms
- 24 patients treated for breast cancer 8-91 months prior to ERT and then observed for 24-44 months
- No recurrences

HRT after Breast Cancer DX

- Guidozzi, F. Estrogen replacement therapy in breast cancer survivors. Int J Gynaecol Obstet. 1999. 64(1): 59-63.
- Study done in South Africa

HRT after Breast Cancer DX

- Objective: perform matched cohort analysis to evaluate the impact of HRT on mortality on breast cancer survivors
- 125 cases matched with 362 controls. 98% received systemic estrogen & 72% also received progestional agent. Median duration of HRT was 22 months. Median interval between diagnosis of breast cancer & initiation of HRT was 22 months.

HRT after Breast Cancer DX

- Risk of death was lower among the HRT survivors; odds ratio 0.28. Analysis does not suggest that HRT after the treatment of breast cancer associated with adverse outcome.
- DiSaia, PJ. et al. Breast cancer survival and hormone replacement therapy: a cohort analysis. Am J Clin Oncol. 2000; 23(6): 541-5.

HRT after Breast Cancer DX

- Purpose: evaluate the impact of HRT on recurrence & mortality after a diagnosis of breast cancer
- Method: data from 2755 women aged 35-74 diagnosed with invasive breast cancer while enrolled in HMO. Pharmacy data identified 174 users of HRT after dx. Each HRT user matched to 4 nonusers.

HRT after Breast Cancer DX

- Relatively low rates of recurrence & death were observed in women who used any type of HRT (oral only = 41%, vaginal only = 43%, both oral & vaginal =16%)
- O'Meara ES, et al. Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. J Natl Cancer Inst. 2001 93(10): 754-624.

HRT after Breast Cancer DX

- Method: 607 breast cancer survivors interviewed concerning ERT usage. 64 used ERT after diagnosis. 8 excluded – only used vaginal ERT. Followed prospectively. Median follow-up from dx was 12.8 years.
- 1 local recurrence & 1 contralateral breast cancer occurred with no regional or distant recurrences, for a 15-year actuarial disease-free survival rate or 92.5%. No breast cancer deaths.

HRT after Breast Cancer DX

- Conclusions: use of ERT in cohort of breast cancer survivors was not associated with increased breast cancer events compared with non-ERT users, even over a long follow-up period.
- Peters, GN. et al. Estrogen replacement therapy after breast cancer: a 12-year follow-up. Ann Surg Oncol. 2001; 8(10): 828-32.

HRT after Breast Cancer DX

- Objective: Because a categorical refusal of ERT from postmenopausal patients with a history of breast cancer **is not based on any research evidence** & may be more harmful than beneficial, we evaluated the safety & efficacy of ERT in these women.
- Methods: Recruited 131 patients with breast cancer & 88 decided to use ERT.

HRT after Breast Cancer Dx

- 81 of 88 patients (92%) using ERT had no recurrence. 5 had recurrence in 12-36 months & 2 developed a cancer of the contralateral breast in 14-24 months. The combined risk was 7/216 woman-years (3% per year)
- In control group, 38 of 43 patients (88.4%) had no recurrence or contalateral cancer.

HRT after Breast Cancer DX

- 4 had recurrence & 1 developed a contralateral breast cancer (5/112 woman-years, 4% per year).
- Marttunen, MB. et al. A prospective study on women with a history of breast cancer and with or without estrogen replacement therapy. Maturitas. 2001, 39(3): 217-25.
- Study done in Finland.

HRT after Breast Cancer DX

- Objective: determine whether HRT after treatment for breast cancer associated with increased risk of recurrence & mortality
- Design: retrospective observational study
- Results: 1122 women followed up to 36 years (median >6)

HRT after Breast Cancer DX

- Results: Compared with non-users, HRT users had reduced risk of cancer recurrence, all-cause mortality, and death from primary tumor
- Durna, EM. et al Hormone replacement therapy after a diagnosis of breast cancer: cancer recurrence and mortality. Med J Aust.2002,177 (7):347-51.

HRT after Breast Cancer DX

- Design: prospective clinical trial to assess safety & efficacy of prolonged ERT of menopausal women with localized (Stage I or II) breast carcinoma & a minimum disease free interval of 2 years if ER- or 10 years if ER unknown
- 56 women on ERT, 243 women not on ERT followed for 5 years at MD Anderson

HRT after Breast Cancer DX

- Results: rate of breast cancer recurrence was 17 per 1000 person-years in HRT users after dx & 30 per 1000 person years in nonusers
- Breast cancer mortality rates were 5 per 1000 person users in HRT users & 15 in nonusers. Total mortality rates were 16 in HRT users and 30 in nonusers.

HRT after Breast Cancer DX

- Results: 2 of 56 women on ERT (3.6%) developed a contralateral, new breast carcinoma. 33 of 243 women not on ERT (13.5%) developed new or recurrent breast carcinoma.
- Vassilopoulou-Sellin, R. et al. Estrogen replacement therapy for menopausal women with a history of breast carcinoma. Cancer. 2002. 95(9): 1817-26.

HRT after Breast Cancer DX

- Objective: prospectively administered ERT to control estrogen deficiency symptoms in breast cancer survivors
- Design: 277 disease free survivors compared to historical matched controls.
- Mean time from diagnosis to ERT was 3.6 years. Mean duration of ERT was 3.7 years

HRT after Breast Cancer DX

- Results: ERT relieved estrogen deficiency symptoms & did not increase the rate or time to an ipsilateral recurrence/ new primary, contraleral new primary, local-regional recurrence, or systemic metastases.
- Decker, DA. et al. Estrogen replacement therapy in breast cancer survivors: a matched control series. Menopause. 2003, 10(4): 269-70.

HRT after Breast Cancer DX

- Method: 524 women diagnosed with breast cancer when premenopausal. Of these 277 reached menopause and 119 took HRT to control menopause symptoms
- Results: women who used HRT had an adjusted relative risk of recurrence or new breast cancer of 0.75 compared to non-users.

HRT after Breast Cancer DX

- Relative risk of death from all causes was 0.36 and death from primary tumor was 0.24.
- Durna, EM. et al. Breast cancer in premenopausal women: recurrence and survival rates and relationship to hormone replacement therapy. Climacteric. 2004, 7(3): 284-91.
- Study done in Australia

Breast Cancer Prevention

Thermography

Comparison between Mammography and Thermography

Mammography	Thermography
Approved by FDA, 1982	Approved by FDA, 1982
Radiation	No Radiation
Compression	No Compression
Anatomic	Physiologic
Problems with dense breasts & implants	No problems with dense breasts/implants
Early detection	Early detection & prevention

Breast Cancer Prevention

- Bioidentical Hormone Replacement
- Appropriate Nutrients
- Estrogen Metabolites
- Genetic Detoxification Abnormalities
- Inflammation
- Acid-Base Balance
- Stress
- Oxidative Stress/ Antioxidants

Breast Cancer Prevention

- Appropriate Diet/Exercise
- Gastrointestinal function
- Detoxify/Avoid Toxins
- Tissue Repair
- Sugar/Insulin/Glycation
- Balance Other Hormones

Breast Cancer Prevention

- Bioidentical Hormone Replacement

Breast Cancer Prevention

- Appropriate Nutrients
  - –Vitamin D
  - –Folic Acid
  - –Iodine

Vitamin D

- Pubmed database search yielded 63 observational studies of vitamin D status in relation to cancer risk, including 30 of colon, 13 of breast, 26 of prostate, and 7 of ovarian cancer.
- Majority of studies found a protective relationship between sufficient vitamin D status and lower risk of cancer.

Vitamin D

- Evidence suggests that efforts to improve vitamin D status, by vitamin D supplementation, could reduce cancer incidence & mortality at low cost, with few or no adverse effects.
- Garland CF. et al. The role of vitamin D in cancer prevention. Am J Public Health. 2006; 96(2): 252-61.

Vitamin D

- Background: inadequate photosynthesis or oral intake of Vitamin D are associated with high incidence & mortality rates of breast cancer in ecological & observational studies
- Methods: literature search for all studies that reported risk of breast cancer by quintiles of 25(OH)D identified 2 studies with 1760 individuals.

Vitamin D

- Individuals with serum 25(OH)D of 52ng/ml had 50% lower risk of breast cancer than those with serum <13ng/ml. This serum level corresponds to intake of 4000IU/day. This exceeds the National Academy of Sciences upper limit of 2000IU/day.

Vitamin D

- Garland CF. et al. Vitamin D and prevention of breast cancer: Pooled analysis. J Steroid Biochem Mol Biol. 2007; 103(3-5): 708-11.

Folic Acid

- Background: in epidemiologic investigations, folate intake has appeared to reduce the elevated risk of breast cancer associated with moderate alcohol consumption. Data relating plasma folate levels to breast cancer are sparse. Investigated association between plasma folate & other vitamins with breast cancer in a prospective, nested case-control study.

Folic Acid

- Blood samples obtained in 1989-90 from 32,826 women in Nurses Health Study who were followed thru 1996 for development of breast cancer. 712 breast cancer patients & 712 controls.
- Conclusions: Higher plasma levels of folate & possibly B6 may reduce the risk of developing breast cancer.

Folic Acid

- May be particularly important for women at higher risk of developing breast cancer because of higher alcohol consumption.
- Zhang, SM. et al. Plasma folate, vitamin B6, vitamin B12, homocysteine, and risk of breast cancer. J Natl Cancer Inst. 2003; 95 (5): 373-80.

Folic Acid

- Methods: prospective cohort analysis of folate intake conducted among 62,739 French menopausal women who had completed a validated food frequency questionnaire & followed for 9 years with 1,812 breast cancers.
- Conclusions: High folate intake was associated with decreased breast cancer risk.

Folic Acid

- Lajous M. et al. Folate, vitamin B12 and postmenopausal breast cancer in a prospective study of French women. Cancer Causes Control. 2006; 17(9): 1209-13.

Iodine

- Iodine appears to be a requisite for the normalcy of breast tissue in lab studies
- When lacking, parenchyma in rodents & humans show atypia, dysplasia, & neoplasia
- Iodine-deficient breast tissues are more susceptible to carcinogenic action & promote lesions earlier & in greater profusion.

Iodine

- Iodine appears to be a compulsory element for breast tissue growth & development. It presents great potential for its use in research directed toward the prevention, diagnosis, & treatment of breast cancer.
- Eskin, BA. Iodine and mammary cancer. Adv Exp Med Biol. 1977; 91: 293-304.

Iodine

- Seaweed is a popular dietary component in Japan & a rich source of both iodine & selenium. Hypothesize that this dietary preference may be associated with the low incidence of benign & malignant breast disease in Japanese women.
- Although suggestive evidence for preventive role for iodine & selenium more studies needed.

Iodine

- Cann, SA. et al. Hypothesis: iodine, selenium and the development of breast cancer. Cancer Causes Control. 2000; 11(2): 121-7.

Iodine

- Paper reviews evidence showing iodine as an antioxidant & anti proliferative agent contributing to integrity of normal mammary gland.
- Seaweed is important dietary component in Asian communities & rich source of iodine.
- High consumption of iodine (25x) associated with low incidence of benign & cancer breast disease in Japanese women

Iodine

- In animal & human studies, iodine supplementation exerts a suppressive effect on the development of both benign & cancer neoplasia
- We propose that an iodine supplement should be considered an adjuvant in breast cancer therapy.

Iodine

- Aceves, C. et al. Is iodine a gatekeeper of the integrity of the mammary gland? J Mammary Gland Biol Neoplasia. 2005; 10(2): 189-96.

Estrogen Metabolites

- Experimental & clinical evidence suggests that 16alpha-hydroxylated estrogen metabolites, biologically strong estrogens, are associated with breast cancer risk.
- Study analyzes association of breast cancer risk with estrogen metabolites (2/16 ratio) in prospective nested case control study.
- 10,786 Italian women (ages 35-69)

Estrogen Metabolites

- Urine collected & stored. After 5.5 years 144 breast cancer cases & 4 matched controls per case.
- Among premenopausal women, higher 2/16 ratio at baseline associated with reduced risk of breast cancer. Women in highest quintile had an adjusted odds ratio for breast cancer of 0.58. In postmenopausal women was 1.29.

Estrogen Metabolites

- Results of this prospective study support hypothesis that estrogen metabolism pathway favoring 2 pathway associated with reduced risk of invasive breast cancer in premenopausal women.
- Muti, P. et al. Estrogen metabolism and risk of breast cancer: a prospective study of the 2:16 alpha-hydroxyestrone ratio in premenopausal and postmenopausal women. Epidemiology. 2000; 11(6):635-40.

Estrogen Metabolites

- Obtained early morning urine from 70 high risk premenopausal women with a first degree family history of breast cancer & 27 low risk women
- Ratio of 2/16 identical in women with & without a family history of breast cancer

Estrogen Metabolites

- Ursin, G. et al. Urinary 2-hydroxyestrone/16 alpha-hydroxyestrone ratio and family history of breast cancer in premenopausal women. Breast Cancer Res Treat. 2002; 72(2): 139-43.

Estrogen Metabolites

- Most, but not all, studies have found that a relatively high 2/16 ratio is associated with a low breast cancer risk.
- Determine if the 2/16 ratio in plasma correlates with breast cancer risk factors & lifestyle factors, including ethnicity, body size, age at menarche, oral contraceptive use, smoking, vegetarian diet, coffee & alcohol consumption in 513 nulliparous women aged 17-35.

Estrogen Metabolites

- Oral contraceptive users had a significantly lower 2/16 ratio than pill non-users
- Reported elevated risk of early onset breast cancer among young OC users could be mediated in part through altered estrogen metabolism induced by synthetic estrogens & progestins.

Estrogen Metabolites

- Jernstrom, H. et al. Predictors of the plasma ratio of 2-hydroxyestrone to 16alpha-hydroxyestrone among pre-menopausal, nulliparous women from four ethnic groups.
- Carcinogenesis. 2003;24(5);991-1005.

Breast Cancer Prevention

- Bioidentical Hormone Replacement
- Appropriate Nutrients
- Estrogen Metabolites
- Genetic Detoxification Abnormalities
- Inflammation
- Acid-Base Balance
- Stress
- Oxidative Stress/Antioxidants

Breast Cancer Prevention

- Appropriate Diet/Exercise
- Gastrointestinal Function
- Detoxify/Avoid Toxins
- Tissue Repair
- Sugar/Insulin/Glycation
- Balance Other Hormones

Thank You!

Optimizing Patient Safety Utilizing Hormonal Pellet Insertion

Presented by

Rebecca Glaser, MD

Handouts
Hormone Treatment with Pellet Implants

Rebecca L. Glaser, M.D., FACS

1

Actual patient monthly medication list

$749.91 $295 co-pay

Monthly Medication List and co-pay cost (retail cost) for DW

• Premarin 0.625mg - $36 ($41.99)	hormone replacement- stopped taking 7/06
• Lasix 40mg - $5 ($9.99)	excessive fluid retention
• Aleve - $12 OTC	migraine and tension headache prevention
• Vitamin - $12	calcium/iron and other, OTC
• Aspirin 81mg - $2	circulation/heart, OTC
• Imatrex 50mg - $50 ($190/9 pills)	migraine preventative
• Phenergan 25mg - $10 ($25.99)	nausea r/t migraine headaches
• Verapamil 240mg - $14 ($22.99)	blood pressure/angina
• Diovan 80mg - $30 ($71.99)*	blood pressure
• Advair 100/50 - $30 ($173.99)	asthma
• Albuterol Inhal - $20 ($26.99)	asthma
• K-dur 20mEg- $10 ($20.99)	potassium replacement r/t diuretic usage
• Lipitor 10mg - $30 ($92.99)	elevated cholesterol
• Claritin- $30	allergy/asthma, OTC
• Prilosec - $30	GERD, OTC

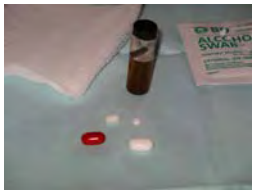
*HCTZ $3.57- 4.25 for 100 pills

Patient Presentation

- Estradiol and testosterone subcutaneous implants are the best method to deliver hormones in both men and women
- Hormone therapy with pellets provide optimal bio-identical hormone therapy
  - Hormones identical to human hormones
  - How the hormones are delivered

What are Pellets?

- Pellets made up of either testosterone or estradiol compressed into very small, solid cylinders
- Testopel® is an 'FDA approved' 75 mg testosterone pellet
- In the U.S. other formulations and dosages need to be 'compounded' by trained pharmacists
- Pellets are slightly larger than a grain of rice and smaller than a 'Tic Tac' (red and white)
- They come in sterile glass vials



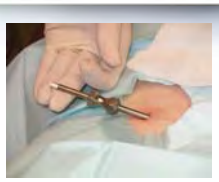
What are proven benefits of pellets?

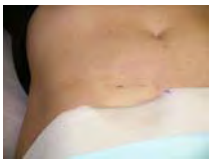
- Pellets deliver consistent, physiologic levels of hormones
  - Pellets avoid the fluctuation of hormone levels seen with every other method of delivery
  - It is the fluctuations in hormones that cause many of the symptoms
- Estrogen delivered by subcutaneous pellets maintains the normal ratio estradiol:estrone (>1.5)
  - This is important for optimal health and disease prevention
- Pellets do not increase the risk of blood clots like conventional (oral) or synthetic HRT

- Pellets are superior to oral, conventional hormone replacement therapy, especially with respect to bone density, insomnia, sex drive, libido, and sexual performance.
- An extremely high level of symptomatic relief is obtained with pellets (men and women)
  - Patients who failed other type of therapy
- Pellets are the most convenient method of hormone delivery

How and where do you insert the pellets?

- The insertion of pellets is a simple, relatively painless, procedure done under local anesthesia.
- The pellets are usually inserted in the lower abdominal wall or hip
- Experience counts, not only in placing the pellets but determining the correct dosage of hormones to be used





Are there any complications from inserting the pellets?

- Complications from the insertion of pellets include:
  - Minor bleeding (rare)
  - Bruising or skin discoloration
  - Infection (rare)
  - Extrusion of the pellet (rare)
- Antibiotics may be given to prevent an infection if a patient is diabetic or has had a total joint replaced

Why haven't patients heard of pellets?

- Pellets are not marketed in the U.S.
- Pellets are frequently used in Europe and Australia. (Riselle, Testopel, Organon)
- Most of the data on pellets is out of England and Australia with some out of Germany, United States and the Netherlands.
- Pellets were frequently used in the United States from about 1940 through the 70's when the patented estrogens were marketed to the public
- Even in the United States there are clinics that specialize in the use of pellets for HRT

What have studies shown in patients treated with pellet implants?

- Increased energy
- Improved sleep
- Relief of migraine or menstrual headache
- Relief from depression, decreased anxiety
- Increased muscle mass and bone density
- Decreased soft fatty tissue
- Increased coordination and physical performance
- Improved skin (increased collagen and elastin)
- Increased concentration and memory
- Improved overall physical health (BP, lipids, glucose)
- Improved libido and sexual satisfaction
- Improved sexual function in men
- *No* increased risk of strokes or blood clots

Do pellets have the same increased risk of breast cancer as conventional synthetic hormone therapy?

- With the exception of high doses of unopposed estrogen, pellets do not have the same risk of breast cancer as conventional hormone replacement therapy
- Nor, do they increase the risk of breast cancer like the synthetic, chemical progestins used in the 'WHI' trial
- Testosterone delivered by pellets does not increase the risk of breast cancer like oral, synthetic methyl-testosterone
- Studies using testosterone hormone implants have shown less stimulation of breast tissue and lower rates of breast cancer
- Data supports that balanced hormones are breast protective

Are there any side effects?

- When a patient first starts hormone therapy, there may be mild temporary breast tenderness which improves on its own
  - The hormone receptors may be very sensitive and take time to adjust
- There may be a temporary water weight gain
  - Overall the body will 'tone up' as bone density and muscle mass increase and the soft fatty tissue decreases
- As with other types of HRT, women with an intact uterus may experience bleeding
- Men may experience an elevated blood count
  - Testosterone stimulates the production of red blood cells

How long after the pellets are inserted will a patient notice a difference?

- Clinical trials show therapeutic hormone levels within 24 hours.
- Most people feel a difference within 24 to 48 hours, while others may take up to 14 days.

How long will the pellet last?

- Pellets, in women, usually last between 3 and 5 months.
- In men, the pellets usually last between 4 and 6 months.

What happens to the pellets?

- The pellets do not need to be removed.
- They completely dissolve over time.

Are pellets a good way to deliver testosterone in men?

- There is no better way to deliver testosterone in men than with pellets.
  - Maintain consistent levels of testosterone while maintaining normal ratios of estrogen and DHT

Are there any side effects to testosterone pellets in women?

- Testosterone therapy, with subcutaneous implants, has no undesirable metabolic consequences
  - Blood pressure
  - Lipids
  - Blood clot formation
- Occasionally a patient may be sensitive to testosterone and may experience oily skin or a slight increase in facial hair. This can be balanced with progesterone and a lower dose of testosterone used at the next insertion
- Less than 1 out of 20 women have a problem with testosterone

Do female patients still have to use progesterone?

- Yes, any time estrogen is prescribed progesterone may be prescribed
- There are progesterone (not progestin) receptors in the bone, brain, heart, breast tissue and uterus
- In patients without a uterus, progesterone may be used as a topical cream, a vaginal cream, oral capsule, or sublingual drops or capsules
- If a patient has a uterus, oral or vaginal progesterone is often prescribed to protect the uterine lining
  - Vaginal progesterone gets a high dose to the uterus without the side effects of oral progesterone
- If a patient is pre-menopausal, she uses the progesterone the last two weeks of the menstrual cycle.

Is there a role for the use of pellets in pre-menopausal females?

- Definitely
- Women may have deficient hormone levels as early as their mid thirties (premature ovarian failure)
- Hormone levels fluctuate greatly in some women before menopause causing:
  - PMS
  - Menstrual or migraine headaches
  - Sleep disorders
- Pellets can 'even out' the fluctuating hormones and dramatically improve symptoms
- Testosterone implants alone can be used if a patient is symptomatic and has low levels of testosterone

Will a patient need to have testing done?

- Yes, hormone levels will be drawn and evaluated before therapy is started. This includes a PSA in men.
- Hormone levels may be rechecked between 3-5 months for women and 4-6 months for men (whenever symptoms begin to return)
- After the first year, hormone levels do not need to be checked as often
- In men, the PSA is monitored every 6-12 months
- In men, a blood count will also be monitored

How old should a man be to consider hormone testing?

- Testosterone levels begin to decline in men in their early 30's. Most men maintain a healthy level into their mid 40's to mid 50's
- Men in their 30's can be deficient in testosterone and even have signs and symptoms of bone loss
- When a man becomes symptomatic he should be tested (rising blood sugar, rising blood pressure, aches, pains, muscle loss, poor memory, concentration, loss of sex drive etc.)
  - Usually between 45 and 55 years of age
  - It's never too late to prevent and reverse disease
  - Even men in their 80's do well on testosterone

How much do pellets cost?

- Pellets cost between $260-$600(men)
  - It depends on the dose and the number of pellets needed
  - Men need a much larger dose of testosterone than women
- Pellets need to be inserted about 2 to 3 times per year.

What is the cost of not doing Pellets?

- Osteoporosis
  - Boniva $94.95/m, Fosamax $87.95/m
  - Forteo 750 mcg $798.95/m
  - Hip fracture…..priceless
- Insomnia
  - Lunesta, Ambien CR $120/m
  - Sleep study
- Depression
  - Welbutrin XL ($120.48/m), Effexor
  - Psych visit
- Sexual Dysfunction
  - Viagra ($250.62/20), Cialis ($142.29/10)
- Arthritis/pain
  - Celebrex ($66.88/m)
- Hypertension, heart disease, diabetes, obesity, chronic fatigue, fibromyalgia, headaches, palpitations, incontinence, divorce etc.

Do insurance companies cover the cost of pellets?

- This varies by insurance company. Most physicians require payment for their services.
- The patient may want to contact their insurance company to see if they will reimburse them for the cost.
- Prevention is much more cost effective than treatment of disease.

Conclusion (patient presentation)

- Estrogen and testosterone therapy by implantation of pellets is a safe and effective method of hormone therapy for both men & women
- Long-continued administration by implantation is convenient and economical for the patient
- Pellet implantation is a simple office procedure
- Pellet implantation has consistently proven more effective than oral, IM, and topical HRT
  - bone density, sexual function, depression, GU sxs., breast health, lipid profiles, hormone ratios and metabolites

AMA Nov 2006

- The nation's largest doctors' group voted this week to seek stricter Food and Drug Administration oversight and regulation of these so-called "bioidentical" hormone compounds.
- “But there's no evidence that bioidenticals are any safer and they may even have other risks”, Dr. Robert Vigersky, a member of the Endocrine Society delegation to the AMA, said Wednesday.
- "This is a safety issue, there's no question about it," said Dr. Ardis Hoven, an AMA board member.

Endocrine Society President Testifies before U. S. Senate Special Committee on Aging

- Dr. Wartofsky supported Dr. Manson's scientific arguments **against** the much promoted idea that **bioidentical** and/or compounded hormones are **safer** or more effective than FDA-approved hormone treatments. Both expressed concern that women were receiving ***scientifically unproven*** information or not receiving enough information to make informed decisions about their treatments.
- For his part, Jacques Rossouw, MD, Chief of the **W**omen's **H**ealth **I**nitiative Branch of NIH, emphasized that….the **risks** and benefits of all estrogens and all progesterones are **equivalent**.

Senator Smith (left) and President Wartofsky (right) at April 19 hearing.

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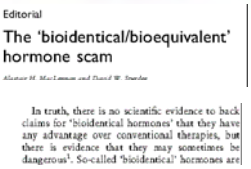
Criticism

- Insurance companies refuse to reimburse patients for the cost of pellets claiming that they are 'experimental'
- "Not approved by ACOG"
- "Not approved by the FDA"
- "In it for the money"



Editorial

The 'bioidentical/bioequivalent' hormone scam

In truth, there is no scientific evidence to back claims for 'bioidentical hormones' that they have any advantage over conventional therapies, but there is evidence that they may sometimes be dangerous[1]. So-called 'bioidentical' hormones are

Climacteric 2006

Data (scientific evidence)

- History
- Dosing
- Clinical Studies Women (timeline)
  - Bone health
  - Body composition
  - Cardiovascular health, lipids
  - Breast health
  - Other: Migraine headaches, birth control, skin health
- Clinical Studies Men
- Practical Applications
- Current Research
- Case Presentations

History

- Subcutaneous implants have been used in women since 1938
- In 1939 Salmon concluded that “25 to 50 mg. (of crystalline estradiol benzoate) should maintain a patient symptom free for many months and suggested that it be given prophylactically to patients following x-ray or surgical castration”

Misnell 41 AJOG

CONCLUSIONS

1. Estrogen therapy by implantation of 50 mg. pellets is a safe and effective mode of therapy in cases of menopause.
2. Long-continued administration by implantation is more economical to the patient.
3. Pellet implantation is a simple office procedure.
4. No untoward effects were observed in a series of 28 cases.
5. Therapy by pellet implantation for the menopausal syndrome has proved more effective than that obtained by intramuscular injection.
6. In patients with primary amenorrhea, complaining of lack of breast development, satisfactory results have been obtained with pellet implantation.

Greenblatt 49 AJOG

- Indications for the Use of Pellets
  - Estradiol (25 mg in weight)
    - Severe menopausal syndrome
    - In young women with hypoplasia of the uterus or breast
    - Dysmenorrhea associated with hypoplasia of the uterus

    It is preferable that estradiol pellets should not be used except in those patients without uteri
  - Progesterone (50 mg in weight)
    - In selected patients with nervous tension states
    - Nyphomaniacal tendencies that prove distressing
    - In treatment of habitual abortion
    - In treatment of pubertal breast hypertrophy

Greenblatt 49 AJOG

- Indications for Use of Testosterone Pellets
  - Menopausal syndrome in whom estrogen therapy has proved unsatisfactory or is contraindicated
  - In combination with estradiol pellets in patients with uteri who have severe menopausal symptoms, in order to prevent the untoward bleeding induced by estrogens
  - Dysmenorrheic patient with endometriosis or small fibroids
  - Fibomyomata for whom surgery is not feasible
  - Nocturia of endocrine origin
  - Increased libido is desired
  - Palliative measure in patients with advanced carcinoma of the breast
  - In combination with Desoxycorticosterone pellets for Addison's disease

Greenblatt 49 AJOG

- Indications for the Use of Pellets
  - Desoxycorticosterone Acetate Pellets (75 mg)
    - Addison's disease
    - In panhypopituitarism, implanted along with testosterone
    - In certain asthenic patients who have low blood pressure, low blood sugar, and marked fatigability, it appears that this form of medication proves helpful. …….'Adrenal Fatigue'

History of the FDA and Hormone Implants

- Testosterone and estradiol pellets were manufactured in the US since 1946
- FDA approved 75 mg testosterone pellet 1972
- 1984 Progynon NDA with the FDA for 75 mg testosterone pellet
  - Problem sterility
- Estradiol pellets were sold in the US from 1946 until 1988 when they were reclassified by the FDA as IND
  - Sold from 1988-93 as 'investigational use only'
  - 1993 they were no longer able to be sold because they were reclassified as a 'new drug'
    - NDA applied for

Dosing

- Physiologic Levels of hormones
- Historical and current dosing

What are physiologic premenopausal levels of estradiol?

Endogenous estrogen production rates and plasma estrogen concentrations[a]

	Approximate estradiol production rate (ug/day)	Plasma concentration	
		Estradiol (E2) (pg/ml)	Estrone (E1) (pg/ml)
Premenopausal woman			
early follicular	100	40–60	40–60
mid follicular	96–160	60–130	–
late follicular	320–640	200–400	170–200
luteal	300	190	100–160
Menopausal woman	14	5–35	30–70
Man	30–60	25–43	25–90

Maintain estradiol between 40 and 60-80 pg/ml.

A 25 mg pellet lasting 100 d delivers ~ 250 ug E2/d

Symptoms may be associated with a rise in FSH or fall in estrogen, not the actual level

Treat the patient, not the lab.

Bone conserving 'dose equivalents' for estrogen Lancet

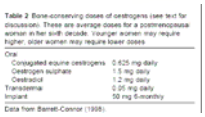


Table 2 Bone-conserving doses of oestrogens (see text for discussion). These are average doses for a postmenopausal woman in her sixth decade. Younger women may require higher, older women may require lower doses

Oral	
Conjugated equine oestrogens	0·625 mg daily
Oestrogen sulphate	1·5 mg daily
Oestradiol	1·2 mg daily
Transdermal	0·05 mg daily
Implant	50 mg 6-monthly

Data from Barrett-Connor (1998)

Data supports 25 mg estradiol conserves bmd

Goel, Neerja Delhi

(Serum level equivalent estrogen formulations)

Table 4. Estrogen formulations and drug serum levels

Formulation	Dose (mg)	Serum level estradiol (pg/ml)
1. Conjugated equine estrogen	0.625 1.25	40 60
2. Micronized estradiol	1 2	40 60
3. Transdermal estradiol patch	0.05 0.10	25-40 60
4. Estradiol Valerate	1	50
5. Estradiol gel	1	40-50

Subcutaneous implants in a dose of 50 mg at six monthly intervals, produces serum level of nearly 40-60 pg/ml

What are physiologic premenopausal levels of testosterone?

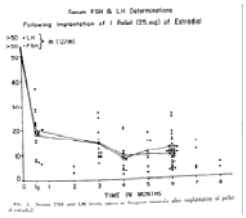
- "Daily production rate (of testosterone) is in the order of 0.1-0.4 mg" (Burger)
- Testosterone declines in women between the age of 20 and 50. A 40 yo has ½ the level of a 20 yo (Zumoff)
- Testosterone measured in serum is inaccurate at lower levels (Princeton consensus)
- For every commercially available testosterone assay studied, the values are in error-by a factor of 2 on average and in some cases by a factor of almost 5 (Taieb)
  - '…guessing appears to be nearly as good as most commercially available immunoassays and clearly superior to some' (Herold)
- Check free testosterone along with total testosterone
- Treat the patient

Dosing Pellets

- Historical dosing: Estradiol 25, 50, 75,100 mg (alone)
  - 3-6 months, variable
  - See accumulation with higher doses of estradiol at less than 4-6 month intervals in some patients.
  - Can develop tachyphylaxis (rare)
    - premature return of menopausal symptoms associated with high E2 levels
  - Supraphysiological concentrations of estradiol from SC pellets do not adversely affect lipid levels and are beneficial to insulin metabolism (Pirwany)
- Do not see accumulation with 12.5-25 mg dosing at 3-5 month intervals.
  - Balance E2 with T to treat symptoms and bone density

Greenblatt 77 J Rep Med

- Dosing based on symptoms
  - 1-4, 25 mg Estradiol pellets
  - 1-2, 75 mg Testosterone pellets
  - Provera 10 mg 5-7 d/m
    - Orderly withdrawl bleeding
- Bleeding
  - Provera 10 mg q2-4 hours until bleeding stops then 1 po BID x 10 d
  - Uterine biopsy



Clinical Studies

45

Staland 78 ActaOGS

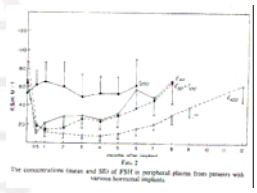
- 94 women post TAH (46 BSO) treated with implant E2 20 mg every 6 months
- Excellent symptomatic relief
  - 75% lasted 6 months or greater
  - Oral estrogens were given as needed, rarely used
  - As a rule, menopausal symptoms return when plasma oestradiol falls below 100-120 pmol/l (27-32 pg/ml).
  - Serum FSH gives a good idea of the effect of oestrogen but need not necessarily drop despite a good effect of treatment
  - Patients felt better with a low but constant estrogen level
- Very few side effects at this dose
  - Mastalgia in 4 patients, all over 60 yo

Thom 81 BJO&G

- 24 patients TAH, BSO
  - E2 100
  - E2 50
  - E2 50 and T 100
  - T 200
- Followed hormone levels 2wks, then monthly to 12 months

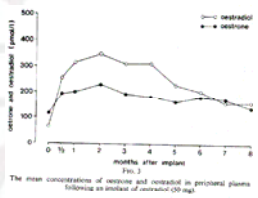
- FSH and LH fell at 2 weeks until month 6-7 100mg E2 and month 4-5 50 mg E2
- Plasma testosterone rose from 1.0 nmol/l to 5.0 and 6.7 nmol/l (100 and 200 mg implants)
- 100 mg E2 602.3 pmol/l at month 3 (from 46.7)
- 50 mg E2 346.7 pmol/l at month 3
- Both E 100 & E 50 reversed the E1:E2 ratio

Thom 81 BJO&G



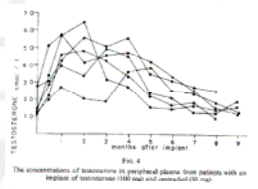
- FSH with various hormone implants
- Testosterone alone has very little affect on FSH
- 100 mg E2 implant suppresses FSH most
- FSH begins to rise between month 4 and 5 with 50 mg implant (as E2 rises) and is suppressed below 20 until month 7 with 100 mg E2 implant

Thom 81 BJO&G



- E2 and E1 levels with a 50 mg E2 implant
- Peaked at month 2 vs. month 1 in other studies
  - 312.6 nmol/L (85 pg/ml)
- Reversed the ratio of E2:E1 from 1:2 to 2:1

Thom 81 BJO&G



- Concentration of testosterone in plasma with 100 mg T implant, with E2 50
- Most patients peak at month 1-2
- Variation in levels between patients
- Levels in most patients begin to decline between month 4 and 5

Brincat 84 Lancet

- Prospective study
- 55 post men on HRT randomized to E50/T100 (33) or placebo (22)
- Mean number of previous implants: 6
- Women with uterus treated with Norethisterone 5 mg 7d/cycle
- T implants usually done for lethargy, depression, loss of libido
- With implant group there was improvement in all symptoms; hot flushes, palpitations, headaches, irritability, lack of concentration, insomnia, depression, aches, dyspareunia, loss of libido, lethargy
- No change in placebo group
- Return of symptoms began between 4 and 6 mos.
- Symptoms occur in response to a fall in oestrogen levels
- Offer re-implantation at 4 months

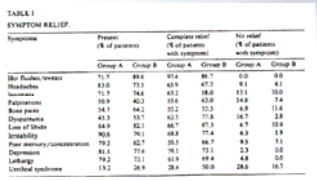
Cardozo 84 Maturitas

- Estradiol 50 mg/ Testosterone 100 mg implants in 120 pre-menopausal (A) and post-menopausal (B) women (469 implants over 4 years)
- Indications
  - Oral HRT unsatisfactory in 51% (pre-men) and 43% (post-men) of patients
  - Psychosexual symptoms
  - Convenience
  - Patient request
- All patients had received at least one (1-6) hormone implant in the past (E2 50, T 100)
- Women with a uterus were treated with Norethisterone 5 mg 7 days/m

Cardozo 84 Maturitas

E2 50 mg

T 100 mg



High percent of patients with relief of symptoms; hot flushes, headache, insomnia, palpitations, bone pains, dyspareunia, libido, irritability, memory/concentration, depression, lethargy, urethral syndrome. Duration of symptom relief was 6 mos. in 85% and 69% of women (range 3-12 mos.)

Cardozo 84 Maturitas

- Side effects were minimal
  - Mild breast discomfort occurred early in treatment and resolved spontaneously 20%
  - Increased facial hair 20%
  - Acne 2%
  - Abnormal uterine bleeding 16% (on progestin therapy 7d/m)
- Abnormal bleeding was corrected with increasing progestin from 7 days to 10-13 days each cycle

Cardozo 84 Maturitas

- Serum FSH and LH fell consistently after each implant
- Estradiol, estrone, and testosterone showed little evidence of accumulation and did not exceed the normal pre-menopausal range
- Plasma testosterone levels at the time of return of symptoms remained in the upper normal range
- Symptoms are due to a change of serum estrogen from moderately high to normal levels
- 'Subcutaneous hormone implants are an effective, acceptable treatment for climacteric symptoms in both pre- and post-men women with few side effects or complications'

Burger 84 Maturitas

- 17 women average age 37.5
  - TAH, BSO (10), TAH (1), BSO (1), spontaneous menopause (5)
- 'Persistent loss of libido' despite oral Premarin 1.25 mg or Estradiol valerate 4 mg daily
- Testosterone 100 mg & Estradiol 40 mg implanted SC
- No change in *lipid profile*
- Max change in E & T at 1 month
- Significant improvement in libido, sexual satisfaction, fatigue, concentration
- 1 patient c/o very mild hirsutism and weight gain
- '…combined hormone implants are highly effective in relieving loss of libido which does not respond to conventional oral oestrogen therapy.'

Burger 84 Maturitas

T 100 mg

E2 40 mg

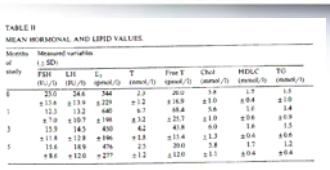


TABLE II

MEAN HORMONAL AND LIPID VALUES

Months of study	Measured variables (± SD): FSH	LH	E_2	T	Free T	Chol	HDLC	TG
0	25.0 ± 12.6	24.6 ± 13.9	344 ± 229	2.3 ± 1.2	26.0 ± 14.9	5.9 ± 1.0	1.7 ± 0.4	1.5 ± 1.0
1	12.3 ± 7.0	13.2 ± 10.7	640 ± 196	6.7 ± 3.2	68.4 ± 25.7	5.6 ± 1.0	1.6 ± 0.6	1.4 ± 0.9
3	15.9 ± 11.8	14.5 ± 12.8	430 ± 196	4.2 ± 1.8	43.8 ± 15.4	6.0 ± 1.3	1.6 ± 0.4	1.5 ± 0.6
5	15.6 ± 8.6	18.9 ± 12.0	476 ± 277	2.5 ± 1.2	29.0 ± 12.0	5.8 ± 1.1	1.7 ± 0.4	1.2 ± 0.4

- No change in Cholesterol, HDL, TG
- E2 peaked at one month (640 pmol/L:174 pg/ml from 93.5 pg/ml, prior estrogen therapy)
  - FSH and LH further decline
- Testosterone peaked at one month (6.7 pmol/L: **192 ± 91** ng/dL) and declined by month 5 (2.5 pmol/L: **71.4 ± 34** ng/dL)
  - Became symptomatic

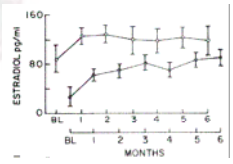
Barlow 86 O & G

- 75 menopausal women
  - 36 E2 50
  - 39 E2 50 T100

  Every 6 months for 3 years
- High symptom relief (started to return by 6 mos.)
- Low incidence side effects
  - No change in body weight, BP or LFT's
- Accumulation of E2 at 3 years with q6mo dosing of 50 mg in some patients (still pre-men follicular levels)
  - Estradiol range at 36 mos 228-1227 pmol/L: 62-334 pg/ml
- No accumulation of testosterone
- E2 50 maintained BD
- E2 50 T100 gained BD
  - The author felt it was due to the estrogen

Notelovitz 87 O&G

- 12 patients with TAH BSO either 25 mg or 50 mg estradiol implant every 6 months for 2 years
- Results
  - Both doses maintained or increased bmd
  - Serum E2 increased significantly in both groups and reversed the E2:E1 ratio
  - Serum testosterone levels were suppressed by 25%
  - Libido improved in 41% of patients with E2 alone



Open Circles 50 mg E2

Closed Circles 25 mg E2

Notelovitz 87 O&G

- Results cont.
  - Serum cholesterol decreased in both groups (significant only in the 25 mg group)
  - Serum TG and HDL remained unchanged
  - No difference in coagulation profiles
  - Carbohydrate and insulin metabolism was unaffected
  - No change in BP
  - No difference between the 25 mg and 50 mg group

Montgomery 87 Lancet

- Double blind placebo trial
  - E2 50 , E2 50 & T 100, placebo
- Psychological complaints
  - Self rated distress (SRD)
    - Anxiety
    - Somatic disturbances
    - Depression
- After 2 months, both treatment group scored better anxiety, somatic complaints and depression
- Postmenopausal women (not pre-menopausal) improved after placebo
- "HRT by pellet implantation does NOT increase anxiety"

Dow 83 BJOG

- 40 postmenopausal women with concern about a decline in their sexual interest
- Estradiol 50 mg vs. E2 50, T100
  - Both groups showed significant reduction in
    - Psychological complaints
    - Somatic complaints
    - Vasomotor symptoms
  - Both groups showed significant improvement
    - Sexual interest
    - Responsiveness
    - Dyspareunia

Stanczyk 88 AJOG

- A randomized comparison of non-oral estradiol delivery
- TD Patch (.1 mg twice weekly) vs. Pellets (2, 25 mg E2)
  - 20 women TAH, 12 BSO
  - Constancy of estrogen delivery and metabolic effects
    - Estrogen delivery
    - Estrogen effect on FSH
    - Lipids
    - Calcium/creatinine ratio

Stanczyk 88 AJOG

Table I. Percentage of subjects in the pellet and patch groups with serum E_2 concentrations <20 and 40 pg/ml

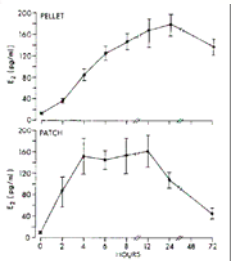
Time of sample	<20 pg/ml, % of subjects		<40 pg/ml, % of subjects	
	Pellet	Patch	Pellet	Patch
72 hrs	0	29	0	50
1 wk	0	0	0	50
2 wk	0	10	0	50
4 wk	0	0	0	70
8 wk	0	0	0	60
12 wk	0	50	0	40
16 wk	0	20	0	40
20 wk	0	10	0	20
24 wk	0	0	0	20

Table II. Percentage of subjects in the pellet and patch groups with serum E_2 concentrations >150 and 200 pg/ml

Time of sample	>150 pg/ml, % of subjects		>200 pg/ml, % of subjects	
	Pellet	Patch	Pellet	Patch
72 hrs	40	0	10	0
1 wk	10	0	0	0
2 wk	20	0	0	0
4 wk	30	20	0	10
8 wk	10	0	0	0
12 wk	10	10	0	0
16 wk	0	0	0	0
20 wk	10	10	0	0
24 wk	10	20	0	0

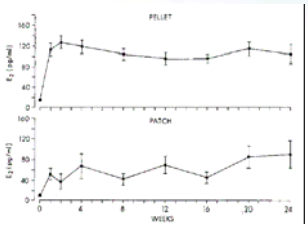
Pellets provided more consistent estradiol levels

Stanczyk 88 AJOG Pharmacokinetics



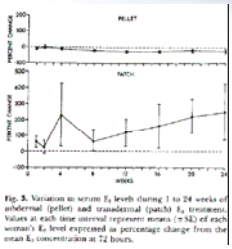
- Pellet: serum estradiol levels peaked at 24 hours and fell to 139 ±16 pg/ml at 72 hours. At one week estradiol measured 113 ±12 pg/ml and remained relatively constant for 24 weeks
- Patch: estradiol peaked at 4 hours, remained constant for the next 8 hours then fell to 46 ±10 pg/ml at 72 hours
  - Wide variation in estradiol levels the entire 24 weeks

Stanczyk 88 AJOG



Mean serum E2 levels

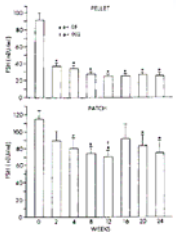
Stanczyk 88 AJOG



Variation in serum E2 levels during 1 to 24 weeks
Values at each time interval represent % change at 72 hours

Stanczyk 88 AJOG

- FSH in both groups was suppressed but was greater and more consistent in the pellet group
- A physiologic ratio of E2:E1 was consistently maintained with both pellets and the patch, but fluctuated widely within the patch group



Stanczyk 88 AJOG

- Total cholesterol and triglycerides unchanged in both groups (lower but not statistically sign)
- HDL increased significantly in the pellet group at both 12 and 24 weeks and at 24 weeks in the patch group
- A reduction in urinary calcium/creatinine ratios occurred at both 12 and 24 weeks in the pellet and patch groups; significant only in the pellet group
- 8 patients in the pellet group and 5 in the patch group c/o mild transient breast pain
- No problems with the incision
- 9 patients c/o minor problems with the patch site

Implants and Bone Density

- Oral and topical estradiol maintain bone density (86% of patients)
- Estradiol and estradiol with testosterone implants significantly increase bone density

"Subcutaneous oestrogen is more effective than oral oestrogen in preventing osteoporosis….It also avoids problems of compliance that occur with oral treatment." Savvas 88

N=37,41; T 8.0, 8.5 years

Studd 90 AJOG

- 23 post men women received E2 75 & T100 for 1 year (q6m)
  - Estradiol levels increased from 80.5 pmol/l to 453 pmol/l (21.9 to 123.2 pg/ml)
    - Range 204-883 pmol/l
      - Similar variation between pts with testosterone and FSH
  - Bone density increased 8.3% at the spine and 2.8% at the femoral neck
  - The percent of increase in bone density at the spine correlated with serum estradiol levels (not testosterone levels)

Garnett 91 O&G

- Effect of hormone implants on bone density in 110 menopausal patients
- E2 50-75 T100 q6mos 2-24 yrs. (5.2)
- Compared to 254 untreated
- Variation in levels E2, T and FSH
  - E2 74-2540 pmol/l (20.1-690 pg/ml)
  - T 0.4-5.9 pmol/L (11.4-169 ng/dL)

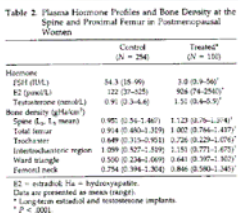
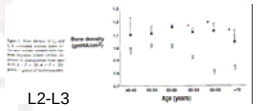


Table 2. Plasma Hormone Profiles and Bone Density at the Spine and Proximal Femur in Postmenopausal Women

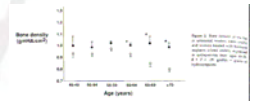
	Control (N = 254)	Treated* (N = 110)
Hormone		
FSH (IU/L)	84.3 (18-99)	3.0 (0.9-56)†
E2 (pmol/L)	122 (37-525)	926 (74-2540)†
Testosterone (nmol/L)	0.91 (0.3-4.6)	1.51 (0.4-5.9)†
Bone density (g/Ha/cm²)		
Spine (L_2–L_4 mean)	0.955 (0.56-1.465)	1.123 (0.79–1.674)†
Total femur	0.914 (0.480–1.319)	1.002 (0.766–1.437)†
Trochanter	0.649 (0.315–0.951)	0.726 (0.229–1.076)†
Intertrochanteric region	1.099 (0.527–1.519)	1.151 (0.771–1.675)†
Ward triangle	0.500 (0.224–1.069)	0.641 (0.397–1.303)†
Femoral neck	0.754 (0.394–1.304)	0.846 (0.580–1.340)†

E2 = estradiol; Ha = hydroxyapatite.
Data are presented as mean (range).
* Long-term estradiol and testosterone implants.
† $P < .0001$.

Garnett 91 O&G



L2-L3

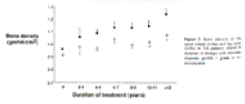


hip

- The differences in bone density became significant between ages 55 and 60
  - Hormone implants (closed circles)
  - Untreated (open circles)

Garnett 91 O&G

- Subcutaneous E & T prevent postmenopausal osteoporosis and maintain normal BD for as long as treatment is continued (>12 yrs.)



Spine closed circles

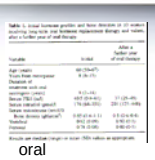
Hip open circles

Garnett 92 O&G

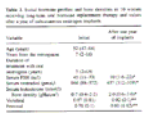
- Prospective Study
- 50 women
  - E2 75 mg or E2 75 with T 100
  - 25 untreated women
- Results
  - Bone density fell in untreated group at all areas
  - E2 alone and E2 with T increased bone density at lumbar spine and femoral neck.
    - No difference between E2 (75 mg) alone and with T
    - Correlated with serum E2 levels
      - In comparison to Premarin 0.625 mg which there is significant decrease in BD in some patients (Lindsay 84)

Savvas 92 BJO&G

- Increase in BD after one year of E2 75 & T100 q 6 mos. in post men women who previously received oral HRT (Prempak)
  - 10 women remained on oral HRT
  - 10 women received the pellets
- Results
  - Bone density in the oral HRT users unchanged
  - Bone density in the implant group increased
    - Spine 5.7%
    - Femoral neck 5.2%



oral



E2 75 & T 100

Owen 92 BJO&G

'25 mg oestradiol implants – the dosage of first choice for subcutaneous oestrogen replacement therapy?'

- 12 symptomatic post-men women for a period of 30 weeks
- 25 mg estradiol pellet (Organon lab UK) buttocks or RLQ
  - Symptomatic relief at 2 weeks
  - Reversal of the E2/E1 ratio (0.56 to 1.5) at two weeks
  - Estradiol concentration within the early follicular range in most women (4 fold variation vs. 10 fold variation after oral or topical HRT)
  - Median serum estradiol was 377 pmol/l (102.5 pg/ml)
  - *Unable to correlate* the return of symptoms with serum levels
  - 10 of 11 patients had symptom relief for 6 months
  - 1 of 11 patients required reimplantation at 16 weeks with return of sxs. at 14 weeks and a serum estradiol of 175 pmol/l (47.6 pg/ml)
  - Combination of serum levels and return of symptoms to time reimplantation
  - Adequate dose unless bone density is an issue (other studies)

Naessén 93 BJO&G

- Bone preserving effects of SC E2 20 mg
- 35 women, mean age 67 years(47-83) , TAH had been treated with E2 implants for 16 years (5.5-31 years)
  - 20-25% higher bone density than non users
  - Physiologic levels of oestradiol
  - No accumulation
- Low dose oestradiol implants maintain bone density long term

Holland 94 O&G

- Effect of E2 25 mg on bone loss
  - 18 post men females compared to 18 women who did not wish treatment
  - 25 mg E2 implanted every 6mos anterior abdominal wall
- Results
  - Post treatment E2 320 pmol/l, range 114-813 (87.0 pg/ml) FSH 28 IU/l (2-66)
  - At 1 year, there was a significant increase in bmd from baseline at lumbar spine (5.65%), femoral neck (3.38%) and hip (3.36%) but not Ward's triangle
- "This dose is effective to prevent postmenopausal bone loss."

Studd 94 BJO&G

'The dose-response of percutaneous oestradiol implants on the skeletons of postmenopausal women'

- 45 women randomized to 25, 50, or 75 mg estradiol implant 1yr
- Known correlation between estradiol levels and BMD
- Significant correlation between plasma E2 level and bmd increase at lumbar spine, total hip, femoral neck, and trochanter
  - Plasma estradiol levels
    - 25 mg 327 pmol/L (114-853)
    - 50 mg 358 pmol/L (220-957)
    - 75 mg 518 pmol/L (167-828)
  - Three women in the 25 mg group lost bone density. All three had serum estradiol levels below 300 pmol/L (81.6 pg/ml)
  - Correlation between plasma estradiol levels and increase in bmd at lumbar spine and femoral neck.
  - No one lost bone density if E2 > 300 pmol/L.

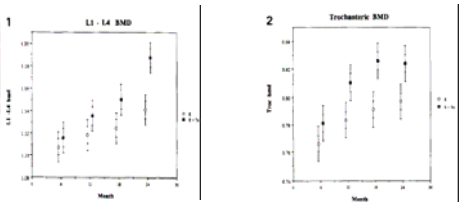
Davis 95 Maturitas

- Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality
  - Prospective, randomized study
  - 34 post-men females
  - E2 50 or E2 50 & T 50 administered every 3 months for 2 years

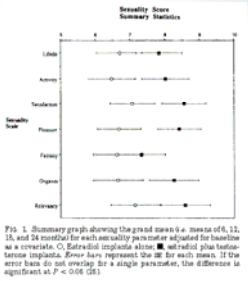
Davis 95 Maturitas

E2 50 mg vs. E2 50 mg & T 50 mg (BMD)

E & T was superior to E2 alone in increasing bmd



Davis 95 Maturitas



- All sexual parameters improved in both groups
- E & T group showed significantly greater improvement

Davis 95 Maturitas

- 24 month results: E2 50, E2 50 & T50 mg
  - Total cholesterol and LDL fell in both groups
  - Total body fat decreased in both groups
  - HDL remained unchanged
  - Fat free mass increased in the E & T group
  - Testosterone did not convert to Estradiol
  - Accumulation at 12 months with every 3 month insertion of 50 mg E2
    - Implants were held
  - No virilizing side effects T 50 mg.
  - No other side effects reported

Anderson 97 St. Thomas Hosp London OFC

- 45 pre-menopausal women, TAH BSO
  - Estradiol implant 50 mg
  - Estradiol patches 50 ug/24 h
  - Estradiol 50 Testosterone 50 mg implants
- Significant decrease in BMD in women treated with the 50 ug patch (lower E2 levels and higher FSH levels at 6, 8, and 12 months)
- BMD was maintained in both implant groups
- Short term menopausal symptoms were relieved in all three groups

(pre-op and 1 yr vertebral BD)

Davis 00 Menopause

- Effect of E2 50 vs. E2 50, T50 on body composition and lipids
  - 33 post-men women implanted q3mos for 2 yrs.
  - Cyclic oral progestins added if had uterus
    - Provera 5 or 10 mg or Noresthisterone 12 d/m
- Results
  - Both therapies reduced total cholesterol and LDL
  - Weight E2 65.1→64.1 kg; E&T 63.4→64.6 kg
  - E2 alone ↓ hip and abdominal circumference
  - Both groups ↓ in total body fat (greater with E&T)
  - E & T ↑ in FFM

- Conclusion

  Testosterone does not negate the favorable effects of estrogen on LDL cholesterol levels

Seed 00 FP ij

- CV risk factors on oral, TD and implant HRT
  - Estrogen alone vs. estrogen plus norethisterone
  - Estrogen alone vs. E2 plus T for the implant group
- All regimens reduced CV risk factors with the synthetic progestin attenuating some of the benefits of estrogen alone (fibrinogen and HDL)
- Implant group
  - E2 50 and E2 50 & T100
    - Lowered Cholesterol, LDL and Apo-B
    - Non significant lowered HDL
    - Non-significant reduction in TG compared to TD estrogen
    - Testosterone did not attenuate the beneficial effects of estradiol on LDL and TG

ESTHER study 07

TABLE 2. Impact of Hormone Therapy on VTE Risk by Route of Estrogen Administration and Type of Progestogens

	Cases (n=259)	Controls (n=603)	Matched OR (95% CI) Crude	Adjustment 1	Adjustment 2
Nonuse	146	384	1	1	1
Oral estrogen use	45	39	3.6 (1.5–8.8)	4.0 (1.6–10.1)	4.2 (1.5–11.6)
Transdermal estrogen use	67	180	0.8 (0.4–1.6)	0.8 (0.4–1.8)	0.9 (0.4–2.1)
No progestogens	14	40	. . .	. . .	. . .
Micronized progesterone	19	63	1.0 (0.4–2.3)	0.9 (0.4–2.2)	0.7 (0.3–1.9)
Pregnane derivatives	39	79	1.0 (0.4–2.3)	0.9 (0.4–2.2)	0.9 (0.4–2.3)
Norpregnane derivatives	40*	37†	3.8 (1.6–8.7)	4.0 (1.7–9.4)	3.9 (1.5–10.0)

Users of oral estrogen combined with nortestosterone derivatives (12 cases, 7 controls) were excluded (OR, 6.7; 95% CI, 2.1 to 21.9 vs nonusers). Estrogen-by-progestogen interaction terms were not significant. Adjustment 1: adjustment for obesity status, familial history of VTE, and history of varicose veins. Adjustment 2: adjustment for obesity status, familial history of VTE, history of varicose veins, education, age at menopause, hysterectomy, and cigarette smoking.

*Twenty-two cases received nomegestrol acetate, and 18 cases received promogestone.

†Nineteen controls received nomegestrol acetate, and 18 controls received promogestone.

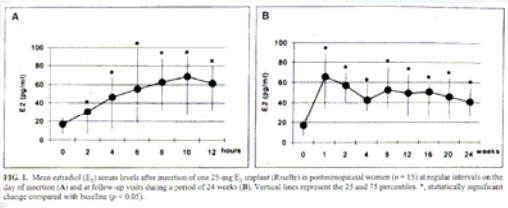
Panay 00 BJOG

- Randomized, double blind study comparing E2 25 mg vs. E2 50 mg (TAH BSO, n=44, age 46 yo)
  - FSH
  - Estradiol
  - Effectiveness and duration of symptom control
- Results
  - Significantly higher estradiol levels and lower FSH levels at month 4 in the E2 50 group
  - Mean duration of symptom control was the same in both groups (5.9-5.6 mos.)
- 25 mg E2 dosage of choice unless bone density is an issue
  - Higher level of E2 until bone loss corrected and then lower the dose

Cravioto 01 Menopause

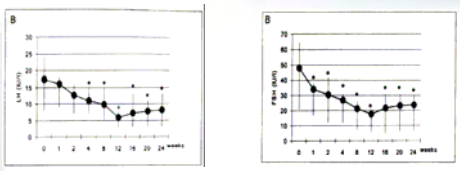
- Pharmacokinetics and dynamics of 25 mg E2 implants
- N=15, TAH with or without BSO, age< 55, FSH >20
- Findings
  - Serum E2 remained fairly constant (early follicular range 24 weeks)
  - Significant symptomatic relief
  - Physiologic ratio of E2:E1
  - No significant metabolic changes occurred
  - Minimal side effects of estrogen, transient breast pain

Cravioto 01 Menopause



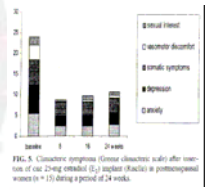
Serum estradiol levels out at about week one and remains consistent over the next 16-20 weeks. Wide variation between subjects.

Cravioto 01 Menopause



FSH and LH begin to rise at about 12 weeks with a 25 mg implant

Cravioto 01 Menopause



- "Subcutaneous implantation of 25 mg of estradiol results in physiological, premenopausal estrogen concentrations in most women and is associated with considerable symptom relief without inducing significant adverse metabolic effects."

Purdie Centre for Met Bone Disease, UK (F133)

- 12 TAH BSO pts. E2 100 on demand for 15-21 years
  - Mean delivered dose 135 mg/y
  - Mean E2 level at time of assessment 1355 pmol/l
  - Bone Density T value (T=No. of SD from young normal mean)
    - Spine +2.03
    - Femoral neck +1.08
    - Hip +3.39

"…that bone gain in implanted women is substantial and progressive and results in BMD values comparable to Peak Density in young adults."

Sands 97 London (OFC)

- The addition of androgen therapy would modify the cardio-vascular protective effects of estrogen
  - Group 1
    - 20 pts. TAH BSO
    - 50 E2 for 4 mos. then 50 E2 & 100 T for 4 mos.
  - Group 2
    - 20 women E 50 &T 100 for 5 years
    - Matched controls (n=20) E 50

Sands 97 London (OFC)

- Group 1
  - E2 levels increased 56 pmol/l to 512 pm/l
  - Month 4 FAI decreased 1.8 to 1.6 then increased to 9.5
  - Chol, LDL, and Apo B levels significantly decreased at each 8 weekly interval
  - No evidence of a differential response to Testosterone (100 mg) SC
- Group 2
  - There were no differences long term (5 years)

"The findings suggest that parental testosterone does not attenuate the favorable changes induces by oestrogen on carbohydrate and lipid metabolism."
(Similar to the results found by Seed 00, Davis 95, 00)

Worboys 00 JCEM

- 33 post men women on stable ERT for >6 months.
  - Testosterone 50 mg. implants.
- Baseline (estrogen alone) and at 6 weeks following implantation (E & T) and compared the hormone treated group to no HRT (control)
- "Exogenous testosterone implants improve both endothelial dependent (flow-mediated) and endothelial independent (glycerol trinitrate) brachial artery vasodilation in postmenopausal women using long term estrogen therapy."
- The control group did not change

Testosterone and Breast Tissue

- Testosterone is the antagonist of estrogen (1930's)
- Testosterone action is anti-proliferative and pro-apototic (increases cancer cell death).
- It is mediated by the Androgen Receptor (AR)
  - AR pos tumors better prognosis, increased survival
- Androgens (testosterone, DHT) inhibit breast cancer in almost every breast cancer cell line
  - Pharmacologic doses (100X) of androgens can stimulate human breast cancer cells (MCF-7) in vitro via the ER

Mazoplasia occasionally occurs and may be lessened by decreasing the estrogen or increasing the androgen dosage. Estrogens may stimulate a small

Greenblatt 77

Testosterone and Breast Tissue

- Testosterone inhibits estrogen-induced mammary epithelial proliferation and suppresses estrogen receptor expression Zhou 00
  - Rhesus monkey, primate breast tissue
    - Estrogen alone increased mammary epithelial proliferation 6x and ER α by 50%
    - No change with progesterone
    - Testosterone decreased estrogen induced proliferation and totally abolished the increase in ER α
    - Tamoxifen increased proliferation 3x but decreased ER α

Testosterone and Breast Tissue cont.

- Endogenous androgens inhibit mammary epithelial hyperplasia. A physiologic dose of T to EP therapy attenuates the estrogen-induced mammary epithelial proliferation (MEP) Dimitrakakis 03
  - Rhesus monkeys
    - Treated with Androgen Receptor (AR) blockade, flutamide
      - 2x increase in MEP
    - Added testosterone to E & P therapy it prevented the estrogen induced MEP
    - Testosterone alone reduced ER α

Testosterone Implants and Breast Cancer

Dimitrakakis 04 Menopause

- 508 Post menopausal women referred for Testosterone supplementation for emotional lability, fatigue, loss of concentration, breast tenderness, loss of libido, sleep disturbances and weakness despite ERT
- FH of BCa 29%
- 508 women T 50-150 mg every 5 month in addition to CHRT (161 E/T, 347 E/T/P), f/u 5.8 years
  - 7/508 (1.4%) diagnosed with breast cancer
    - 1/161 (0.6%) on E/T alone
    - 6/347 (1.7%) E/P/T

Dimitrakakis 04 Menopause

TABLE 2. *Breast cancer cases in women using testosterone compared with major studies*

	N	Age	Cases/100,000 woman-years	Years observed
Schairer et al[15] (E/P)	1,854	57.4 y	628	10.2
WHI[4] (E/P)	8,506	63.2 y	380	5.2
Million Woman[3] (E/P)	142,870	55.9 y	521	2.6
Million Woman[3] never-users	392,757	55.9 y	283	2.6
Adelaide (E/P/T)	347	57 y	293	5.9

Current E/P users are analyzed in comparison with never-users from the Million Woman Study) and E/P/T users from Adelaide, South Australia. Citations refer to the "References" section at the end of the article. WHI, Women's Health Initiative; E/T, estrogen + testosterone; E/P/T, estrogen + progestin + testosterone.

Cases/100,000 woman years

- Adelaide E/P/T 293
- WHI E/P 380
- Million Woman
  - E/P 521
  - Never users 283
- Adelaide total 238
- Adelaide E/T 115

•The addition of testosterone to CHRT does not increase, and may reduce the incidence of BCa

Balanced HRT Submitted for publication Tutera

- 967 women treated for 10 years
  - 1 case of breast cancer at year 2
- HRT with pellets
  - Estradiol and testosterone subcutaneous implants
  - Lower doses of estradiol
  - Progesterone not progestins
  - Measured hormone levels
  - Adjusted doses
- BALANCE
  - Physiologic doses of estrogen
  - Balance with progesterone & testosterone

Gambrell / Natrajan Climacteric 06

- 814 pts.
- Continuation rate 96.7% pellets at 10 years vs. 53.5% other forms of HRT
- 81% prescribed progestogens
- Common dose of estradiol 50-75 mg (>80%)
  - Some accumulation with every 4 month dosing
  - No problem with every 6 month dosing
- Testosterone 75-150 mg

16 patients with breast cancer mean duration of F/U 22 years
10 of 16 continued estrogen therapy. 1 death from BCa.
Stated incidence of BCa was not dose dependent. Typically ran estrogen levels 265 pg/ml for 20-40 years.

Davelaar 91 Netherlands

- 'No increase of the incidence of breast cancer during use of subcutaneous oestradiol.'
  - 261 mostly pre-menopausal women
  - TAH-BSO for fibroids, endometriosis, combination of fibroids/endometriosis, benign ovarian tumors, malignant ovarian tumors and other complaints
    - High risk group for breast cancer
  - 20 mg every 4 months (2-6 mos.)
    - Vs. Million Women's Trial
  - Observed 8.25 years
  - 3 cases of breast cancer
  - 1.4 per 1000 person-years vs. 2 per 1000 person-years expected

Estrogen Replacement Therapy in BCa pts.
Natrajan / Gambrell 02 AJO&G

123 Breast Cancer patients (65.4 y, ER/PR +/-, Up to 3 LN pos.)

- 69 pts. ERT
  - 14 T150, E2 50
  - 14 T150, E2 25
  - 12 T 75, E2 50
  - 6 T 75, E2 25
  - 2 T 225, E2 25
  - 4 T 75, oral E
  - 2 T 75, oral E
  - 2 E2 50
  - 1 E2 75, T 75
  - 5 Estra test
  - 3 oral E
  - 2 E vag cr
  - 1 T 75, TD E2
  - 1 TD E2

  17 tamoxifen or megase
- 22 pts. Non E HRT
  - 11 T 150 (7 megase)
  - 1 T 75 + megase
  - 2 T 75 + tam
  - 6 tam
  - 1 megase
  - 1 tam + raloxifene
- 32 pts. No HRT

Results Natrajan / Gambrell 02 AJO&G

- 18 deaths /123 patients
  - 6 ERT (90% received T) 8.69% up to 32 years
    - 2 breast cancer 4.28 %
  - 2 Non E HRT 9.09%
    - 1 breast cancer 4.5%
  - 10 No HRT 31.25%
    - 6 breast cancer 11.3%
- Conclusion: Estrogen replacement therapy does not increase the risk of recurrence or death in patients with early breast cancer (Stage 1 disease with <3 nodes pos.)

Menstrual Migraine Magos 83 JNNP

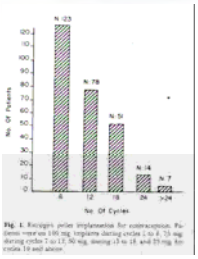
- 24 patients with menstrual migraine for an average of 23.3 years
- Initial dose of 100 mg E2 implant with a maintenance dose of E2 50 mg. every 6.2 months (4-7 mos)
- 23 of 24 patients headaches improved with 20 of 24 becoming completely or almost completely headache free

(Cardoza 84: 90% partial relief and 65% complete relief)

Birth Control Women

- Greenblatt 76 AJOG
  - Step-down estradiol dosing (100 mg to 25 mg q 6 mo)
  - 2 pregnancies out of 1,668 cycles
  - Cyclic progestogen
  - Advantage over OCP
    - Absence of GI sxs.
    - Minimal side effects
      - No HA, nausea
    - No missed pills

"It is believed that by using natural estrogens, the incidence of thromboembolic disease may be greatly reduced."



Skin health

- Hormone loss at menopause has a profound influence on skin
  - Collagen, dermal thickness and elasticity, skin water content, vascularity, photo-protection, wound healing and cutaneous injury repair (Thorton 02)
- Hormones delivered by subcutaneous hormone implant prevent and reverse wrinkles
  - E2 & T implants for 2-10 years; 48% increase in collagen (Brincat 83)
  - Decrease in collagen was preventable with HRT by E2 & T pellets (Brincat 87)
  - Maintenance or improvement of skin collagen with E2 alone or E2 & T implants (Brincat 87)
  - Significantly greater collagen in women treated with SC E2 and T (Saavas 93)

Ganger 89 BMJ

- 12 cases of supra-physiologic plasma levels of estradiol
- Tachyphylaxis; symptoms of estrogen deficiency (flushes, sweats, mood swings, and irritability) in women with E2>1200 pm/l (326 ng/dl)
  - Rare, 3% of cases
- High doses of (E2 50, 75, 100, 200 mg) usually implanted at intervals of every 4 months or less
- If there is any risk of accumulation, check estradiol levels prior to reinsertion

- Pirwany 02 HR
  - Supra-physiologic E2 levels had no adverse affect on lipids and beneficially influenced fasting insulin and waist/hip ratio

Testosterone Pellets MEN

- Have been used since 1940
- Implanted in the subcutaneous tissue of the lower abdominal wall or hip
- 4-6 200 mg pellets provide a physiologic dose of testosterone for 4-6 months
- Extremely effective form of therapy with complete bioavailability
- Release rate of 1.3 mg/d testosterone per 200 mg implant
- 4 pellets release ≈ 5.2-6 mg testosterone per day
- 6 pellets release ≈ 7.8-9 mg per day
- Neither implantation site* nor tract geometry influence release rate

Testosterone Pellets MEN cont.

- No elevation (ratio) of DHT or estradiol
- Suppression of FSH and LH are dose dependent
  - Suppression of gonadotropin levels correlates with clinical effects and the maintenance of physiologic testosterone levels
- Lack of 'swings in testosterone levels' are desirable
- Testosterone implants are able to maintain bmd long term
- A single implantation with 1200 mg of testosterone was more effective in increasing bone density than oral or IM testosterone in men with primary hypogonadism

Testosterone Pellets MEN cont.

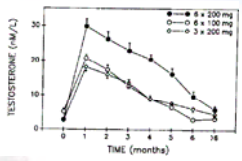
- Extrusion <1%-8%, minor bleeding 0-2%, minor infection 1-5%
  - Complication rate is related to operator skill
- Early physical activity is a predisposing factor for extrusion
- No scarring to interfere with further implants
- Downside
  - Difficulty in reversing Testosterone effects (dx. of prostate Ca)
  - Minor procedure (5 minutes two to three times yearly)
  - Minimal discomfort
- Continuation rate of 93%
- Consistency
- Compliance
- Convenience

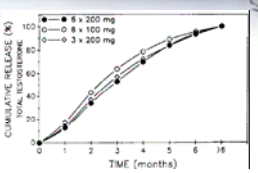
Handelsman 90,92,97, Kelleher 01, 04, Conway 88, Jockenhoval 96, Zacharin 03, Schubert 03

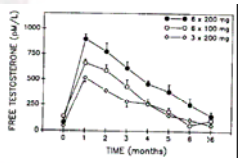
Handelsman 90 JCE&M

- Pharmacokinetics and Pharmacodynamics of Testosterone Pellets in Man
- Prospective, crossover trial
- 6x100, 3x200, and 6x200 mg testosterone pellets inserted at least 6 month intervals in 43 men
  - Testosterone pellets, no fillers
    - Diameter 4.5 mm and length 6mm (100 mg), 12mm (200)
    - Total Surface Area (TSA)117 mm² and 200 mm²
  - Complete bioavailability
  - Time course predictable based on dose and to a lesser extent TSA of pellet

Handelsman 90 JCE&M





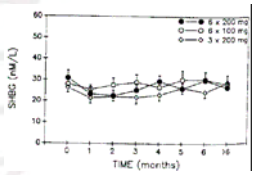


Consistent, near linear release rate

TT and fT peaked at 1month and maintained physiologic doses for about 4 mos (600 mg dose) and 6 mos (1200 mg dose)

No difference between 6 x 100 mg and 3 x 200 mg pellets in TT and the dif in fT was not sign after the 1'st insertion

Handelsman 90 JCE&M

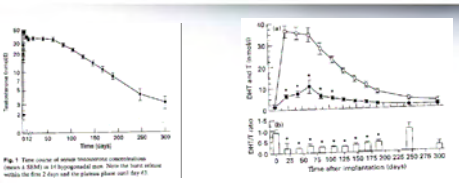


- All three regimens caused no change in SHBG, in contrast to IM testosterone esters and oral testosterone undecanoate which markedly lowers SHBG.
- 'This is consistent with the postulate that decreases in SHBG are a manifestation of toxic androgen effects on the liver rather than a physiologic effect of androgens.'

Jockenhöval 96 CE

- Pharmacokinetics of 6, 200 mg (1200 mg) testosterone implants, lower quadrant of 14 men
- Findings
  - Initial short burst of T followed by stable levels until day 63 then a gradual decline close to baseline day 300
  - Half life was 70 days, therapeutic levels to 180 days
  - Zero order release
  - Initial decline in SHBG
  - Elevation of DHT and E2 which correlated with T
  - Lower ratio of DHT:T
  - 13/14 patients preferred implants to other methods of testosterone delivery

Jockenhöval 96 CE

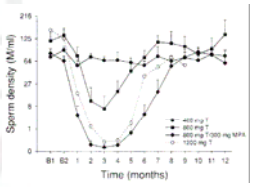


- Time course of Testosterone
  - Peak burst at 2 days
  - Maintains therapeutic levels until about day 180
- DHT and DHT:T ratio

Testosterone Implants and Birth Control in Men

- Suppression of Spermatogenesis by Testosterone Implants Handelsman 92 JCEM
  - Six, 200 mg implants suppress sperm output to near 'azoospermia' between 2-4 mos after insertion returning to normal at 6 mos.
  - Testosterone and Estradiol remained in the eugonadal range (vs. Testosterone cypionate injections, 200 mg IM weekly)
  - Inhibits LH and FSH
- Minimum effective dose and additive effects of depot progestin Handelsman 96 JCEM
  - 300 mg of depot MPA with 4, 200 mg testosterone implants suppressed spermatogenesis equivalent to 1200 mg T

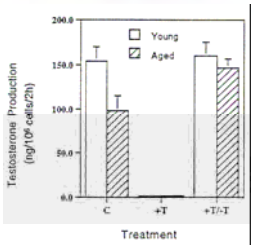
Handelsman 96 JCEM



- Sperm suppression is dose dependent
- 4, 200 mg testosterone pellets, delivering 6 mg per day, were inadequate to suppress spermatogenesis vs. 1200 mg of T or 800 mg & 300 DMPA
- Metabolic Effects *
  - No effect on PSA, cholesterol fractions, glucose, phosphate, LFT's, renal function tests or hematological variables. No evidence of hepatotoxicity.

Interesting Study Long-term suppression of Leydig cell steroidogenesis prevents Leydig cell aging

- Chen 99 Cell Biology
- Male aging; reduced T production in Leydig cells
- Contraceptive doses of T to young (3 mos) middle-aged mice (13 mos)
  - Suppressed endo T
- Removed the implant (13 and 23 mos)
  - Both groups found to produce testosterone at high levels of young mice
- Leydig cells in 'hibernation' the reduction of T that normally occurs with aging did not occur

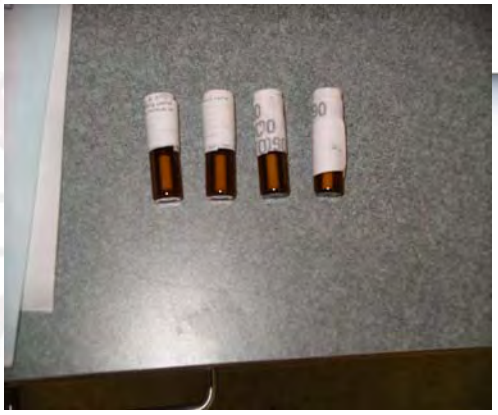


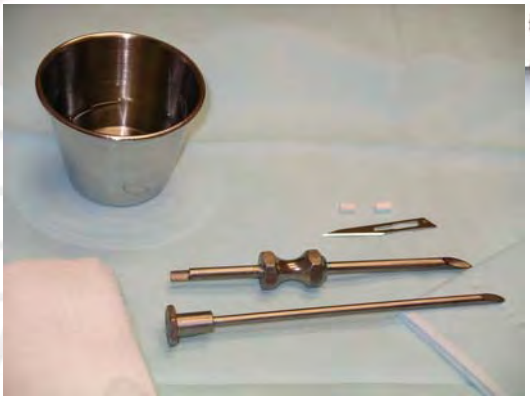
Dunning 04

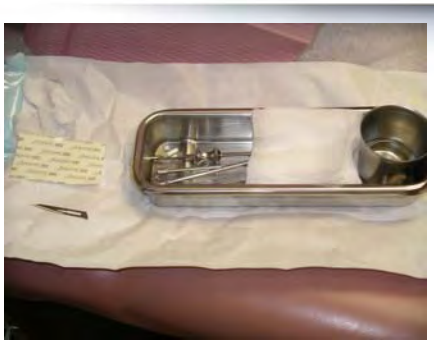
- "Testosterone replacement is safe and almost always successful by all methods, but implants are the most effective in maintaining sexual function and have fewer side effects."

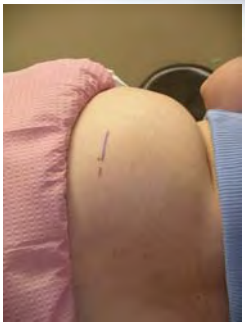
Inadequate evidence?

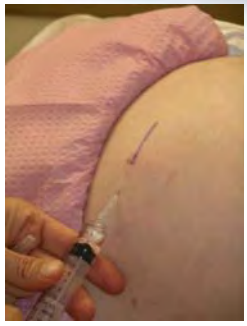
- The following compounded preparations are examples of preparations that **Aetna** considers to be experimental and investigational, because there is inadequate evidence in the peer-reviewed published medical literature of their effectiveness:
  - Implantable estradiol pellets (see Medical CPB 0345: Implantable Hormone Pellets: http://www.aetna.com/cpb/data/CPBA0345.html)\
- Lancet, Maturitas, AJOG, J Rep Med, Acta OGJ, BJOG, O&G, Menopause, Climacteric, FPij, London (OFC), JCEM, FASEP, JNNP, FP, Hormone Research, CE, GOI, IJGO, EJE, JBMR, MR, IJP, J Neuro, JCR, Aging Male etc.



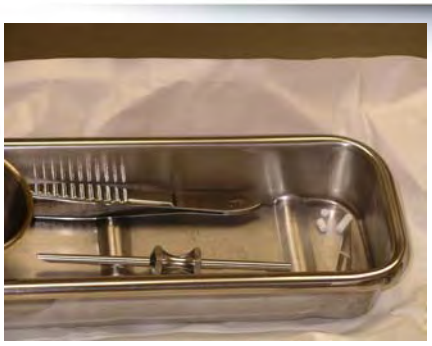


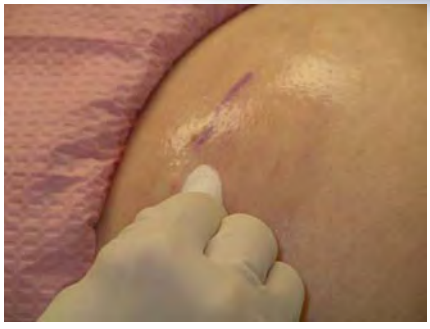


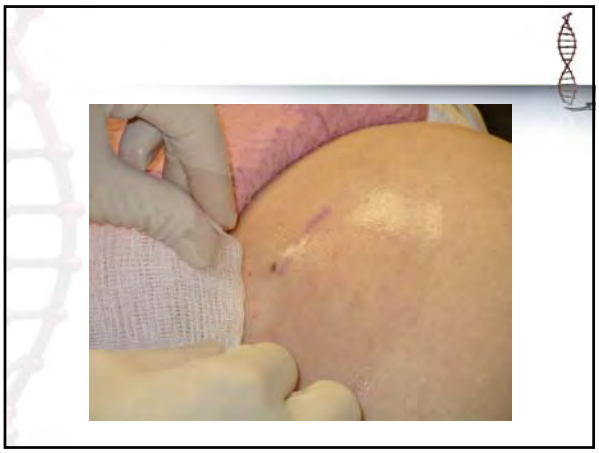


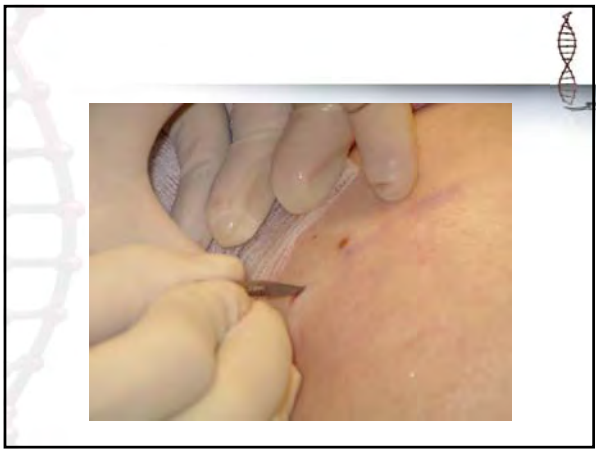


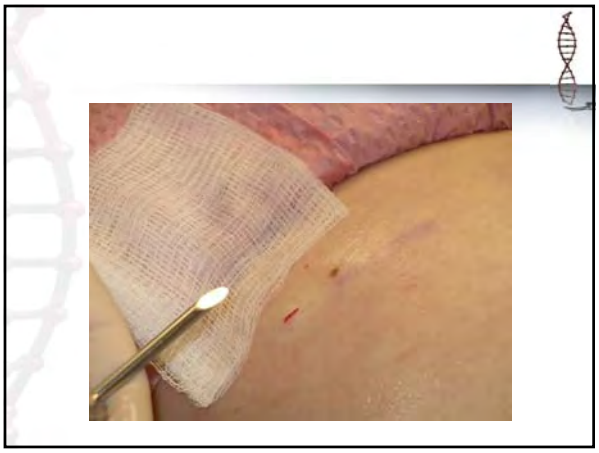
E2 12.5 mg, T 112.5 mg (37.5 mg, 75 mg)

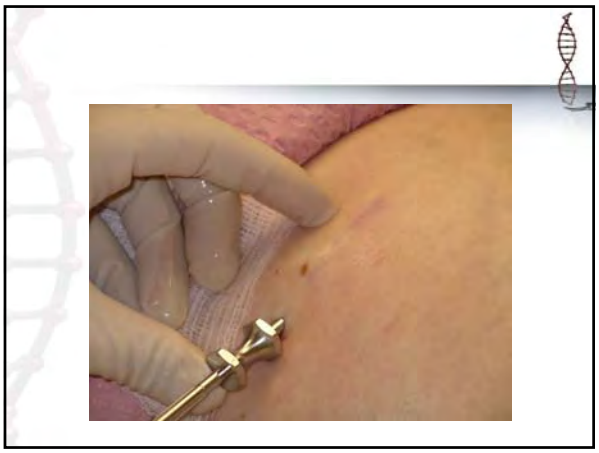


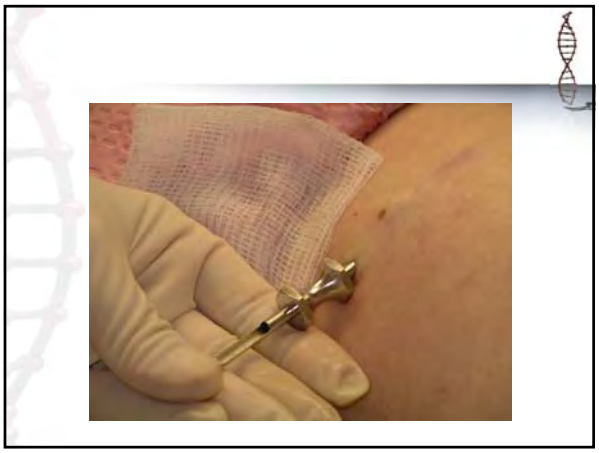


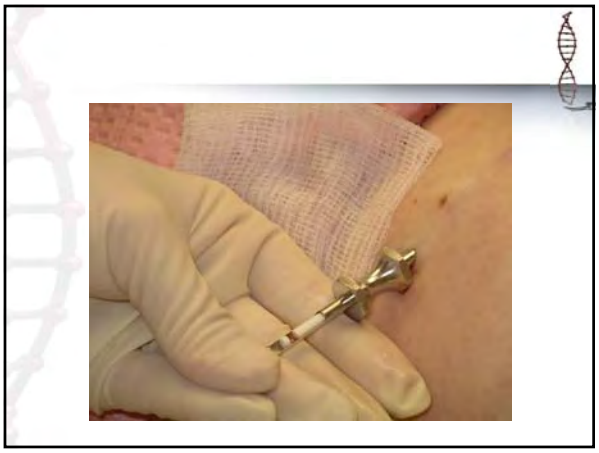


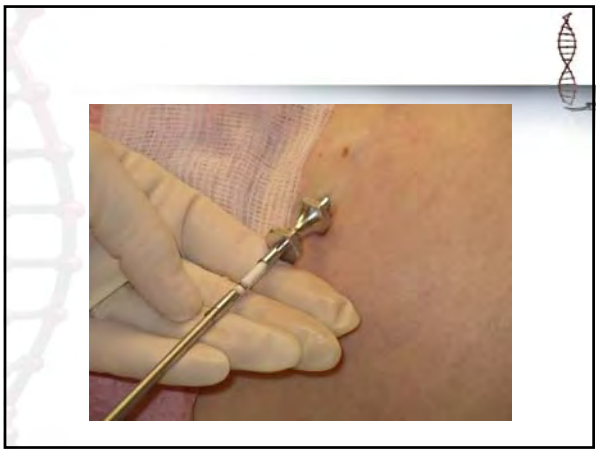


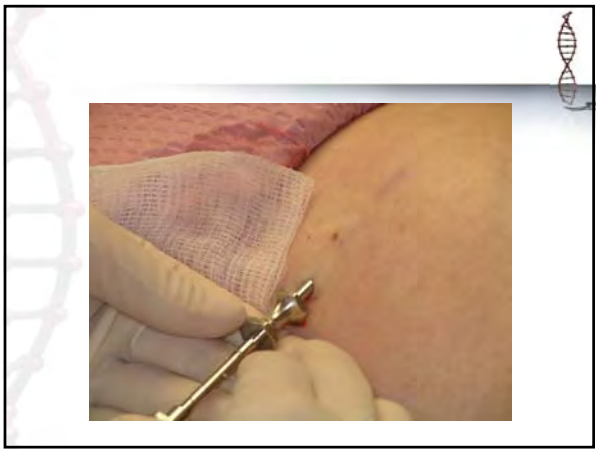


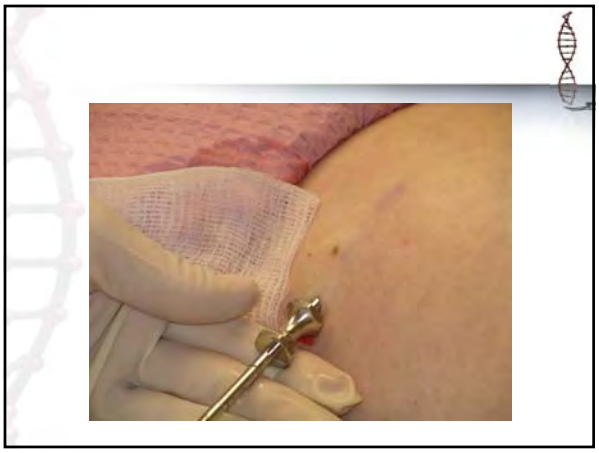


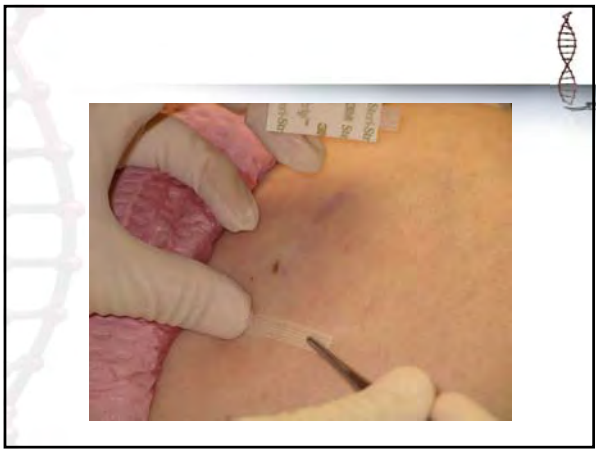


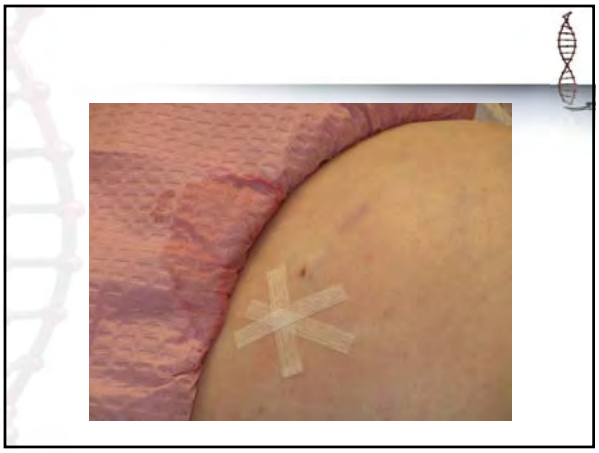


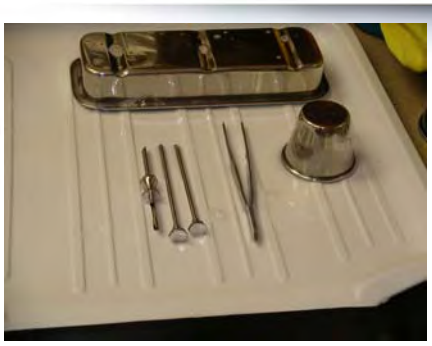












In practice

- Restore testosterone levels to within the normal range for young adult men
- Replace pellets in men at about 4-5 months the first time pellets are placed vs. 5.8 described in the literature
- Variability in levels and how long symptoms are controlled
- Minor redness at the incision is common
- Most commons doses in women: Estradiol 12.5-25 mg, and Testosterone 75-125 mg
- Most common dose of testosterone in men: 800-1200 mg (4-6, 200 mg pellets; 75 or 100 mg pellets)
- Always use progesterone vs. progestins

Treatment Levels

- FSH < 20-30, trend
- *Estradiol (variable)
- Maintain Testosterone upper limits of normal
  - Despite wide ranges in serum levels, patients consistently do well without signs of excess
- Measure levels early if patient not doing well
- Surgical menopause may need higher doses of estradiol
- History of bleeding, fibroids, endometriosis etc., lower dose of E2

- Men, testosterone at the upper limits of normal at month one
- Maintain over 600-700 ng/dl
- Dosing based on BSA, age, chronic disease
- Donate blood for Hb>18, Hct>55 especially with a H/O heart disease
- Do not check PSA in the first 3 months, transient rise

"Tenfold differences in serum estradiol levels are common when using fixed doses, given either as a single dose or by continuous application to the skin" Tuimala 96
Less variance for pellets (4 fold)

Problem: Accuracy of Testing

- KG 41 yo female with sxs of testosterone deficiency
  - 12/5/05 TT 17 (8 to 60 ng/dL) Mayo Clinic
  - 3/31/06 TT 17, free T 0.4 (0.3 to 1.9 ng/dL)
  - 11/28/06 TT 48 (14 to 76 ng/dL) fT 1.25 (0.1-0.85 ng/dL) LabCorp
- JH
  - TT 71 (14-76 ng/dl): TT 22 (2-45 ng/dl), FT 2.0 (0.1- 6.4 pg/ml)
- PB
  - Saliva* T 60 elevated (8-20 pg/ml): Serum TT 6 (2-45), FT 1.0
- ST
  - TT 60 (14-72 ng/dl) : TT 6 ng/dl (2-45), FT 0.6 pg/ml (.1-6.4)
- TK male on therapy
  - TT 656 (250-1100): TT 1124 (241-827)
- CV 65 yo female 5 months post insertion of E2 12.5, T 100
  - FU testosterone by RIA 147 (14-75 ng/dl) still therapeutic
  - FU testosterone by LC/MS 36 (0-45 ng/dl)

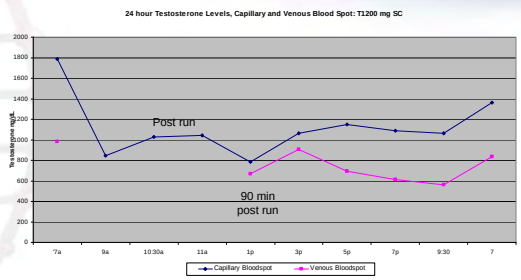
Testing

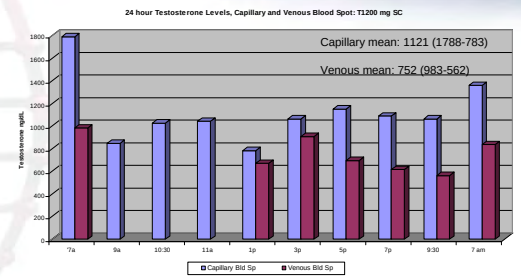
- CK male E2 47 (0-54 pg/ml): E2 16 (10-50 pg/ml), F E2 0.27 L
- DG male E2 51 (0-54 pg/ml): E2 9 L, FE2 0.28 L

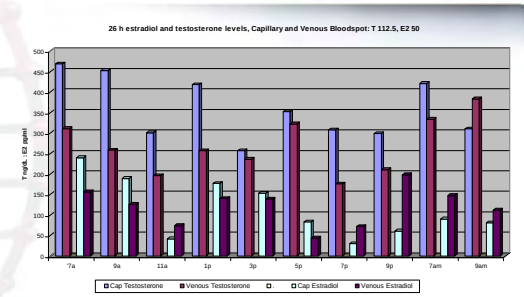
- "None of the immunoassays tested was sufficiently reliable for the investigation of sera from children and women" Taieb 03
- "Guessing would be more accurate and additionally could provide cheaper and faster testosterone results for women." Herold 03
- 'Different methodologies, different results. Every test has a foible. Sex hormones are tricky. Doctors make the diagnosis not labs.'

- Criticism of pellets
  - Do not get the diurnal variation
- Variation throughout the day
- Hormone release does vary with blood flow to the area

48 yo male, 12 weeks post insertion T 1200mg

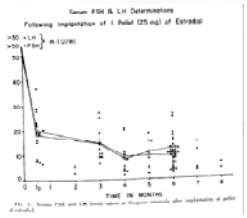


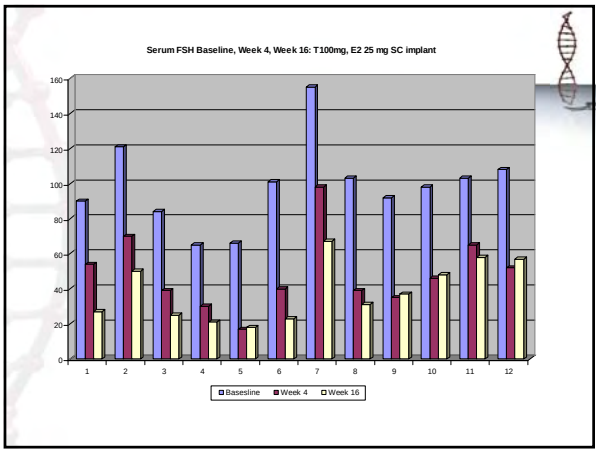


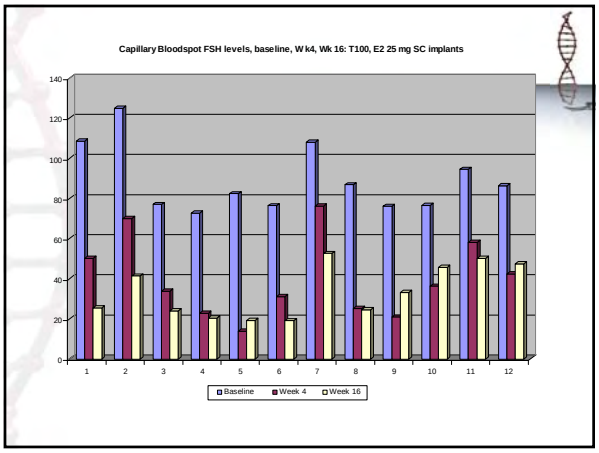


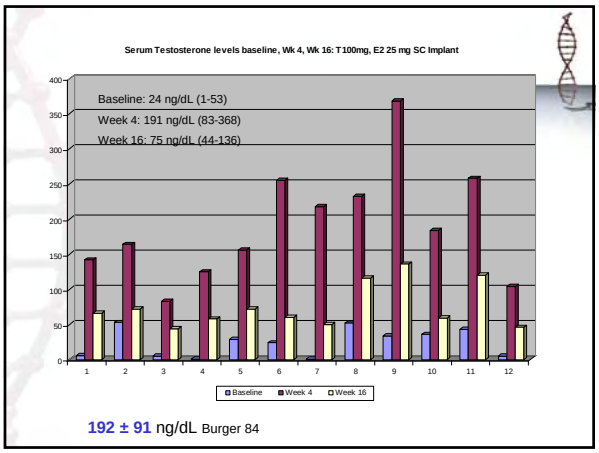
FSH

- Greenblatt 1977
  - Staland, Thom, Cardoza, Burger, Stanczyk
- Superior to fluctuating estradiol levels
  - Guide
  - Trend
  - Patients may become symptomatic before FSH rises
- Measurable by serum or bloodspot
- Use FSH to guide estrogen dosing
  - Lower estrogen dose when T< 60-70 and FSH still suppressed

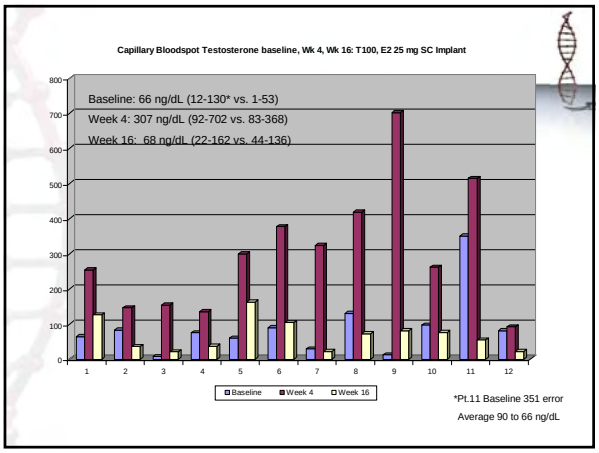




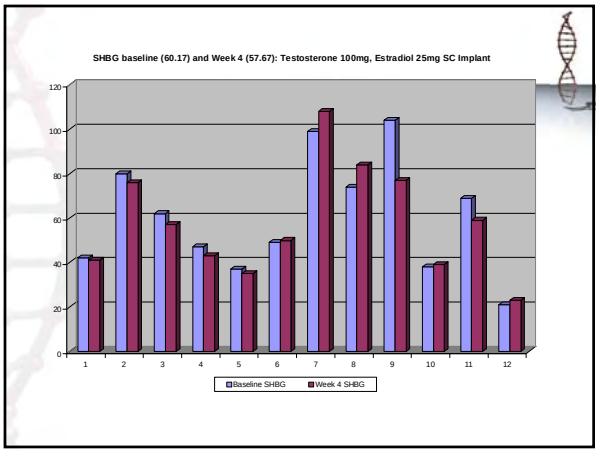




192 ± 91 ng/dL Burger 84



*Pt.11 Baseline 351 error
Average 90 to 66 ng/dL



Number one problem with pellets

- Vaginal Bleeding
  - Spotting
  - Bleeding requiring a tampon or pad
- 30-50% of patients have bleeding the first year of any HRT
- <5% of patients continue to bleed by year 3
- Often a history of bleeding in the past
  - Uterine fibroids, polyps, endometriosis (take a history)
  - *Inadequate use of progesterone*
- If a postmenopausal patient bleeds, she needs a workup
  - Vaginal US
  - Possible endometrial biopsy
- Inform the patient of possibility
  - Ask her opinion
  - Note it on the consent

Options

- OMP 100 to 200 mg qhs
  - May need to dose Prometrium twice daily
- Vaginal progesterone
  - 90 mg daily 6 days per week
    - No problem with daily
- Cycle progesterone or progestin
  - Historically done with estradiol implants
  - Monthly or every 3 months (Europe)
- Mirena IUD (Europe)
- Topical progesterone (skin) may not adequately protect the uterus with adequate estrogen replacement
  - Useful in premenopausal females

Table 6.4. Progestin dosages for endometrial protection

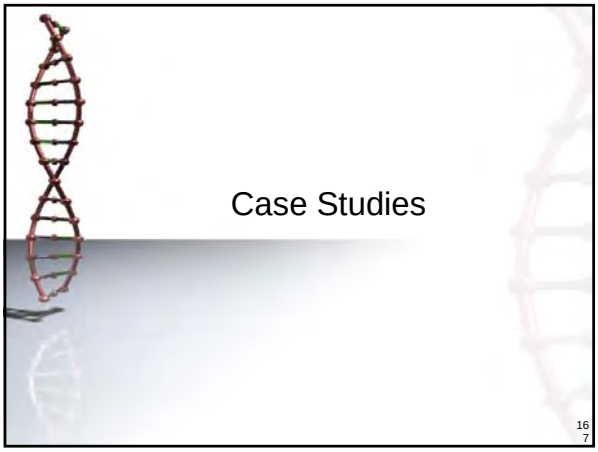
	Cyclic 10–14 d/mth (mg)	Continuous daily (mg)
Oral		
Medroxyprogesterone acetate	5–10*	2.5
Medrogesterone (medrogestone)	5–10*	
Megestrol	20	
Micronized progesterone	200–300*†	100
Norethindrone	0.35–0.7*	0.35
Transdermal		
Norethindrone acetate‡	0.14 or 0.25	0.14
Intrauterine		
Levonorgestrel IUS		52 mg/IUS

*Larger doses of estrogen may necessitate higher doses of progestin while ultralow-dose (0.014 mg/d) may require lower doses of progestin.
†May be administered vaginally.
‡Available in combination with 17-estradiol reservoir patches.

SOGC 06 Practice Guidelines

Complaints

- Weight gain
  - Stress, diet, lifestyle, lack of exercise
  - Pellets do not cause weight gain
    - Loss of fatty tissue
    - Testosterone increases fat free mass (bone density, muscle mass)
    - Lower estradiol dose
- Peri menopausal women
  - Irregular cycles, bleeding, PMS, anxiety
- Symptoms of Estrogen Dominance
  - Non compliance with progesterone
  - Breast pain: Apply progesterone cream to breast 10-14d/m



RA

- 47 yo male presented (6/04) with HTN, elevated glucose (Hb A1c), elevated cholesterol
- Insomnia, low libido, lack of concentration, memory loss, depression, and anxiety
  - "I'm going downhill fast."
- Serum testosterone
  - 11/00 302 (241-827 ng/dl) "Testosterone level is fine"
  - 2/04 292
  - 6/04 211
- Salivary testosterone 48 (50-200) 6/04

RA

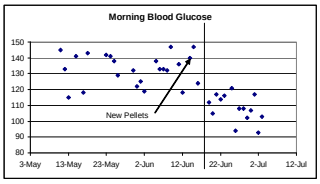
	Dose	Testosterone ng/dl
Testosterone Cream	50 mg/gm 50-100 mg dose	235 (241-827) "did not notice much of a change"
Testosterone NCB	100 mg	305
Testosterone Lozenge	10 mg	1382 "felt somewhat better"
Testosterone HA gel	50 mg/gm 100 mg dose	471
Pellets	1200 mg	705 (241-827) "felt great"

RA

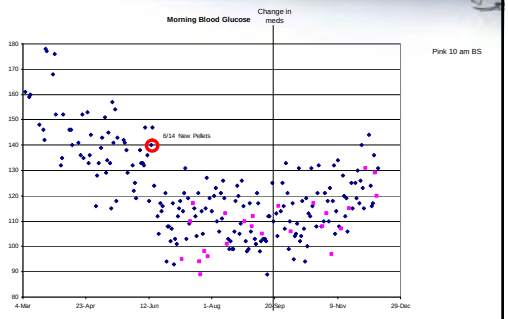
- No longer depressed
- Anxiety improved
- HbA1c came down
- BP came down
- Cholesterol improved
- Toning up
- Increased dose to 1400 mg (7 pellets) next insertion
  - Wanted one month levels slightly higher and the pellets to last longer
- RLQ to hip

Blood Sugar (E.R.)

- 44 yo obese male with AODM and depression
- No energy, lack of motivation, central obesity, elevating cholesterol



ER cont.



Testosterone and Blood Sugar

- Low testosterone is associated with metabolic syndrome and diabetes Laaksonen 03, 04; Muller 05; Robeva 06

Menstrual / Migraine Headache (LN)

- 39 yo female presents with a 5 mo H/O severe daily headaches worse 1 week to 10 days prior to menstrual cycle
  - Associated nausea
  - Cycles irregular, q 21d, lighter
  - Depression
  - Hot flashes, vaginal dryness, low libido, mood swings, aches, pains, weight gain, memory lapse, fatigue, salt cravings, allergies, sinusitis, chemical sensitivities, muscle stiffness, low BP, frequent UTI's

L.N.

- Work up
  - CT, MRI, EMG, Renal Panel, Liver Panel, ANA, Neurology consultations, 2 different neurologists
    - "You're fine."
  - OB-GYN
    - "You're at that age. You just have to accept it."

L.N.

- Saliva
  - Estradiol 1.1 pg/ml (1.0-5.0)
  - Progesterone <15 (100-600 Luteal)
  - Estriol <3.0 L
  - Estrone <1.3 L
  - Testosterone 24 (20-50)
  - DHEAS <2.5 ng/ml L
  - Cortisol am 1.0 L
  - Cortisol pm 0.4L
- Thyroid normal

L.N.

- E3 2, E2 1, P 200, D 25, T 1 mg
  - 0.25 mg daily vaginally (level out hormones)
- BiEst SL drops prn HA (0.5 mg: E2 .25, E3 .25)
  - Better, no change, worse
- Progesterone OMP 100 mg capsule SL prn HA
  - Better, no change, worse
- Cortef 10 mg po BID
- Fluctuating estrogen levels vs. progesterone….both
  - Uzzi Reiss Natural Hormone Balance for Women
- Cortisol

L.N.

- Improvement within 48 hours
- 2 weeks later felt much better, no headache for 3 days in a row
  - Start of headache night before…no relief with progesterone
    - Mild headache, did not feel like getting out of bed to get the estrogen drops
  - Sometimes estrogen helps, sometimes progesterone helps (100 mg BID-TID)

L.N. 2 month FU

- "So much has improved"
  - HA's were 8-9/10 and worse before cycle
  - Now 2-4/10, pressure at occipital area
  - Cycles still light and HA still worse before cycles
  - Still has mood swings, irritable, memory lapse, weight gain and fatigue….not nearly as severe
  - Pellets E2 12.5 T 100 mg SQ
  - Progesterone SL drops 50 mg per 0.2 ml
    - 0.4-0.6 ml qhs last two weeks of menstrual cycle and 0.2-0.4 SL prn HA
- FU call headaches gone patient 'feels great'

LN

- Vaginal Bleeding
  - History of bleeding
  - WU uterine US
    - D&C, endometrial ablation
- Continued with pellets
  - E2 12.5, T 112.5 maintained
  - Vaginal and SL progesterone

LD

- 50 yo female who works full time, presents with insomnia, headaches and migraine headaches
- C/O decreased libido, hot flashes, vaginal dryness, heart palpitations, fatigue, decreased stamina, anxiety, irritability, foggy thinking, memory lapse, aches, pains, allergies, low blood sugar, low blood pressure
- LMP age of 44 following the death of her 18 yo son from Ewing's sarcoma
- Tried every know supplement for sleep

Work up

- Diagnostic x-rays of head and sinuses (headaches and migraine headaches) $170
- Consultation Sleep Disorder Clinic Dr. GB $170
- Apt. Dr. MO family practice, insomnia $99
- Sleep disorder clinic $2052
  - Discharged early because she could not fall asleep and they would be unable to observe her for 6 hour
- Repeat sleep study, took an Ambien to fall asleep ($2052)
- Apt. Dr. GB 'officially diagnosed her with acute insomnia' $72
- Lunesta 30 d supply $118.79 per month
- Apt. Dr. GB changed medication, wasn't working $72
- Ambien CR 30 d supply $114.29 per month
- Imitrex for Headaches $230 for 9 tablets
- Apt. Dr. MO for headache, lack of sleep $99
- CT of head neg $500
- Library to hear me speak … free

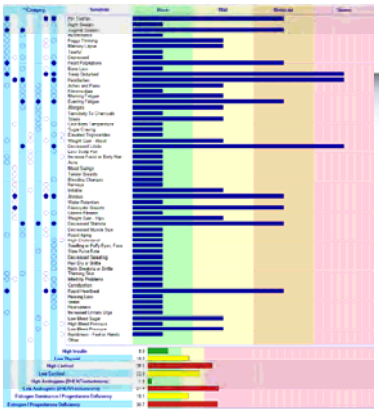
Work up

- No one recommended looking at hormones in a menopausal female with difficulty sleeping (coincided with stress and cessation of menses) and headaches

Saliva Test LD

Menopausal Status: **Postmenopausal** Age: 50

Hormone Test	In Range	Out Of Range		Units	Range
Estradiol (saliva)		<0.5	L	pg/ml	1.0-1.5 Postmenopausal
Progesterone (saliva)		<15	L	pg/ml	25-100 Postmenopausal
Ratio: Pg/E2			Ok		50 - 200 Optimal, 200 - 1000 Proges
Estriol (saliva)		<3.0	L	pg/ml	3-7 Pre- and Post-menopausal
Estrone (saliva)	6.6			pg/ml	2-10 Pre- and Post-menopausal
Testosterone (saliva)		<10	L	pg/ml	20-50
DHEAS (saliva)	3.7			ng/ml	3-10
Cortisol Morning (saliva)	4.1			ng/ml	3-8
Cortisol Night (saliva)	0.7			ng/ml	0.5-1.5



LD

- E2 25, T100 implanted RLQ $230/4 mos
- SL progesterone drops 50 mg per 0.2 ml 60 ml $55/4 mos.
  - 0.4-0.6 ml SL qhs
  - May use 0.2-0.4 ml SL prn anxiety or headaches
- 'Did great'
- Within 2 days after the insertion of pellets she able to sleep, headaches were 'almost' gone, no more migraines, libido was back, increased energy
- Symptoms began to return at about 4½ mos.
  - Testosterone 44 ng/dl (want to maintain >70)
  - Estradiol < 30, FSH 77.2
  - No breast pain, no bleeding
- E2 37.5, T 125…..felt even better! Headaches gone.

LD

- 'After not being able to sleep well night after night and after experiencing rebounding migraine headaches, I felt that I would pay anything and pursue any type of treatment that would give me relief and quality of life. It is unfortunate that my insurance carrier does not recognize the need for or the benefits of hormone therapy. Because I have excellent health insurance, my insurer has paid a considerable amount towards pursuing traditional therapy for menopause and headache symptoms. I feel that it is an unrecognized and underutilized medical therapy that could give countless men and women an improved health lifestyle, and more importantly, quality of life.'

DV

- 39 yo female complaining of anxiety and heart palpitations
  - Vaginal dryness, foggy thinking, memory lapse, depression and HA's (worse before cycles), fatigue, allergies, asthma, tender breasts, mood swings, decreased stamina, sleep disturbance, dx. Chronic Fatigue Syndrome, Myalgic encephalomylitis
- Cardiac W/U included
  - Office visit $120
  - Event monitor $425
  - Echocardiogram $670
  - EKG $40
  - Stress Echo $410
  - Office visit $120
- Considering a TAH to 'make pt feel normal'
  - S/P LSO for endometriosis

DV

- Saliva Testing
  - E2 1.7, P 36 L, T 37, DHEAS 6.0
  - am cortisol 4.8, pm cortisol 0.4 L
- Serum testing
  - TSH 1.421, T4 8.8, free T3 2.5 (2.3-4.2)
- Therapy
  - SL progesterone 50 mg per 0.2 ml, 0.4-0.6 ml day 10 -28 of cycle
  - Cortef 5 mg ½ po TID. May increase to 1 po TID.
- Suspected low Testosterone
  - Ordered T, free T, IGF1, Pregnenolone

DV

- FU serum
  - Testosterone 28 ng/dl (14-76), free T 0.3 (0.0-2.2), IGF-1 247 (109-284), Pregnenolone 51ng/dl (20-150)
- FU sxs.
  - Abdominal pain due to 'Candida infection aggravated during cycle',12-15 d spotting, CFS symptoms worse, Still having heart palpitations and headaches before cycle.
  - Asthma improved, quit dropping blood pressure, no premenstrual depression
- Therapy
  - E2 6 mg, T 100 mg, Rx. Vaginal progesterone (patient is allowed to alternate with Progesterone drops), Pregnenolone 20 mg daily (trial)
    - Heart pounded heavily and legs hurt by the end of the day; "responds to anesthetic"
    - 2 day later doing fine. Felt really good.

DV

- Fu labs at one month
  - Test 219
  - FSH 6.8
  - E2 73
- Patient feels great!

MS

- 53 yo female post TAH BSO who presents with decreased libido (#1, no results with methyl test), hot flashes, vaginal dryness, night sweats, sleep disturbances, memory lapses, anxiety, stress, depression and thinning skin
  - .05 mg Vivelle patch
- At her follow up appointment …3 year history of 'right knee pain'
  - WU included x-rays, MRI
  - Dr. FM diagnosed 'arthritis' recommended PT.
    - Saw a personal trainer 3 times weekly for 3 years. No improvement
  - Dr. BF recommended PT and discussed surgery

MS Saliva Test

Hormone Test	In Range	Out Of Range	Units	Range
Estradiol (saliva)		<0.5 L	pg/ml	1.5-10 (optimal 1.5-3) Estrogen Replacement
Progesterone (saliva)		<15 L	pg/ml	25-100 Postmenopausal
Ratio: P/E2		30 L		50 - 200 Optimal, 200 - 1000 Progesterone Therapy
Estriol (saliva)		<3.0 L	pg/ml	3-7 Pre- and Post-menopausal
Estrone (saliva)		<1.0 L	pg/ml	2-10 Pre- and Post-menopausal
Testosterone (saliva)	20		pg/ml	20-50
DHEAS (saliva)	8.4		ng/ml	3-10
Cortisol Morning (saliva)	7.6		ng/ml	3-8

Current Hormone Therapies:
0.05 mg transdermal (Patch) Vivelle (estradiol) (daily Last used)

MS

- Pellets RLQ: E2 37.7, T 100
  - Felt great.
  - Knee pain totally gone. No problems with stairs.
  - Minor nipple tenderness.
- Follow up levels
  - 1 month: T 192 ng/dl, E2 96 pg/ml, FSH 22.4
  - 4 months: T 8 ng/dl, E2 58 pg/ml, FSH 22
- Had symptoms return at about 3.5 months
  - Libido
  - Metabolized testosterone more rapidly than estradiol
- Reinserted pellets L hip: T 112.5, E2 25
- Next insertion wanted to go back up on E2 (37.5)
  - Will recheck E2 to make sure she doesn't accumulate

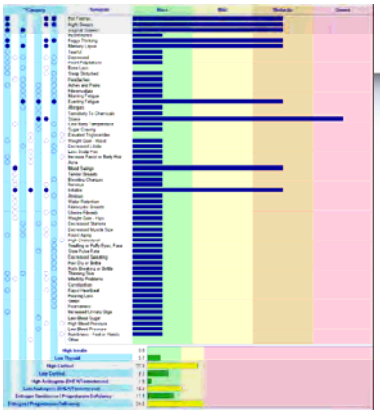
SS

- 56 yo female, referred from a compounding pharmacist, presents with hot flashes, night sweats, vaginal dryness, foggy thinking, memory lapse, fatigue, anxiety, stress, mood swings and irritability
- Benign *essential tremor* of her right hand
- PMH: T1NO IDC L breast 2001 s/p bilat mastectomy with reconstruction

SS Saliva test

Hormone Test	In Range	Out Of Range	Units	Range
Estradiol (saliva)		0.9 L	pg/ml	1.0-1.5 Post-menopausal
Progesterone (saliva)		<15 L	pg/ml	25-100 Postmenopausal
Ratio: Pg/E2		17 L		50 - 200 Optimal, 200 - 1000 Progesterone Therapy
Testosterone (saliva)		18 L	pg/ml	20-50
DHEAS (saliva)	5.0		ng/ml	3-10
Cortisol Morning (saliva)	5.5		ng/ml	3-8
Cortisol Night (saliva)	0.6		ng/ml	0.5-1.5

- Saliva Test
  - Estradiol 0.9 L
  - Progesterone <15 L
  - Testosterone 18 L
  - DHEAS 5.0
  - Am Cortisol 5.5
  - Pm Cortisol 0.6



SS

- Sign a release
- E2 12.5 mg, T 112.5 R hip, SL progesterone drops
- FU labs
  - Month 1: E2 36.1, FSH 7.3, T 253, fT 22.0
  - Month 4: E2 12.7, FSH 7.8, T 105, fT 10.5
- Becoming symptomatic... “not nearly as severe”
  - Memory
  - Noticed her tremor completely disappeared 4 days after the insertion of her first set of pellets.

BK

- 65 yo patient with complaint of insomnia
  - Hot flashes, night sweats, vaginal dryness, headaches
  - Further questioning arthritis and hair loss
    - 'just part of aging'
- Ibuprofen, Evista, Synthroid, Calcium, MVI, Ambien CR
  - Had been on Lunesta for 1 year, worked for about 3 months
- D&C twice, late 80's, fibroids, always had heavy bleeding
  - Does not want a period
- Testosterone 39 (2-45 ng/dL), fT 2.3 (0.1-6.4), Estradiol < 30, FSH 41.6, thyroid WNL

BK

- Can't sleep
- Doesn't want to bleed
- Vaginal cream E3, P, T and small amount of E2
- OMP 100 mg at bedtime
  - One to two orally at bedtime
- No pellets
- May offer a trial of pellets with a low dose of E2. She would understand that she would have a very high chance of bleeding and may need an ablation or even hysterectomy
  - Feelings about her uterus: she 'would love to get rid of it'

RV

- 74 yo female c/o weight gain
- Walks, plays tennis, exercise equipment, bikes, eats whole foods
- B12, Red Yeast Rice (refused statins to lower cholesterol, now nl), Vit E, Lecithin, Calcium, Evista (to prevent bone loss), Premarin tab .625 mg (1 every 2-3 weeks for hot flashes), HCTZ 25 mg prn
- No medical illnesses, TAH BSO, colon polyp
- Testosterone 7 (2-40), fT 0.6 (0.2-3.7), E2 39, FSH 99.5, TSH 1.8, fT4 0.79 L, fT3 2.9
  - Slight fullness neck, no mass
  - She loves sweets and bakes

RV

- Treat the patient…not the lab
- No pellets
- No symptoms
- Diet
- Lugol's iodine
- Trial of Synthroid 50 ug in one month
  - Will pay attention to how she feels
- Add hormones later if she becomes symptomatic

TG

- 57 yo female 6.5 years post lumpectomy and axillary dissection, radiation therapy, chemotherapy for T1c (1.5 cm), N1 (1/29 LN), M0 infiltrating lobular carcinoma of the breast
- C/O fatigue, muscle stiffness, memory problems, foggy thinking, very low libido (unusual for patient), vaginal dryness, heart palpitations, insomnia, allergies, anxiety, decreased stamina
- Meds: Clarinex, Lorazipam
- Labs: T 15 (2-45), fT 1.5 (0.1-6.4), E2<30, FSH 28.1, TSH 1.8, f T3 3.0 (2.3-4.20), f T4 1.06 (0.8-1.8)

TG

- Most of her symptoms were testosterone deficiency
- FSH < 30
- *Does not want to have a cycle*
- Treatment
  - Testosterone 100 mg implant L hip
  - Vaginal Estriol with Progesterone daily for 14 days then every other day
  - Lugol's iodine solution
    - Townsend letter 2005 Gaby, Abraham/Brownstein
  - May test salivary cortisol
  - May add estradiol (vaginal) if needed

Chronic diseases helped with Pellets

- Parkinson's disease
- Essential tremor
- Fibromyalgia
- Polymyalgia Rheumatica
- Memory loss 'Alzheimer's disease'
- Arthritis
- Osteoporosis
- Diabetes
- Insomnia
- Heart palpitations
- Incontinence

The Ultimate Bio-identical Hormone Therapy

- Data supports that estrogen and testosterone therapy by implantation is a safe and effective mode of therapy for both men & women
- Long-continued administration by implantation is convenient and economical for the patient
- Pellet implantation is a simple office procedure
- Pellet implantation has proven more effective than oral and topical hormone therapy
  - libido, bone density, depression, GU sxs., lipid profiles, consistent serum levels, hormone ratios, relief of menopausal symptoms, protection against breast cancer

MD 44 yo

"Thank you for suggesting I get tested for low testosterone. I knew I was feeling low energy and anxiety. I assumed it was due to the stress of my work. I never would have guessed it was due to my hormones being out of balance."

M.D. 44 yo

"After the test results came back, you suggested testosterone implant pellets. Within a very short time I felt much better than I had in a long time. The strange thing about it is that I had forgotten how well I use to feel both physically and emotionally. After the treatment I found I had more energy and drive. Issues of life that felt like heavy burdens became much easier to handle. Choices seemed clearer, and decisions were easier to make, in a nutshell I felt younger and more vital."

Storm

- 10 yo blind, diabetic Siberia Husky
- PMH neutered at 6 mos of age
- Totally incontinent
- Testosterone plo gel
- Testosterone cypionate injections
- Testosterone pellets
  - 200 mg pellet
  - Maintained on 400 mg q 3-4 months
- Totally continent, more energy, back to begging

Think outside the box

The Business Aspects of a Pellet Implant Practice

Presented by

Melanie Parsons

The Business Aspect of a Pellet Implant Practice

Leading the Field in Health and Anti-Aging

History of BHRT

- Hormone therapy received bad publicity from studies such as WHI
- Patients and doctors do not know the difference between conventional and bio-identical hormone therapies

BHRT

- Most conventional physicians do not know or understand the difference and are quick to judge and criticize, often changing the patient mind
- Be prepared to defend yourself and what you are doing
- Arm yourself with data and research to support BHRT

BHRT

- More patients today are prepared to follow their own intuition and make informed decisions rather than rely on their doctor
- Make sure patients are educated before coming to see you
- Number of patients that are dissuaded by their doctor when they tell them they are doing BHRT
- Find a new physician!
- Your body, your decision

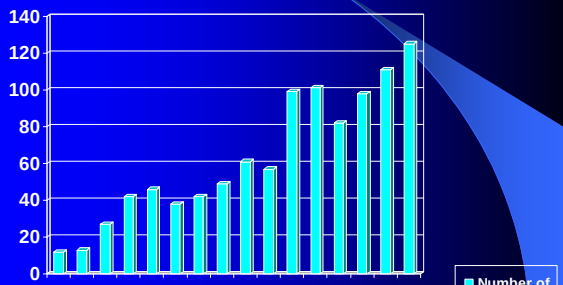
Advertising

- “Word of mouth”
- Community talks. Go to local health food stores, library, church groups, support groups
- Use a presentation
- Usually see 30-40% of people that attend as patients. They then bring in family and friends

Retention Rate

- Pellet therapy has a retention rate of 90%.
- Reasons for not continuing: cost, not covered by insurance, other doctors comments, works too well
- Growth of business is exponential

Pellet Patients over 17 Months



Why A Pellet Practice?

- Best way to deliver hormones
- No insurance billing
- Choose your hours
- Happy patients and staff
- Low start up cost (trochars $200, autoclave $3600)
- Great money
- Potential patients demographic is growing

Why A Pellet Practice?

- Depending on your area you can charge $250-$400 for female patients and $350-$800 for males
- Need 600-700 patients to make over $300,000
- Low continuing cost
- Aging population

Earnings

Per Week	10pts/20hrs	40pts/20hrs	60pts/40hrs
Revenue Weekly	**$**2,600	$10,400	$15,600
Nurse p/hr $25-$50	500	1,000	2,000
Receptionist p/hr $15	300	300	600
Rent	500	500	500
Office supplies	100	200	300
Insurance	150	150	150
Pellet supplies $30	300	1,200	1,800
Total Expenses	1,850	3,350	5,350
Operating Profit	**$750**	**$ 7,050**	**$10,250**
Per week			
Operating Profit	**$36,200**	**$351,200**	**$511,200**
Per annum (50 week)			

Insurance

- More people becoming frustrated with insurance high deductibles
- More people prepared to pay out of pocket
- More insurance companies are paying for the procedure. Aetna has paid 80%
- With research proving that this therapy is more than experimental, more companies are paying
- Insurance companies would save money in the long run by paying for preventative therapies
- Send a letter to insurance company

Fee for Service

- If you already have a business that is registered with insurance, it is difficult to then charge a fee for service
- May need to set up a new business in separate location
- Be aware of any contracts you have with physicians groups

Osteoporosis

- 10 million people have osteoporosis
- 30 million at risk
- 68%-80% women
- **Boniva**-swallowing, heartburn, and ulcers. Common side effects-diarrhea, pain in extremities and dyspepsia (upset stomach)
- Cost $260 a month
- **Evista**- difficulty breathing, leg pain or swelling, skin rash, itching

Osteoporosis

- **Evista**-common side effects- difficulty sleeping, fluid build-up, hot flashes, leg cramps, muscle aches, sinus pressure or drainage, stomach or intestinal gas, stomach pain, sweating, weight gain cost $100 month
- **Forteo**-bone pain, confusion, constipation, dizziness or feeling lightheaded, fatigue, headache, heartburn, leg cramps, nausea, vomiting, pain, redness, irritation or swelling at the injection site
- Cost >$100 a month

Osteoporosis

- **Fosamax** - More common: stomach pain, heartburn, pain or difficulty swallowing
  Rare or uncommon: allergic reactions such as skin rash or itching, hives, swelling of the face, lips, throat or tongue, black or tarry stools, constant jaw pain, especially burning or cramping, eye inflammation, pain or change in vision, muscle twitching, redness, blistering, peeling or loosening of the skin, including inside the mouth, vomiting.

Osteoporosis

- **Fosamax** - Side effects that usually do not require medical attention- diarrhea or constipation, headache, stomach gas or fullness, nausea, changes in taste, bone, muscle or joint pain, rash, which may be made worse by prolonged exposure to sunlight
- Cost $95 month daily or weekly

FDA Debate

- There are pellets that are FDA approved
- FDA approval needed when marketing to the public or for an implant able medical device
- Does not guarantee safeness or effectiveness

Where to Start

- Training
- Business set up
- Mentoring
- Continuing education
- Research database

Training

- One on one
- At least 16 hours of practical
- 8 hours of theory and office set up and running
- Training for staff member is a bonus

Business Set Up

- Manual for training office staff and nursing staff
- All consent forms, letters to insurance companies, waivers
- Prescriptions and blood orders
- How to run the office
- Ready to start the day after training

Mentoring

- As this therapy is not taught in any school or documented in any text book, it is important to have a mentor that can guide you through dosing strategies
- You will have questions from patients that you will not be able to answer
- Having access to someone like Dr. Glaser will ensure you are up to date on the latest research and developments without losing focus on your pellet business

Research Database

- Dr Glaser is a recognized expert in this field and a leading researcher in BHRT (which you can become involved in)
- You will need access to a database of thousands of studies relating to BHRT. This may take years to put together
- Use of power point presentations to educate patients and other physicians

Questions

- Melanie Parsons
- 937 478 0469

Estrogen Metabolism and the Adult Male:
The New Frontier of Testosterone Replacement Therapy

Presented by

John Crisler, DO

Estrogen Metabolism and the Adult Male Patient

--The New Frontier of TRT Medicine--

John Crisler, DO
Lansing, MI USA

Benefits of Estrogens

- Brain function
- Lipid Profile
- Endothelial function
- Bone deposition
- Libido
- Fertility
- Growth and differentiation of target tissues

Detriments of Elevated Estrogen

- Suppresses HPTA
- Elevates SHBG
- Impotence
- Infertility
- Psychological morbidities
- Vasospasm
- Increases clotting factors
- Water retention
- Prostate morbidity
- Cancers
- Female fat distribution
- Fx on thyroid function

ESTROGEN ELEVATORS

- Age
- Obesity
- ETOH over-consumption (incl HOPS in beer!)
- Liver Dz
- Zinc deficiency (50mg Zn/2mg Cu QD)
- Vitamin C deficiency
- Excessive DHEA supplementation (100mg QD)
- Androstenedione supplementation
- Xenoestrogens (incl Vinyl IV bags!)
  --Lavender, Tea Tree Oil
- Liver Detoxification issues

INCREASING FREE ESTROGENS

Anything that lowers SHBG:

1. DMII → ↑ insulin → ↓ SHBG ⊢→ ↑ Free E
2. Exogenous androgens
   --TRT
   --DHEA
3. GHRT

The MAJOR PLAYERS:

- Estrone (E1)
  "the good, the bad, the ugly"
- Estradiol (E2)
  --most important active E physiologically
- Estriol (E3)
  --protective?

ESTROGEN TESTING

- Do not Tx until post F/U labs
  --E2 may actually DROP with TRT
  --insight into body's response
- Maintain E2 at mid-range
  --with mid-range SHBG

IMPORTANT ABOUT ESTROGEN ASSAYS

- Total Estrogens is not a valid assay for adult males
- Estradiol MUST be by "ultrasensitive" or "Extraction Method" assay
- Gold standard is 24 hour urine, esp w/ TD's, due to production delay
- Be extra mindful of SHBG level
- NO SALIVA TESTING

WHAT DO WE DO WHEN WE FIND ELEVATED ESTROGENS?

Elevated Estrogens

- Via laboratory analysis
  --Aromatase Inhibition (AI)
- Via patient complaint (i.e. gyno Sc), w/ good E level
  --SHBG
  --Estrogen antagonism as Tx
  --Estrogen metabolites as Dx
- Good laboratory value, no c/o, but patient desires “cutting edge” Anti-Aging Medicine
  --Estrogen metabolites

ANASTROZOLE

- Aromatase (“Estrogen synthase”) Inhibitor (AI)
- Competitive Inhibitor
- Probably less brain function issues
- #1 use of this med in world: Male TRT
- Other AI’s available
- Concerns with Endocrine pathway disruption (as with finasteride)
- 0.25mg QOD, 0.5mgQ3D initial dose
- 5 day t1/2
- “Frontload” (double initial dose)
- Titrate from there
- SHBG will likely drop (be mindful of consequences)
- DO NOT DRIVE ESTROGEN TOO LOW!

CHRYSIN

- Flavonoid
- Isolated from Passion Flower
- AI activity
- Weak E antagonism
- Antioxidant
- Anxiolytic?
- Variable response (no standardization)
- Oral, TD

SERM's

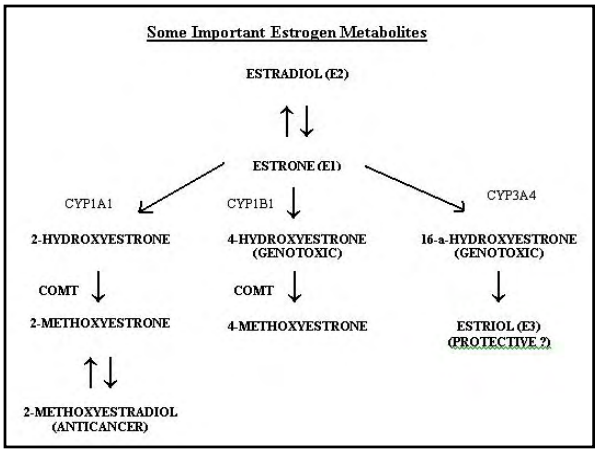
- DO NOT LOWER ESTROGENS—MAY ELEVATE E's and even SHBG…
- Can not assay E's until washout
- Antagonize, agonize E at various target tissues
- Clomid is SERM, elevates SHBG
- Tamoxifen is pure E antagonist
- Great for Tx of gynocomastia

Oxidative Stress Plays an Important Role in the Pathogenesis of Drug-Induced Retinopathy

Data are reviewed that suggest that indomethacin,TAMOXIFEN, thioridazine, and chloroquine all produce retinopathies via a common mechanism—they produce ocular oxidative stress.

Tolar, Steven. *Experimental Biology and Medicine* 229:607-615 (2004)

ESTROGEN METABOLITES



ESTROGEN METABOLITES

- 2-hydroxyestrone (2-OHE)
  --"the good"
  --Phase I hydroxylated product
  --weak estrogenic properties
  --very beneficial
  --catechol (may produce quinones)
- 2-methoxyestradiol
  --Phase II methylated product of 2-OHE
  --weak estrogenic properties
  --anti cancer properties
  --role in Hashimoto's?

ESTROGEN METABOLITES

- 16-α-hydroxyestrone (16-OHE)
  --"the bad"
  --powerful cell proliferation
  --DNA damage
  --responsible for bone mineral deposition

ESTROGEN METABOLITES

- 4-hydroxyestrone
  --the "ugly"
  --very powerful estrogen
  --powerful free radical generator
  --increased by severe exercise (esp. w/ COMT deficiency
  --catecholamine methyl transferase deficiency (COMT) elevates

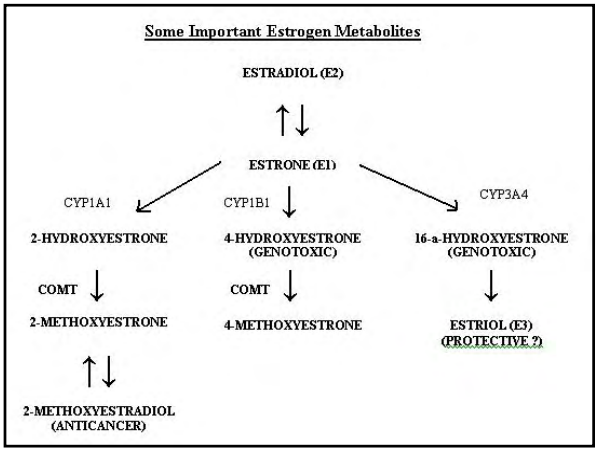
2-Methoxyestradiol, an endogenous estrogen metabolite, induces thyroid cell apoptosis.

Wang, et al. Molecular and Cellular Endocrinology 165 (2000) 163–172

2-OHE/16-aOHE<2.0
=increased risk of cancers

ESTROGEN METABOLISM

- Phase I
  --hydroxylation
- Phase II
  --methylation
  --glucuronidation
  --sulfation
- Excretion
  --urine, feces



Phase I E optimization is accomplished by manipulating hydroxylation in favor of 2-OHE, to detriment of 16-OHE production. Reducing 4-OHE is accomplished via Phase II manipulation.

DECREASE 2-OHE/16-OHE

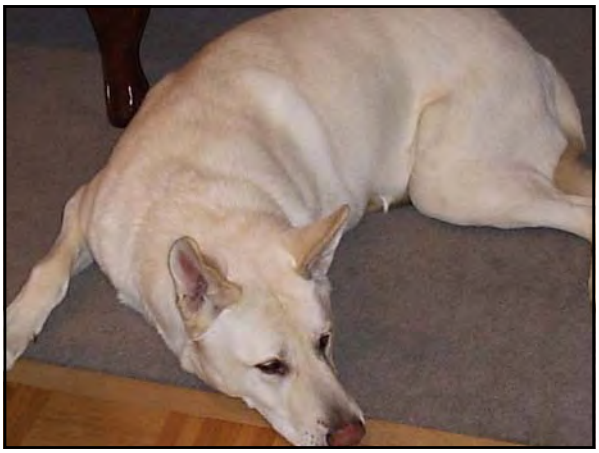
- Obesity
- Genetic predisposition
- Pesticides
- Carcinogens
- Cimetidine (also androgen blocker)
- Cyclosporine
- Xenoestrogens act as 16-OHE

INCREASE 2-OHE/16-OHE

- Cruciferous vegetables (cabbage, broccoli, brussel sprouts)
- Soy and Flax (but add to Total E burden)
- I-3-C
- DIM
- Lose weight
- Healthy diet
- Long-chain Omega-3's (Fish Oil)
- High protein/low fat diet
- Reduce AA and Omega-6's

Catechols (2-OHE, 4-OHE)

- Readily oxidized to quinones
- Quinones
  --highly reactive
  --damage DNA
  --generate Reactive Oxygen Species (ROS)
- Combat by promoting Phase II methylation
  --COMT
  --s-adenosylmethionine (SAM)
  --magnesium
  --methyl group donor (TMG, DMG)
  --anti-oxidants



I-3-C vs. DIM

PROBLEMS

- Paucity of scientific studies
- Shortcomings of *in vitro* studies
- Studies conducted on different species
- Misinformation for proprietary purposes

I-3-C

- Stomach acid produces metabolites of interest
  --absorbs intact to many target tissues
  --provides other metabolites of interest as well
- Highest levels to liver (host to detox pathways)
- Then DIM peaks in 2 hours, detectable for 6 hours (necessitates split dosing)
- Effects from I-3-C directly, DIM conversion at stomach, local DIM conversion, or all?
- Strong anti-proliferative fx on Prostate CA lines, lowers PSA
- May provide E antagonism?

DIM

- 3,3'-diindolylmethane
- Just one single byproduct of I-3-C
- Claims of ↑ stability over I-3-C not supported
- Claims "safer" than I-3-C not supported
- Available in more "bioactive" forms
  --price point to be determined

TAKING BOTH

- BOTH upregulate PI and PII detox
- BOTH induce apoptosis
- 700 genes affected!
- May be synergistic
- Some conversion in target tissues?
- BOTH have been shown to ↑ CYP1B1
  --jury not in
- BOTH shown to possess health benefits NOT related to anti-CA properties

REMEMBER:

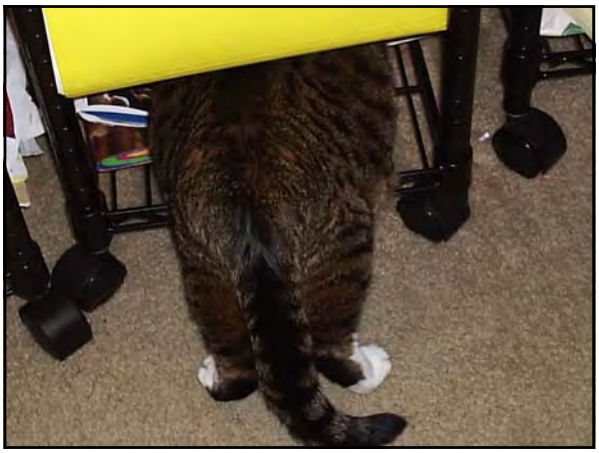
- Food is #1
- Fresh is best!
- Also provides other bioactive substances
- Vitamins, minerals, fiber
- Be mindful in hypothyroid patients:
  --Cruciferous ”goitrogins” block Iodine uptake

“By far the preponderance of evidence shows these compounds to function as agents which prevent cancer growth by numerous mechanisms in multiple cell types.”

Cruciferous Indole Deriviatives as Dietary Supplements. Point Institute of Nutraceutical Research. April 2006.

TAKE BOTH!

- I-3-C 300-400mg QD
- DIM 75-300mg QD
- TMG 500-2000mg QD
- Split doses for all



PHASE II DETOXIFICATION

SUPPORT METHYLATION

- Trimethylglycine (TMG)
  500-1500mg QD, divided dose
- Dimethylglycine (DMG) (distant second)
- Folate

GLUCURONIDATION

- Key Phase II liver detoxification of E's
- Glucuronic acid congugated with E to facilitate elimination
- Intestinal flora (mostly pathogenic) make β-glucuronidase, but found in all cells
- β-glucuronidase uncouples glucuronic acid/E matrix, so…
- …E re-enters body via enterohepatic circulation
- Incr β-glucuronidase ↑ CA risk, esp Breast CA
- High fat/low fiber ↑ β-glucuronidase activity
- Combat with Calcium D-glucarate

CALCIUM D-GLUCURATE

- Natural compound found in foods
- Inhibits β-glucuronidase
- Lowers E in animal models
- 1500-3000mg QD in divided doses

Some studies have shown that elevating 2-OHE/16-OHE may also elevate 4-OHE, so always add methyl donor to supplementation while manipulating 2-OHE/16-OHE.

COFACTORS

- Zinc (with copper)
- Magnesium
- B6, B12
- Folate
- 5-formyltetrahydrofolate

ESTROGEN MANAGEMENT:

The New Frontier of TRT

Nutritional Considerations for Optimizing BHRT

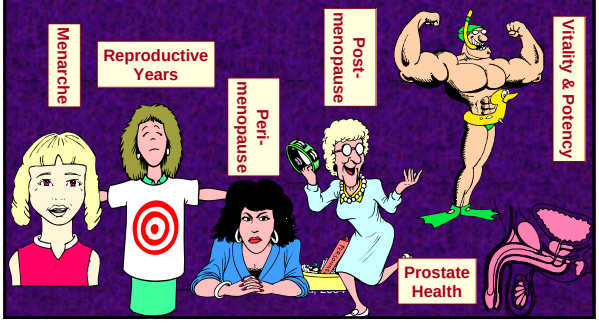
Helping the Patient with Osteoporosis

Presented by

Tiffani Schilling, PharmD

A Nutritional Approach to Hormone Balance

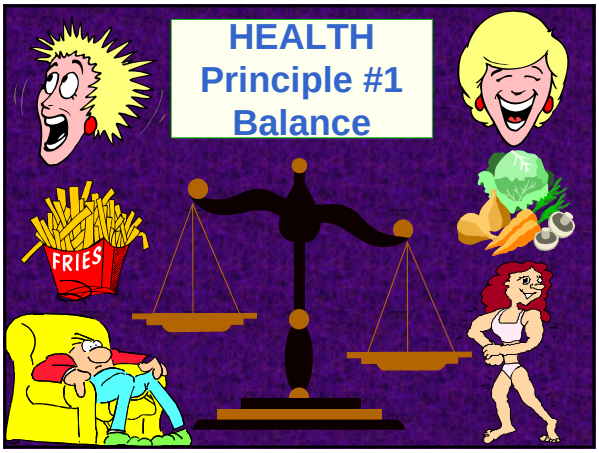
Tiffani Schilling, Pharm.D/Herbalist
Diabetic Specialist



The Overall Plan -- Balance

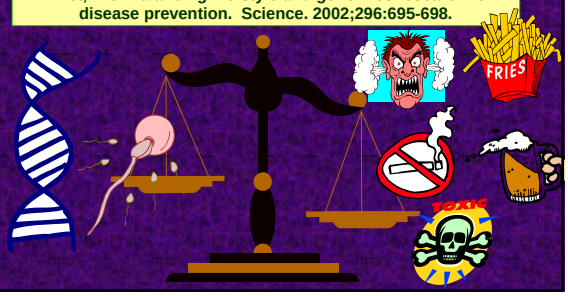
- Improve diet, environment, and lifestyle
- Correct hormone deficiencies
- Balance the hormone therapies with one another

- Fully involve the patient in the treatment and adapt the treatment to the patient's compliance and motivation to be treated.



"For most diseases contributing importantly to mortality in Western populations, epidemiologists have long known that nongenetic factors have high attributable risks, often at least 80 or 90%, even when the specific etiologic factors are not clear."

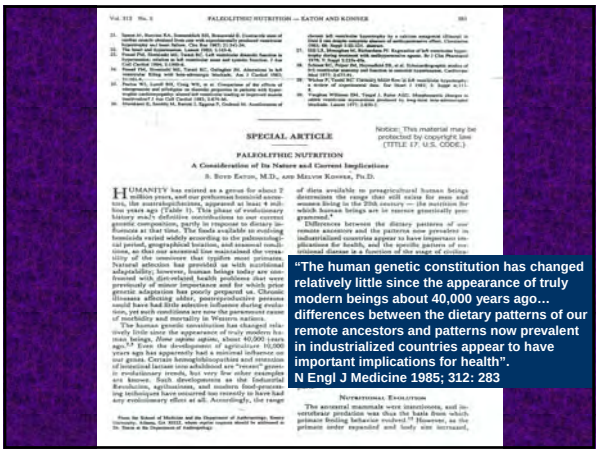
Willet, WC. Balancing life-style and genomics research for disease prevention. Science. 2002;296:695-698.



The Diet Controversy

What Diet is Best for Optimizing Healthy Hormone and Insulin Signaling?

Should we all be Paleoliths?



SPECIAL ARTICLE

PALEOLITHIC NUTRITION

A Consideration of Its Nature and Current Implications

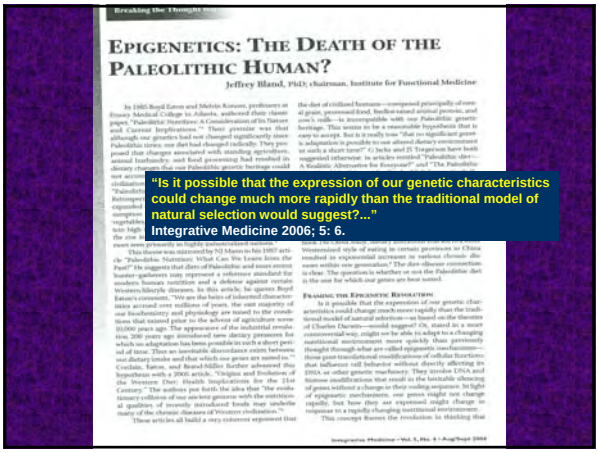
S. Boyd Eaton, M.D., and Melvin Konner, Ph.D.

HUMANITY has existed as a genus for about 2 million years, and our prehuman hominid ancestors, the australopithecines, appeared at least 4 million years ago. Only in the last 10,000 years of history study definitive contributions to our current genetic composition, partly in response to dietary influences at that time. The finds available to studying hominids varied widely according to the paleontological period, geographical location, and ecological conditions, so that our ancestral line maintained the versatility of the omnivore that typifies most primates. Natural selection has provided us with nutritional adaptability; however, human beings today are confronted with diet-related health problems that were previously of minor importance and for which prior genetic adaptation has poorly prepared us. Chronic illnesses affecting adult, postreproductive persons could have had little selective influence during evolution, yet such conditions are now the paramount cause of morbidity and mortality in Western nations.

The human genetic constitution has changed relatively little since the appearance of truly modern human beings, *Homo sapiens sapiens*, about 40,000 years ago.[1,2] Even the development of agriculture 10,000 years ago has apparently had a minimal influence on our genes. Certain hemoglobinopathies and retention of lactase into adulthood are "recent" genetic evolutionary trends, but very few other examples are known. Such developments as the Industrial Revolution, agribusiness, and modern food-processing techniques have occurred too recently to have had any evolutionary effect at all. Accordingly, the range of diets available to preagricultural human beings determines the range that still exists for men and women living in the 20th century — the nutrition for which our human beings are to success genetically programmed.[3]

Differences between the dietary patterns of our remote ancestors and the patterns now prevalent in industrialized countries appear to have important implications for health, and the specific patterns of nutritional disease is a function of the stage of civiliza-

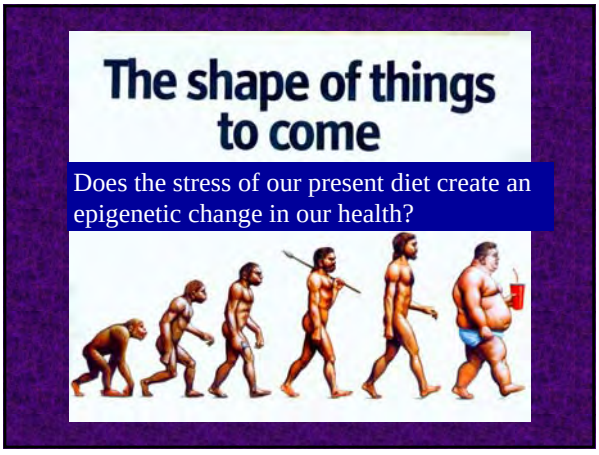
"The human genetic constitution has changed relatively little since the appearance of truly modern beings about 40,000 years ago… differences between the dietary patterns of our remote ancestors and patterns now prevalent in industrialized countries appear to have important implications for health".
N Engl J Medicine 1985; 312: 283



EPIGENETICS: THE DEATH OF THE PALEOLITHIC HUMAN?

Jeffrey Bland, PhD; chairman, Institute for Functional Medicine

"Is it possible that the expression of our genetic characteristics could change much more rapidly than the traditional model of natural selection would suggest?..."
Integrative Medicine 2006; 5: 6.



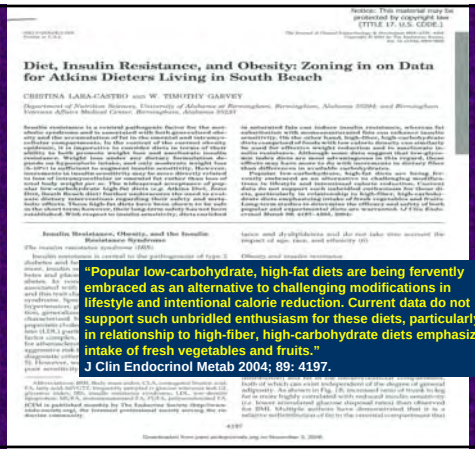
The shape of things to come

Does the stress of our present diet create an epigenetic change in our health?

What is “Epigenetics”?

- Metabolic events that change cellular function after the genes have been transcribed
  - Glycation, Oxidation, Nitration, Sulfation, Phosphorylation, Methylation, Acetylation
- Is the Paleolithic Diet best for our modern society?

So what about Low Carbohydrate Atkins, Zone, Ornish or Weight Watchers Diet Influences?”



Diet, Insulin Resistance, and Obesity: Zoning in on Data for Atkins Dieters Living in South Beach

CHRISTINA LARA-CASTRO and W. TIMOTHY GARVEY

“Popular low-carbohydrate, high-fat diets are being fervently embraced as an alternative to challenging modifications in lifestyle and intentional calorie reduction. Current data do not support such unbridled enthusiasm for these diets, particularly in relationship to high-fiber, high-carbohydrate diets emphasizing intake of fresh vegetables and fruits.”
J Clin Endocrinol Metab 2004; 89: 4197.

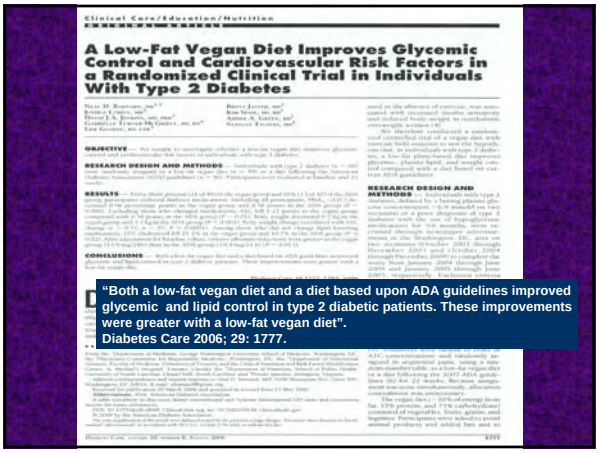
ARTICLE

K. A. McAuley · C. M. Hopkins · K. J. Smith · R. T. McLay · S. M. Williams · R. W. Taylor · J. I. Mann

Comparison of high-fat and high-protein diets with a high-carbohydrate diet in insulin-resistant obese women

"In clinical practice a reduced carbohydrate, increased protein diet may be the most appropriate overall approach to reducing the risk of cardiovascular disease and Type 2 diabetes. To achieve the same benefit on a high carbohydrate diet it may be required to increase the intake of fiber-rich whole grains, legumes, vegetables and fruits."
Diabetologia 2005; 48: 8-16.

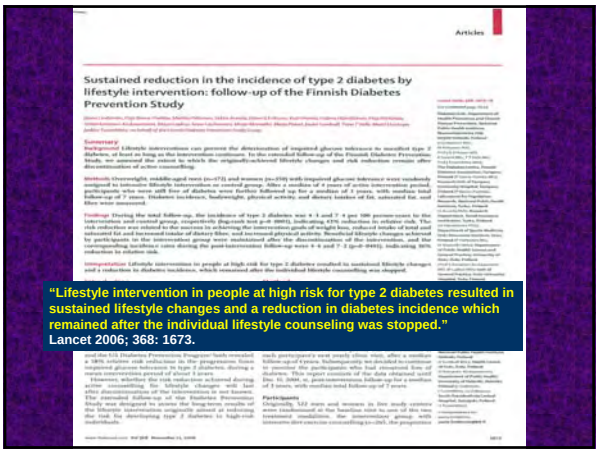
How About Focusing Vegan Diets that lower Glycemic Load?



Clinical Care/Education/Nutrition

A Low-Fat Vegan Diet Improves Glycemic Control and Cardiovascular Risk Factors in a Randomized Clinical Trial in Individuals With Type 2 Diabetes

"Both a low-fat vegan diet and a diet based upon ADA guidelines improved glycemic and lipid control in type 2 diabetic patients. These improvements were greater with a low-fat vegan diet".
Diabetes Care 2006; 29: 1777.



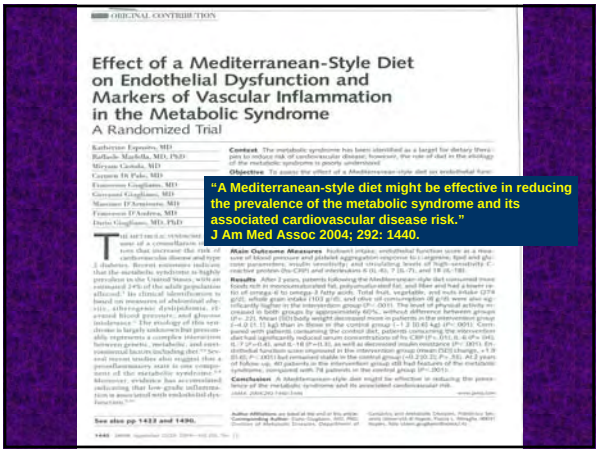
Articles

Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study

"Lifestyle intervention in people at high risk for type 2 diabetes resulted in sustained lifestyle changes and a reduction in diabetes incidence which remained after the individual lifestyle counseling was stopped."
Lancet 2006; 368: 1673.

Maybe it's more than the ratio of protein to carbohydrate to fat?

How about other factors that regulate cellular signaling?



ORIGINAL CONTRIBUTION

Effect of a Mediterranean-Style Diet on Endothelial Dysfunction and Markers of Vascular Inflammation in the Metabolic Syndrome
A Randomized Trial

"A Mediterranean-style diet might be effective in reducing the prevalence of the metabolic syndrome and its associated cardiovascular disease risk."
J Am Med Assoc 2004; 292: 1440.

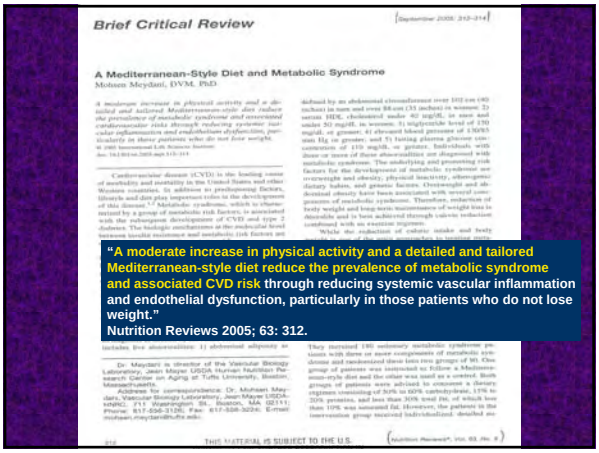
ORIGINAL CONTRIBUTION

Mediterranean Diet, Lifestyle Factors, and 10-Year Mortality in Elderly European Men and Women

The HALE Project

"Among individuals aged 70 to 90 years, adherence to a Mediterranean diet and healthful lifestyle is associated with a more than 50% lower rate of all-causes and cause-specific mortality".

J Am Med Assoc 2004; 292: 1423.



Brief Critical Review

A Mediterranean-Style Diet and Metabolic Syndrome

Mohsen Meydani, DVM, PhD

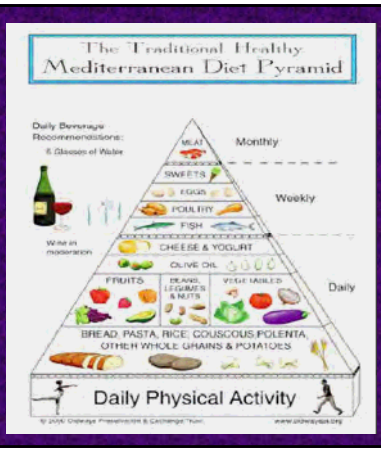
"A moderate increase in physical activity and a detailed and tailored Mediterranean-style diet reduce the prevalence of metabolic syndrome and associated CVD risk through reducing systemic vascular inflammation and endothelial dysfunction, particularly in those patients who do not lose weight."
Nutrition Reviews 2005; 63: 312.

EDITORIAL

Diet, Lifestyle, and Longevity—The Next Steps?

"In this issue of JAMA Esposito et al report the results of their investigation exploring possible mechanisms underlying dietary intervention. The authors randomized 180 patients with metabolic syndrome to a Mediterranean diet including whole grains, vegetables, fruits, nuts, and olive oil with a prudent diet with fat intake less than 30% and lower in carbohydrate and higher in protein."

J Am Med Assoc 2004; 292: 1490.



25% FAT 50% CARBOHYDRATE 25% PROTEIN

Therapeutic Lifestyle Change Diet

- *High in phytochemicals and fiber*
- *Low glycemic index foods*
- *Healthy oils*
- *Contains elements of healthy traditional eating,(PaleoMediterranean Diet)*

Mediterranean vs. Vegan vs. Paleomediterranean Diets

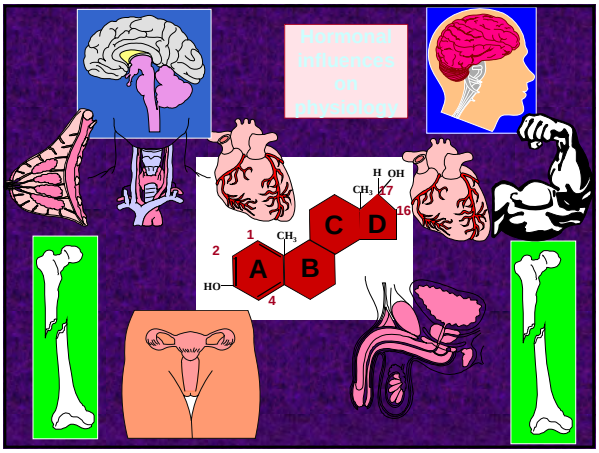
Diet	Mediterranean*	Vegan	TLC
↑ fruits, vegetables, grains, potatoes, beans, nuts & seeds	Yes	Yes	Yes, except limited grains & potatoes
Olive oil as an important source of monounsaturated fat	Yes	Yes	Yes
Dairy products, fish & poultry in low to moderate amounts, little red meat	Yes	No animal products eaten	Yes, and virtually no red meat is eaten
Eggs consumed 0 to 4 times a week	Yes	No	Yes
Wine consumed in low to moderate amounts	Yes	-	Yes

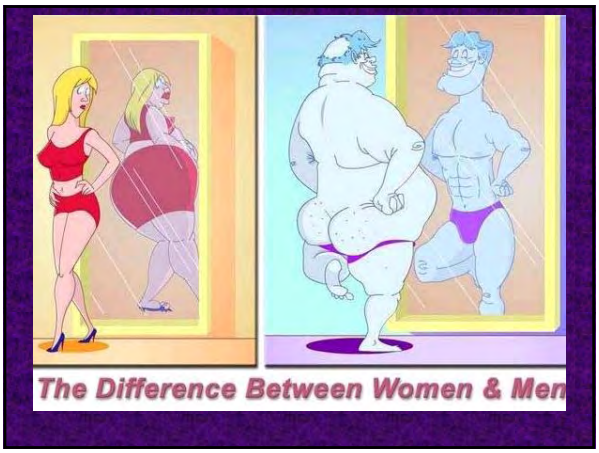
** As defined by the AHA, http://www.americanheart.org/presenter.jhtml?identifier=4644*

The Potential Takeaways in Dietary Management of Disorders of Hormone and Insulin Signaling

- It is more than generic macronutrients
  - Difference in type of protein
  - Family of fatty acids
  - Type of carbohydrate
- Micronutrient density
- Conditionally essential nutrients
- Fibers
- **Phytochemicals**
  - **Key signaling substances have been overlooked in many studies from which current traditional clinical recommendations have been derived**

Hormone activity	Good Protein	Bad Protein	Complex Carbs	Simple Carbs	Alcohol	Saturated fats
Melatonin	reduces	?	No effect	No effect	Severely reduces	?
Growth/ IGF-1	increases	reduces	No effect	No effect	reduces	increases
Thyroid	reduces	reduces	increases	increases	reduces	reduces
Cortisol	increases	reduces	No effect	No effect	reduces	increases
DHEA	increases	?	No effect	No effect	reduces	increases
Estradiol	increases	reduces	No effect	reduces	reduces	increases
Progesterone	increases	reduces	No effect	reduces	reduces	increases
Testosterone	Increases	reduces	No effect	reduces	reduces	increases





How to optimize Male/Female Hormone activity & Tx

What?	What to do	What to avoid
Diet	1. Eat sufficient calories 2. Follow a Paleomedit. Diet 3. Add amino acids – glutamine 2g/d in old and young, arginine 7g/d in young-lean, lysine 1g/d in young-lean, glycine 5g/d old and young (whey/rice/soy) 4. Eat organic foods	1. Avoid alcohol and caffeinated drinks 2. Avoid simple carbs 3. Avoid milk products 4. Avoid excessive cereal fiber (bread, bran)
Weight	Stay lean	Avoid being overweight
Sleep	Get adequate sleep	Avoid sleep deprivation
Stress	Practice stress reduction – yoga, meditation, guided imagery, etc.	Avoid excessive prolonged stress
Abuse		1. Avoid tobacco 2. Avoid marijunana, etc. 3. Avoid or reduce beta blockers

Glutamine

"The most abundant amino acid in the bloodstream, L-glutamine fulfills a number of biochemical needs.

It operates as a nitrogen shuttle, taking up excess ammonia and forming urea. It can contribute to the production of other amino acids, glucose, nucleotides, protein, and glutathione.

Glutamine is primarily formed and stored in skeletal muscle

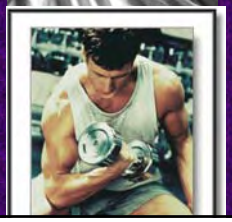
and lungs, and is the principal metabolic fuel for small intestine enterocytes, lymphocytes, macrophages, and fibroblasts."

Altern Med Rev 1999;4:239-248.
ABSTRACT Below

Arginine

"Arginine is conditionally essential since it becomes necessary under periods of growth and after recovery after injury. Arginine also promotes wound healing and functions as a secretagogue stimulating the release of growth hormone, insulin-like growth factor 1, insulin, and prolactin. Furthermore, arginine has several immunomodulatory effects such as stimulating T- and natural killer cell activity and influencing pro-inflammatory cytokine levels. The discovery that l-arginine is the sole precursor for the multifunctional messenger molecule nitric oxide (NO) led to investigation into the role of arginine in numerous physiologic and pathophysiologic phenomena including cancer."

Lind DS. Arginine and cancer. J Nutr. 2004 Oct;134(10 Suppl):2837S-2841S; discussion 2853S. PMID: 15465796



The American Journal of CLINICAL NUTRITION

Results: The insulin responses were higher after both breakfast (31%) and lunch (57%) when whey was included in the meal than when whey was not included. After lunch, the blood glucose response was significantly reduced [−21%; 120 min area under the curve (AUC)] after whey ingestion."

Frid, AH et al. Effect of whey on blood glucose and insulin responses to composite breakfast and lunch meals in type 2 diabetic subjects1,2,3 American Journal of Clinical Nutrition, Vol. 82, No. 1, 69-75, July 2005

PMID: 16002802 ARTICLE BELOW

"Background: Whey proteins have insulinotropic effects and reduce the postprandial glycemia in healthy subjects. The mechanism is not known,"

"In addition, whey has the ability to act as an antioxidant, antihypertensive, antitumor, hypolipidemic, antiviral, antibacterial, and chelating agent. The primary mechanism by which whey is thought to exert its effects is by intracellular conversion of the amino acid cysteine to glutathione, a tripeptide that [illegible]. *A number of clinical trials have successfully been performed using whey in the treatment of cancer, HIV, hepatitis B, cardiovascular disease, osteoporosis, and as an antimicrobial agent.* Whey protein has also exhibited benefit in the arena of exercise performance and enhancement."

(*Altern Med Rev* 2004 9(2):136-156) ABSTRACT BELOW

Whey
antioxidant, antihypertensive, antitumor, hypolipidemic, antiviral, antibacterial, and chelating agent.

Great for athletes

26% BCAA

proteins. IBID page 146

EAT SOON AFTER WORKOUTS! (45 minutes)

Journal of Applied Physiology

"We conclude that essential amino acids with carbohydrates stimulate muscle protein anabolism by increasing muscle protein synthesis when ingested 1 or 3 h after resistance exercise."

J Appl Physiol. 2000 Feb;88(2):386-92. PMID: 10658002

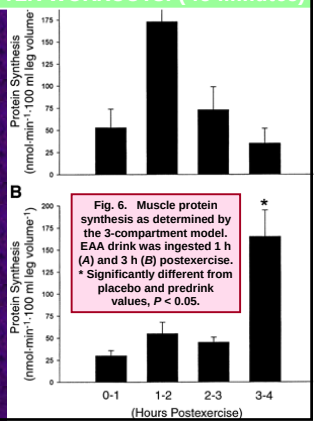


Fig. 6. Muscle protein synthesis as determined by the 3-compartment model. EAA drink was ingested 1 h (*A*) and 3 h (*B*) postexercise. * Significantly different from placebo and predrink values, $P < 0.05$.

Balance of Actions

- The ultimate biologic response reflects the BALANCE OF ACTIONS of the different hormones with each other and their respective receptors.
  - *Speroff Leon, et al, Clinical Gynecologic Endocrinology and Fertility 5th edition.*

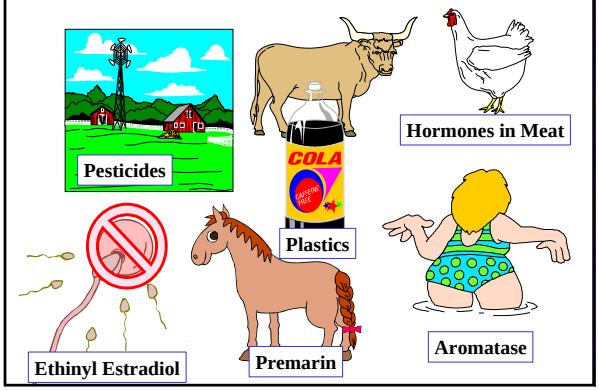
If We Had It To Do Over Again… Where Would We Start??

- Gain/Maintain our respect for The Matrix
  - Sex hormones don't operate in isolation
  - All the hormones are embedded in a highly interconnected web

If We Had It To Do Over Again… Where Would We Start??

- Review/learn theses facts:
  - Estrogen levels do not drop drastically for most women after menopause
  - Progesterone drops drastically
  - Testosterone and DHEA can decrease or increase with age
  - Cortisol output doesn't change drastically; some increase in bedtime cortisol levels

What is Causing the Problem



The Case For Progesterone Replacement

Women in North America are exposed to much higher levels of exogenous estrogens now

- Water supply
- Commercially-raised meat, poultry and seafood

- Pesticides, plasticizers, and other industrial chemicals

The Case of Progesterone Replacement

- Stressors are no longer accompanied by physical exertion

- Stress-induced glucose/insulin surge is no longer offset by physical exertion/ growth hormone surge
- Higher insulin → more fat storage → more endogenous estrogen

The Case of Progesterone Replacement

- We get less sleep

- Sleep deprivation causes elevated cortisol in the latter half of the following day

- Cortisol drives synthesis of estrogens from androgens in fatty tissue

The Case of Progesterone Replacement

- North America 2005 AD vs 2005 BC
  - Nutritional problems promote estrogen overload
    - Increased consumption of refined carbohydrates (leading to high insulin)

    - Consumption of estrogen-laden animal tissue
    - Decreased whole food intake
      - Nutrient deficiencies: B, Zn, Cr, B Vitamins
      - Decreased fiber intake

The Case of Progesterone Replacement

We are living in an environment with higher estrogen "pressure"

- Increased breast cancer
- Earlier onset of breast cancer
- Increased breast cancer in men
- Earlier onset of puberty

- More Estrogen after menopause *doesn't* make sense for most women
- It makes sense to replace progesterone in order to offset this extra estrogen, if the clinical situation warrants

Dr. Speroff: Clinical Gynecologic Endocrinolgy and Infertility, 6th. edition

- Estrogen levels in postmenopausal women can be significant, principally due to extraglandular conversion of androstendione and testosterone to estrogen. The clinical impact will vary from one postmenopausal woman to another depending on the degree of extraglandular production modified by a variety of factors.

Dr. Speroff: Clinical Gynecologic Endocrinology and Infertility, 6th. edition

- The percent of conversion of androstenedione to estrogen correlated with body weight. Increased production of estrogen from androstendione is probably due to the ability of fat to aromatize androgens. This fact and a decreased SHBG (which results in increased free estrogen) contribute to the well known assoc. between obesity and endometrial cancer. Aromatization of androgens is not limited to adipose… almost every tissue tested has this activity.

What Does Excess Estrogen Cause?

- Breast tenderness
- Depression, Anxiety, Fatigue, Poor concentration
- Endometriosis
- Fibrocystic Breasts
- PMS
- Fibroids
- Water retention and bloating
- Weight gain
- Increases risk of Breast and Uterine Cancer

Functions of Progesterone

- Pro-Gestation
- Natural Diuretic- blocks aldosterone receptors
- Thermogenic- decreases TBG
- Natural antidepressant and anxiolytic- binds GABA receptors
- May increase libido

Functions of Progesterone

- Promotes cell differentiation
- Promotes normal cell death
- Decreases estrogen receptor synthesis
- Improves estrogen receptor sensitivity
- Decreases estrogen induced mitosis

Progesterone, MPA and CRP

- Analysis of data from PEPI trial
- Oral estrogen elevates C-reactive protein (can be a cardiac risk marker)
- Oral E plus MPA: much larger increase in CRP
- Oral E plus oral progesterone: no additional increase in CRP compared to E alone

–Cushman M, et al. Circulation 1999;100:717-722

Vasomotor Symptom Relief With Topical Progesterone

- Postmenopausal Women
- 1 year, placebo-controlled trial, N = 102
- 20 mg/day progesterone cream
- Pg relieved vasomotor sx in 83% versus 19% for placebo
- No difference in bone density between groups
- Unpublished findings include lower TGs

What About Oral Progesterone?

- Progesterone is subject to first-pass metabolism in the gut and liver
- Metabolites are anxiolytic/sedating
- Oral progesterone does not appear to exert a significant effect on hepatic protein synthesis

Getting Started with Topical Progesterone

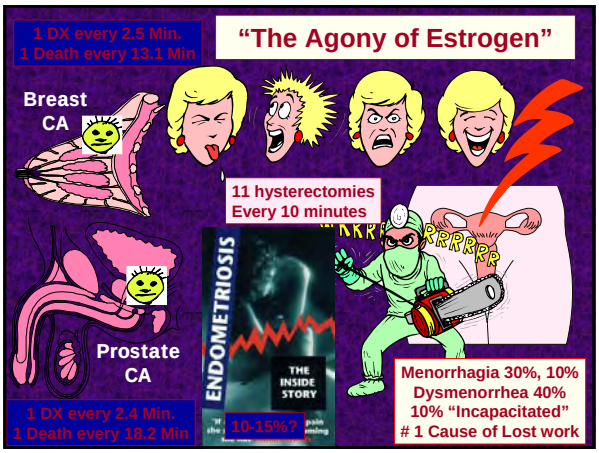
- Premenopause or postmenopause, no estrogen:
  - 10-30mg/day skin cream 14 to 25 days/month in luteal phase or by calendar if postmenopausal (surgical/natural)
- Postmenopausal in opposition to estrogen:
  - 20-40mg/day, divided doses or at hs, 25 days/month or continuous or off one day a week
  - Less estrogen: less progesterone
  - Maintain endometrial stripe on U/S < 4mm
- If initial good results wane, the starting dose was likely too high

Getting Started with Progesterone

- Expect 1-2 periods if starting cyclic progesterone within 6 months of "menopause"
- New onset bleeding/spotting (no matter how scanty) after stable amenorrhea on HRT must be investigated
- Recognize that there is a baseline risk of endometrial cancer (0.2 to 0.4%) if no HRT after menopause
- So… If you give BHRT to enough women, eventually someone may develop endometrial cancer due to the underlying natural incidence

When to change dose

Dose	Increase dose of Progesterone (25-100% or more) Decrease dose of Estrogen (25-75% or less)
Chronic	Excessive estrogen effects
Occasional	High protein diet High fat diet High calorie diet Yeast infection Unstressed, vacation, holiday Decreased physical activity Summertime
Occasional to permanent	Growth Hormone treatment (rarely)



Estrogen Replacement

Oral Estrogen and Hepatic Protein Synthesis

- Oral estrogen increases hepatic production of:
  - Binding Globulins
    - SHBG
    - Thyroid hormone binding globulin
    - Cortisol binding globulin
  - Clotting factors (pro and anti-thrombotic)
  - IGF binding proteins
  - C-reactive Proteins

Oral Estrogen = Estrogen Overdose

- Hormone replacement with estradiol: conventional oral doses result in excessive exposure to estrone. Friel PN, Hinchcliffe C, Wright JV. *Altern Med Rev* 2005;10:36-41.

Oral Estrogen = Estrogen Overdose

- Measured 24 hour urinary excretion of estradiol and estrone conjugates in women supplementing with oral estradiol
- At an oral dose of 1.5mg/day, estradiol excretion was 3 times normal and estrone excretion was 10 times normal
- The threshold dose for normal excretion was 0.5mg estradiol

Key Questions

- What pattern of metabolites is present for a given type of hormone delivery?
- What are the activities and half-lives of the metabolites?

Estradiol (E2), Estrone (E1) and Oral Estrogen Supplementation

- Oral supplementation of E2 or E1 leads to supraphysiologic amounts of estrone
- Supraphysiologic amounts of estrone lead to supraphysiologic amounts of estrone metabolites

Estrogen Metabolism

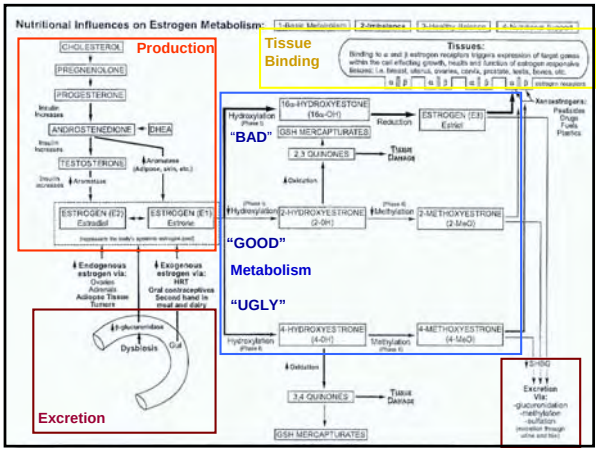
- **2-OH estrogens**: regarded as “good”. They are weaker estrogens and are precursors to methoxyestrogens (good).
- **4-OH estrogens** damage DNA and are implicated in breast cancer
- **16-OH estrogens** are also linked to breast cancer but the evidence is much weaker than for the 4OH estrogens.
  - Zhu B. Cooney A. Carcinogenesis 1998;19 1-27

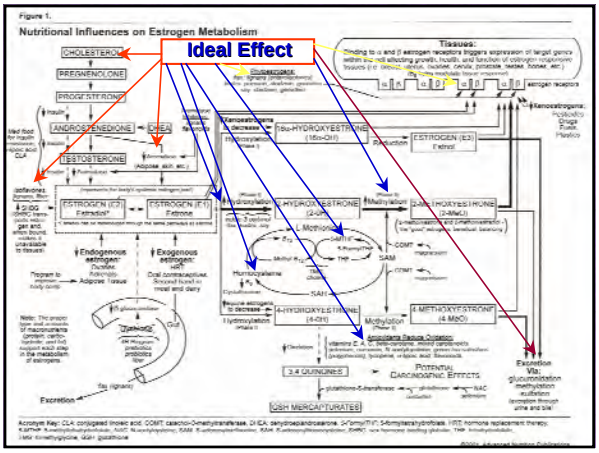
Estrogen Metabolism Chart

This estrogen metabolism chart was designed to simply depict the 4 main areas of estrogen metabolism and demonstrate the role nutrition plays in allowing the body to balance it’s own hormonal signals

Four Key Areas of Estrogen Diagram

- Production
- Metabolism
- Binding
- Excretion





Diagram

- Starting with cholesterol as the basic building block, these hormones are synthesized in a cascade that leads to estrogen production
- Estrogen is metabolized in the liver in three pathways, the 2-hydroxyestrone, 16 and 4. Then it is either excreted or binds to the target tissues and affects the growth, health & function of responsive tissue (breast, uterus, prostate)

Diagram (cont)

- The 2-methoxyestrone metabolite is the "good" estrogen and has a weaker estrogenic activity.
- Women who metabolize mainly through this pathway are 40% less likely to develop breast cancer compared to the 16 or 4 hydroxyestrone.

Diagram (cont)

- The 16 a-hydroxyestrone & 4 hydroxyestrone metabolites have stronger estrogenic activity and promote more negative characteristics associated with excess estrogen such as enhanced tissue proliferation.

Ways to Increase 2 OH Estrone

- Increase flow down 2-pathway:
  - Oil of Rosemary
  - Progesterone
  - Exercise
  - T3
  - Flaxseed
  - Cruciferous Vegetables
  - Di-indolemethylane, Indole 3-carbinol
  - Isoflavones (1-2 mg/kg body weight)
  - High fiber diet
  - Smoking

Can We Avoid “Estrogen Angst”?

- Don’t give estrogen unless the patient needs it
- Don’t rely on the FSH levels to indicate need for estrogen
- Start with low doses of estrogen if you give it, and ask the patient to be just that: be patient!!
- Administer estrogen in ways which avoid first pass metabolism (vagina, skin, sublingual rapid absorption)

Skin Delivery of Estradiol

- Efficient (25-50mcg vs 1000-2000 mcg oral dose
- Does not result in an excess of estrone/ estrone metabolites (if dosed <100 mcg/day)
- No perturbation of clotting cascade or CRP
- Triglycerides don’t increase
- Allows the true benefits of estradiol to show through

Can We Avoid “Estrogen Angst”?

- Use other weaker human estrogens
  - e.g. Estriol

What Do We Know About Estriol?

- High levels in pregnancy (we all swam in it)
- Oral estriol has been studied worldwide and especially in Japan
- Oral estriol widely used in Europe
- Estriol skin cream and oral estriol used in North America for at least 25 years
- New papers every few months

Recent Estriol Study

- Efficacy of low-dose intravaginal estriol on urogenital tissues in postmenopausal women.

  Dessole S et al. Menopause. 2004;11:49-56
- N=88, placebo-controlled
- 2 mg/week x 6 months
- Objective and subjective improvements compared to placebo

Metabolites of Oral Estrogens

- Oral Estriol
  - Glucuronides
  - Sulphates
- Oral E2/E1
  - Estrone
  - Estrone sulphate
  - 2 OHE1
  - 4 OHE1
  - 2 OHE2
  - 16 OHE1
  - E3
  - Glucuronides and sulphates of all the above

Estriol

- Clearly estrogenic, although weaker than estradiol
  - Regresses vaginal atrophy
  - May be effective for recurrent UTI
  - Relieves vasomotor symptoms
  - Probably not strong enough to build bone
  - Role in breast cancer prevention unproven

Estriol

- Must be accompanied by progesterone
- Skin cream more efficient than oral (more free estriol with cream)
- Saliva testing indicates 2-5 mg/day (topically) is too high → accumulation
- European dosing: 0.5 mg (topically) every other day

TriEst, BiEst, Estradiol or Estriol?

- Formulations with 8-10x excess of estriol have been in use for 20+ years with no evidence of adverse effects
- Estriol can be given orally without concerns about metabolites
- The body may convert estradiol into whatever it needs, if estradiol is given transdermally, so transdermal estradiol monotherapy also makes sense
- The estrone in combination formulas is probably unnecessary

TriEst, BiEst, Estradiol or Estriol?

- There is no clear answer when it comes to choice of human estrogen replacement
- Estrogens are often third-line after lifestyle interventions and progesterone
- Estrogen supplementation should be supported by demonstration of estrogen deficiency.

Vasomotor symptoms are not an automatic indication for estrogen supplementation

Getting Started with Estrogens

- Slow release patches: 25 to 50 ug/day (2 year controlled trial shows 50 ug will build bone)
- Compounded: aim for delivery of no more than 250 mcg estradiol per day.
- Start low, go slow

Getting Started with Estrogens

- 25 days/month
- Stop estrogens and progesterone at same time (4-5 day break)
- No Bleeding!

OR

- "Never on Sunday" (No E or Pg one day out of seven)
- No bleeding!!

Getting Started with Estrogens

- "Priming" is often necessary. (Higher dose for two weeks, then decrease dose.)
- Older women who have not used hormones may not respond to progesterone unless they are first primed with estrogen

Troubleshooting

- If you are getting into a "upward spiral" with dosing, you are missing something
  - Poor absorption
  - Current dose is already too high
  - Conversion into unwanted metabolites
  - Other hormone imbalances (low thyroid, high cortisol)
  - Nutritional issues (neurotransmitter synthesis, enzyme cofactor deficiencies, iodine deficiency)
  - Stress

When to change dose

Dose	Increase dose of Estrogen (25-100% or more) Decrease dose of Progesterone (25-75% or less)
Chronic	Insufficient estrogen effects
Occasional	Low protein diet High fiber diet Diarrhea Intensive and/or chronic stress Increased physical activity, sports Wintertime
Occasional to permanent	Androgen treatment Adult growth hormone deficiency Melatonin treatment (rarely) Hyperthyroidism

Testosterone Replacement

- Many women and men benefit from supplemental testosterone after menopause or andropause.
- Women/Men who have experienced chronic high stress levels may be more likely to have low testosterone after menopause/andropause (after menopause, testosterone comes from DHEA, chronic stress can impair DHEA synthesis)

Testosterone Replacement

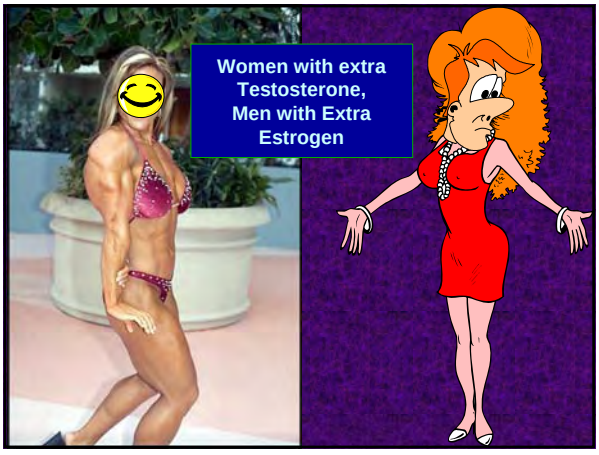
- The same concepts apply:
  - Skin delivery is better than oral delivery
  - Test to indicate deficiency before supplementing
  - Saliva testing is a good way to pick up low testosterone. Normal ranges are firmly established. Sampling within 1 hour of waking minimizes variation due to diurnal variation

Getting Started with Bio-Identical Testosterone

- Compounded testosterone cream: 0.5-2mg/day
- If you have to exceed this dose
  - Absorption issue
  - Metabolism issue
  - Hormonal imbalance (high cortisol, low T3)

When to change dose

Dose	Increase dose of Testosterone (25-100% or more)
Chronic	Insufficient testosterone effects
Occasional	Low protein diet High fiber diet Low calorie diet Diarrhea Intensive and/or Chronic stress Increased physical activity
Occasional to permanent	Growth Hormone deficiency Excess thyroid hormones (hyperthyroidism) Oral Estrogen Treatment



When to change dose

Dose	Decrease dose of Testosterone (25-50% or less)
Chronic	Excessive testosterone effects
Occasional	High protein diet High fat diet High calorie diet Unstressed, vacation, holiday Decreased physical activity
Occasional to permanent	Growth Hormone treatment Excessive body hair (hirsutism) Women with male pattern baldness (androgenic alopecia)

Net Effect	melatonin	GH	T3,T4	cortisol	DHEA	IGF-1	Insulin	Estradiol	progesterone	testosterone
melatonin		incr?	decr	decr	?	?	?	Incr transE	Incr?	?
GH	incr		incr	Inc,no, dec	incr	incr	Inc,no, dec	Incr only transE	incr	incr
thyroid	incr	incr		Inc,no, dec	incr	incr	incr	decr	decr	incr
cortisol	decr	decr	Incr, decr		decr, no eff	decr	Decr?	Decr oralE	Incr?	incr
DHEA	?	?	incr	decr		?	Decr?	Decr oralE	?	incr
IGF-1	Incr?	incr	incr	Inc,no, dec	incr		incr	incr transE	incr	incr
Insulin	incr	Dec or inc	incr	Inc,no, dec	incr	incr		Incr transE decr oralE	?	incr
estradiol	decr	incr	incr	Inc,no, dec	incr	incr	Incr (decr)		decr or incr	Decr (incr)
progesterone	decr	incr	incr	Inc,no, dec	Incr (decr)	incr	incr	Incr or decr		decr
testost	Decr?	incr	Incr or	Inc,no,	incr	incr	incr	decr	decr	

Hormone Imbalances: Progesterone

- **Low Progesterone** – may see estrogen deficiency symptoms
- **High Progesterone** – leads to down regulation of progesterone and estrogen receptor synthesis. May see estrogen excess/deficiency symptoms
- Progesterone blocks the cortisol-induced expression of aromatase in human adipose tissue
  - Schmidt M, Renner C, Loffler G. *J Endocrinology 1998;158:401-7*

Hormone Imbalance: Cortisol

- Cortisol can shut off testosterone by shutting down LH
- Cortisol turns on aromatase enzyme in adipose tissue and convert androgens to estrogen (leads to estrogen dominance)
- Elevated cortisol will decrease progesterone production
- Modestly elevated cortisol in chronic stress can increase rT3 and decrease T3 (low T3 can increase SHBG leading to more free hormones)

T3 and the Hormone Symphony

- T3 is needed for the hormone cascade – cholesterol…pregnenolone…progesterone……. cortisol
- T3 stimulates production TIF (thyroid hormone induced factor) which stimulates the release of progesterone from ovarian granulosa cells.
  - *J Endocrinology 1998;158:319-325. Datta et al.*
- Increased T3 stimulates the production of increased SHBG

Estrogen Dominance

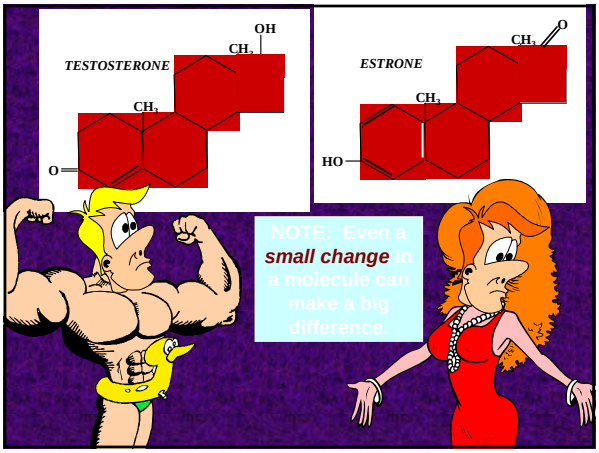
- Think about the impact of T3 signaling
- Is it due to elevated cortisol?
- Is there too much DHEA supplementation?
- B6 deficiency?

Estrogen Deficiency

- Low percent body fat?
- Low progesterone may be causing decreased estradiol signaling
- Is is due to low DHEA output secondary to chronic stress/illness?
  - Adrenal Fatigue: The 21st Century Syndrome

Low Androgen Symptoms

- Are they due to high Cortisol?
- Secondary to low T3?
- Due to low DHEA?



T3 and Cortisol

- Can't ignore these hormones when dealing with HRT patients
- Learn to identify people whose primary issue is adrenal/thryoid
- Must fix these problems first, in a percentage of patients

Oral Estrogen and Thyroid Hormones

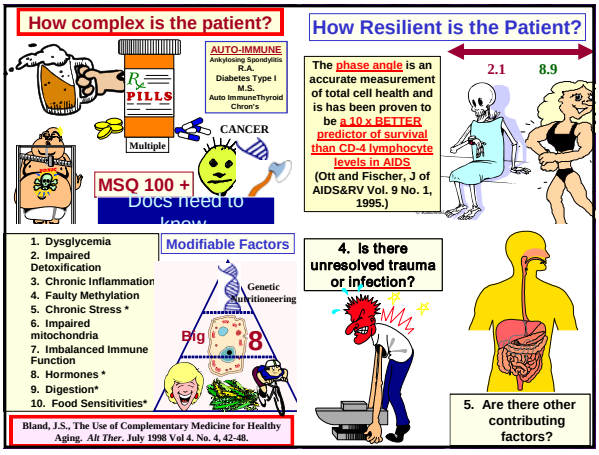
- Oral estrogen can increase TBG synthesis in the liver and decrease FT3 and FT4
- In men, high estradiol will switch off testosterone production via decreased LH
  - J Clin Endocrinology Metab. 2000 Sep:85(9);3027-35

DHEA Replacement

- Chronic stress and chronic illness such as RA, lupus, MS predispose to low DHEA
- If both testosterone and DHEA are low, it may be worth supplementing with DHEA alone to start
- Oral dosing in women should likely be 5 to 10 mg, not 25 to 50mg!!
- Transdermal may be the preferred route if the aim is to deliver intact DHEA (as opposed to metabolites) (oral DHEA can be converted to estrone and testosterone)

DHEA Replacement

- Check DHEA/S levels before supplementing
- High DHEA/S accompanies insulin resistance
- Additional DHEA may make things worse if insulin resistance/metabolic syndrome is present
- Check cortisol levels by saliva prior to initiating DHEA replacement



Presenting …

Nutrition and Osteoporosis

1

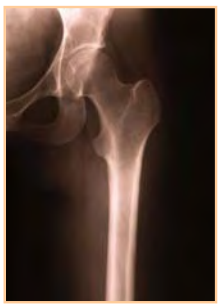
The problem in America

- Major health threat for an estimated 44 million (55%) of people 50 years and older
- 10 million estimated to have osteoporosis
- 34 million have low bone mass placing them at risk
- 1 in 2 women and 1 in 4 men over 50 will have an osteoporosis-related fracture

2

Source: National Osteoporosis Foundation Web site; retrieved July 2005 at http://www.nof.org

A woman's hip fracture risk equals her combined risk of breast, uterine and ovarian cancer.



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Source: National Osteoporosis Foundation Web site; retrieved July 2005 at http://www.nof.org

Hip fractures account for 300,000 hospitalizations annually.

People who break a hip might not recover for months or even years.

Source: The 2004 Surgeon General's Report on Bone Health and Osteoporosis: What It Means to You at http://www.surgeongeneral.gov/library/bonehealth

4

1 in 5 people with a hip fracture end up in a nursing home within a year.

Some people never walk again.

Source: The 2004 Surgeon General's Report on Bone Health and Osteoporosis: What It Means to You at http://www.surgeongeneral.gov/library/bonehealth

5

The most common breaks in weak bones are in the wrist, spine and hip.

Source: The 2004 Surgeon General's Report on Bone Health and Osteoporosis: What It Means to You at http://www.surgeongeneral.gov/library/bonehealth

6

You're never too young or old to improve bone health!

7

Definition

- Which of the following patients have a clinical diagnosis of osteoporosis?
  - A) 65 F with nl bone density, but frequent falls
  - B) 70 M very low bone density, asymptomatic
  - C) 58 F with a hip fx after minor fall, no BMD
  - D) 39 M with hip fx after major MVA, no BMD

Definition

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  - **C) 58 F with a hip fx after minor fall, no BMD**
  - D) 39 M with hip fx after major MVA, no BMD

Key Points

- Don't treat the T-score, treat the fracture risk
- Nonpharmacologic measures are very effective

Epidemiology

- What percent of white women will have osteoporosis by the age of 80?
  - » A) 10 %
  - » B) 30 %
  - » C) 50 %
  - » D) 70%
- Which type of fractures are associated with the most mortality?
  - » A) Vertebral
  - » B) Hip
  - » C) Colles' fractures

Epidemiology

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  - **» D) 70 %**
- Which type of fractures are associated with the most mortality?
  - » A) Vertebral
  - **» B) Hip**
  - » C) Colles' fractures

Pathophysiology

- Bone resorption / Bone formation balance
- Favors formation until age 30-45
- Type I – postmenopausal (ages 50-70)
- Type II – senile (ages 70+)
- Type III - secondary

Pathophysiology

- 2 factors dictate the development of OP
  - Peak bone mass achieved
  - Rate of bone loss
- Attack one of these factors to prevent OP

Who to screen

- Which of the following patients should be screened for osteoporosis?
  - A) 70 F with no medical problems
  - B) 57 F thin postmenopausal smoker
  - C) 50 F with Colles fracture after minor fall
  - D) 37 F premenopausal with bone pain
  - E) 58 M with incidental vertebral fx noted on CXR

Who to screen

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  - **A) 70 F with no medical problems**
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  - **C) 50 F with Colles fracture after minor fall**
  - D) 37 F premenopausal with bone pain
  - **E) 58 M with incidental vertebral fx noted on CXR**

Who to screen

- All males and females over the age of 65
- Younger patients if they have fracture risk factors
  - *** Low body weight (< 70 kg)
  - Prior fracture
  - FH osteoporotic fracture
  - Chronic diseases which increase fall risk
  - smoking, physical inactivity, alcohol, caffeine

Who to screen for secondary causes

- Search for secondary causes of OP:
  - T score < -2.0
  - History of minimal trauma fracture
  - Physical evidence of vertebral fracture:
    - Loss of height > 2 inches
    - Wall-occiput distance > 0 inches
    - Rib-pelvis distance < 2 fingerbreadths
    - Fewer than 20 teeth

Secondary causes of OP

- Which of the following is not a secondary cause of osteoporosis?
  - A) Hyperthyrodisim
  - B) Hypogonadism
  - C) Hypertension
  - D) Steroid use

Secondary causes of OP

- Which of the following is not a secondary cause of osteoporosis?
  - A) Hyperthyrodisim
  - B) Hypogonadism
  - **C) Hypertension**
  - D) Steroid use

Secondary causes of OP

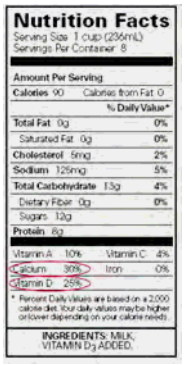
- Endocrine
  - Hypogonadism, hyperthyroidism, DM type I, cushings, hyperparathyroidism
- Nutritional
  - Malabsorption, vit D deficiency, Ca deficiency, EtOH
- Meds
  - STEROIDS, thyroxine, anticonvulsants, loop diuretic
- Other
  - COPD, RA, Multiple myeloma, CKD

Secondary search

- Ca, Phos, Protein/Albumin, Alk Phos, creatinine
- CBC
- TSH
- 25-hydroxyvitamin D
- Testosterone (men)
- Consider: PTH, Urinary calcium, Urinary cortisol

Food and supplement labels

Assess calcium and vitamin D intake by using food and supplement labels.



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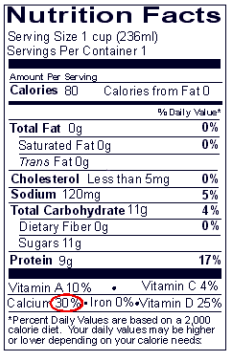
Nutrition labels & calcium

- **FDA uses "Percent Daily Value" (% DV) to describe amount of calcium needed by general U.S. population daily**
- **100% DV for calcium = 1,000 mg**
- **Look for this label:**
  - **"Nutrition Facts" on foods**
  - **"Supplement Facts" on vitamin/mineral supplements**



Sample "Nutrition Facts" label

FROZEN CHOPPED BROCCOLI

Nutrition Facts
Serving Size 1/2 cup (93g)
Servings Per Container 4

Amount Per Serving	
Calories 25	**Calories from Fat** 0
	% Daily Value*
Total Fat 0g	0%
Saturated Fat 0g	0%
Cholesterol 0mg	0%
Sodium 20Mg	1%
Total Carbohydrate 5g	2%
Dietary Fiber 3g	12%
Sugars 2g	
Protein 3g	
Vitamin A 35% • Vitamin C 60%	
Calcium 4% • Iron 4%	

*Percent Daily Values are based on a 2,000 calorie diet.

Nutrition Facts
Serving Size 1 cup (236mL)
Servings Per Container 8

Amount Per Serving	
Calories 90	**Calories from Fat** 0
	% Daily Value*
Total Fat 0g	0%
Saturated Fat 0g	0%
Cholesterol 5mg	2%
Sodium 125 mg	5%
Total Carbohydrate 13g	4%
Dietary Fiber 0g	0%
Sugars 12 g	
Protein 8g	
Vitamin A 10% • Vitamin C 4%	
Calcium 30% • Iron 0%	
Vitamin D 25%	

*Percent Daily Values are based on a 2,000 calorie diet.

SKIM MILK

Example of "Daily Value"

If a food or supplement has 200 mg of calcium per serving, the "Nutrition Facts" or "Supplement Facts" panel shows:

20% DV for calcium
(200 mg ÷ 1,000 mg = 20%)

MACARONI & CHEESE

Nutrition Facts
Serving Size 1cup (228g)
Servings Per Container 2

Amount Per Serving	
Calories 250	**Calories from Fat** 110
	%Daily Value*
Total Fat 12g	18%
Saturated Fat 3g	15%
Cholesterol 30mg	10%
Sodium 470mg	20%
Total Carbohydrate 31g	10%
Dietary Fiber 0g	0%
Sugars 5g	
Protein 5g	
Vitamin A 4% • Vitamin C 2%	
Calcium 20% • Iron 4%	

*Percent Daily Values are based on a 2,000 calorie diet.

Example: Calculating total % DV for calcium from "Nutrition Facts" labels

Food	% DV
Fruit yogurt	35%
Oatmeal	10%
Nachos	20%
Turnip greens	15%

Total % DV = 80%

Source: "Calcium! Do You Get It?, " FDA/CFSAN at http://www.cfsan.fda.gov/~dms/ca-toc.html

Using Nutrition Facts "serving size"

- Serving size on "Nutrition Facts" panel based on what people typically eat—it's not a recommended amount.
- Adjust calcium % DV if you eat a different serving size than on label.

Example: If label says a half cup serving provides 4% DV, one cup provides 8% DV

28

Calcium requirements vary by age

If this is your age	Then you need this much calcium each day (mg)
0 to 6 months	210
7 to 12 months	270
1 to 3 years	500
4 to 8 years	800
9 to 18 years	1,300
19 to 50 years	1,000
Over 50 years	1,200

Growth spurt

Source: The 2004 Surgeon General's Report on Bone Health and Osteoporosis: What It Means to You at http://www.surgeongeneral.gov/library/bonehealth

29

Calcium

- We prefer calcium intake to be from diet rather than supplements:
  - A) True
  - B) False

Calcium

- We prefer calcium intake to be from diet rather than supplements:
  - **A) True**
  - B) False

Calcium

- RDA is 1000-1300 mg
- Average intake is 600-800 mg
- Preferred from dietary sources
- Take Ca with food (needs acid to absorb)

It's important to remember …

Some age groups need MORE or LESS than 100% DV for calcium and vitamin D.

- **Calcium requirements vary by age:**
  - **More is needed as we grow older**
  - **Need is highest during rapid growth of adolescence.**
- **Vitamin D requirements increase as we age.**
- **100% DV for calcium and Vitamin D are based on 1,000 mg calcium and 400 IU vitamin D.**

33

Vitamin D

- Deficiency is prevalent
- Recommendations 200 to 2000 IU daily
- MVI has 400 IU
- Safe and effective
- Vit D + Calcium decrease fracture risk by 30%

Calcium & vitamin D recommendations

- **Birth - 6 months**
  210 mg calcium (21% DV)
  200 IU vitamin D (50% DV)

- **6 months - 1 year**
  270 mg calcium (27% DV)
  200 IU vitamin D (50% DV)

Some age groups need MORE or LESS than 100% DV for calcium and vitamin D

35

Calcium & vitamin D recommendations

- **1 - 3 years**
  500 mg calcium (50% DV)
  400 IU vitamin D (100% DV)

- **4 - 8 years**
  800 mg calcium (80% DV)
  400 IU vitamin D (100% DV)

Some age groups need MORE or LESS than 100% DV for calcium and vitamin D

36

Calcium & vitamin D recommendations

- **9 - 18 years**
  1,300 mg calcium (130% DV)
  400 IU vitamin D (100% DV)

- **19 - 50 years**
  1,000 mg calcium (100% DV)
  400-800 IU vitamin D (150% DV)

Some age groups need MORE or LESS than 100% DV for calcium and vitamin D

37

Calcium & vitamin D recommendations

- **51 - 70 years**
  1,200 mg calcium (120% DV)
  800-2000 IU vitamin D (200% DV)

- **71 and older**
  1,200 mg calcium (120% DV)
  2000 IU vitamin D (500% DV)

Some age groups need MORE or LESS than 100% DV for calcium and vitamin D

38

Calcium & vitamin D recommendations

Pregnant & Lactating

- **14 - 18 years**
  1,300 mg calcium (130% DV)
  400 IU vitamin D (100% DV)

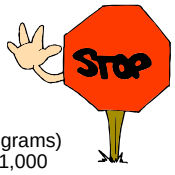
- **19 - 50 years**
  1,000 mg calcium (100% DV)
  400-800 IU vitamin D (150% DV)

Some age groups need MORE or LESS than 100% DV for calcium and vitamin D

39

Upper daily limits: calcium & vitamin D

The National Academy of Sciences (1997) suggests the following tolerable daily upper intake levels (UL) from foods and supplements combined:



- **Calcium:** The UL for 1 year and older (including pregnant and lactating women) is 2,500 mg/day. It was not possible to establish an UL for infants under age 1.
- **Vitamin D:** No higher than 50 mcg (micrograms) or 2,000 IU for ages 1 and over; 25 mcg (1,000 IU) for 0 to 12 months

The National Osteoporosis Foundation recommends limiting Vitamin D to 800 IU/day unless your doctor prescribes it.

40

Percent Daily Value (DV) of calcium in common foods

Approximate % DV for foods based in part on The 2004 Surgeon General's Report on Bone Health and Osteoporosis: What It Means to You at http://www.surgeongeneral.gov/library/bonehealth

41

An easy way to meet calcium needs is consuming 3 cups (8 oz.) each day of fat-free or low-fat* milk or equivalent milk products in combination with a healthy diet.

Children ages 2–8 years need 2 cups.

* Fat-free and low-fat are for health but not for calcium differences

MyPyramid equivalents:

- **8 oz. milk**
- **1 cup yogurt**
- **1-1/2 oz. natural or 2 oz. processed cheese**

42

% DV calcium: Milk group

Choose fat-free or low fat most often

- **Yogurt**
  1 cup (8 oz.) = 30% DV
- **Milk**
  1 cup = 30% DV
- **Cheese**
  1½ oz. natural/2 oz. processed = 30% DV
- **Milk pudding**
  1/2 cup = 15% DV
- **Frozen yogurt, vanilla, soft serve**
  ½ cup = 10% DV
- **Ice cream, vanilla**
  ½ cup = 8% DV
- **Soy or rice milk, calcium-fortified**
  1 cup = varies—check label

43

% DV calcium: Grain products group

- **Cereal, calcium-fortified**

  Serving size and amount of calcium varies—check label

44

% DV calcium: Vegetable group

- **Broccoli, raw**
  1 cup = 9% DV
- **Collards**
  1/2 cup = 20% DV
- **Turnip greens, boiled**
  1/2 cup = 10% DV

45

% DV calcium: Fruit group

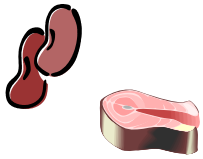
- **Orange juice and other calcium-fortified beverages**

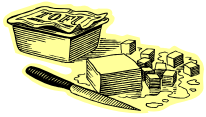
6 oz. = 20 to 30% DV, varies—check label

Look for 100% juice

46

% DV calcium: Meat & Beans Group





- **Baked beans**
  1 cup = 14% DV
- **Salmon, canned, with edible bones**
  3 oz. = 18% DV
- **Sardines, canned, in oil, with edible bones**
  3 oz. = 32% DV
- **Soybeans, cooked**
  1 cup = 26%
- **Tofu, firm, with calcium**
  ½ cup = 20% DV; check label

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What about Vitamin D?

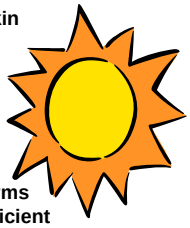
Main dietary sources of vitamin D are:

- **Fortified milk (400 IU per quart)**
- **Some fortified cereals**
- **Cold saltwater fish (Example: salmon, halibut, herring, tuna, oysters and shrimp)**
- **Some calcium and vitamin/mineral supplements**

48

Vitamin D from sunlight exposure

- Vitamin D is manufactured in your skin following direct exposure to sun.
- Amount varies with time of day, season, latitude and skin pigmentation.
- 10–15 minutes exposure of hands, arms and face 2–3 times/week may be sufficient (depending on skin sensitivity).
- Clothing, sunscreen, window glass and pollution reduce amount produced.



49

Source: National Osteoporosis Foundation Web site; retrieved July 2005 at http://www.nof.org

Additional dietary considerations

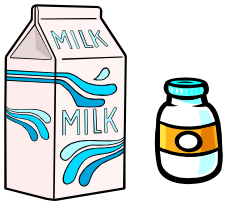
50

Food is the best calcium source

- There may be additional substances in foods that affect the body's absorption and use of their calcium.
- A balanced diet that promotes a healthy weight may provide additional benefits to protect against osteoporosis.

51

Calcium amount at one time



- Body can best handle about 500 mg calcium at one time from food and/or supplements.
- Consume calcium sources throughout day instead of all at one time.

52

Fiber

Excessive fiber—such as from overusing fiber supplements—could interfere with calcium absorption.

Fiber naturally present in food should not be a problem and is beneficial to health.

53

Excessive sodium

- Can increase urinary calcium excretion
- Food and Nutrition Board recommends limit of 2,300 mg daily
- Sodium given on "Nutrition Facts" panel on foods

54

Oxalic acid

Present in foods such as spinach, chard, beet greens and chocolate:

- **Binds calcium in those foods**
- **Doesn't seem to affect calcium in other foods, including chocolate milk**
- **These greens still good for you; may help calcium absorption in other ways**

55

High protein

Unbalanced, excessively high protein diets could increase urinary excretion of calcium.

56

Rice/Soymilk

- **Not all rice/soymilk is calcium-fortified or contains vitamin D; check "Nutrition Facts" panel.**
- **4 (8-oz.) glasses of rice/soy milk may equal 3 (8-oz.) glasses of cow's milk in availability of calcium.**
- **Part of added calcium may be left in container when drinking some rice/soymilks.**

57

Calcium supplement considerations

58

Calcium carbonate vs. citrate

Calcium carbonate

- Needs acid to dissolve and for absorption
- Less stomach acid as we age
- Often taken at meals when more stomach acid

Calcium citrate

- Doesn't require stomach acid for absorption
- May be taken anytime—check with your healthcare provider
- May cost more

59

Vitamin D necessary for calcium absorption

Vitamin D is like a key that unlocks the door and lets calcium into the body.

- Choose a supplement with vitamin D unless obtaining vitamin D from other sources.
- Follow age group recommendation. Avoid going over a daily combined total of 2,000 IU or 50 mcg from food and supplements.
- It's not necessary to consume calcium and vitamin D at the same time to get the benefit of enhanced calcium absorption.

60

Limit calcium to 500 mg at a time

Our bodies can best handle about 500 mg calcium at one time from food and/or supplements.

Spread your calcium sources throughout the day.

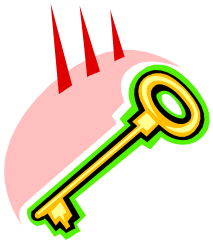
61

Increase amount slowly

- Start supplements with 500 mg calcium daily for about a week, gradually adding more.
- Gas and constipation can be side effects:
  - Increase fluids and high fiber foods if diet is low in whole grains and fruits and vegetables.
  - Try a different type of supplement if side effects continue.

62

Food is still important



- High calcium foods contain other KEY nutrients which are important in the diet.
- Try to obtain some (or all) of your calcium from your diet, not just supplements.

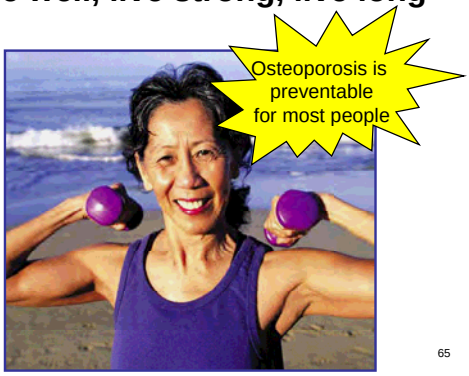
63

Also, follow the other four prevention steps …

- Engage in regular weight-bearing exercise.
- Avoid smoking and excessive alcohol.
- Talk to your doctor about bone health.
- Have a bone density test and take medication when appropriate.

64

Live well, live strong, live long



65

The Effect of National & State Government on BHRT Practices

Presented by

Steven Hotze, MD

The Effect of State & National Government on Medicine

Steven F. Hotze, M.D.
SFH@hotzehwc.com

Level II BHRT Symposium…The Next Step in Patient & Practice Optimization
Denver, Colorado
June 3, 2007

1

Contrasting Economic Systems

Free Enterprise Capitalism

vs.

Socialism

2

Free Enterprise Capitalism

– Capitalism is the organization of economic activity through private enterprise - the voluntary exchange of goods and services for money - operating in a free market.

3

Socialism

- Socialism is the organization of economic activity through ownership of the means of production and central planning by the state.
- Socialism inevitably involves coercion by the state.

4

Free Enterprise Capitalism

- The principle which determines the distribution of income among members of society is, "To each according to what he produces with his labor and with his equipment and property."

5

Socialism

- The principle which determines the distribution of income among members of society is "From each according to his abilities, to each according to his needs."

6

Free Enterprise Capitalism

– Views all rights as being inalienable and endowed by the Creator.

7

Socialism

- Views all rights as being alienable and endowed to the individual by the state.

8

Free Enterprise Capitalism

– The individual is accountable for his own actions and reaps the results.

9

Socialism

- Promotes dependency upon the state through entitlement programs and welfare.
- Creates disincentives to take initiative and transfers blame for life situations to society.

10

Free Enterprise Capitalism

- Income and wealth is obtained through individual effort and production and may be transferred to family members, friends or charitable organizations.

11

Socialism

- Redistribution of income and wealth is accomplished by government coercion.

12

Free Enterprise Capitalism

- Provides economic liberty without which there can be no personal or political liberty.

13

Socialism

- Economic liberty is eliminated and political liberty is concomitantly lost.

14

Free Enterprise Capitalism

Natural Law

American jurisprudence was established upon the concept of "Natural Law" rather than "Positive Law". Because of their Christian faith, our founding fathers believed that each person was endowed by God with certain unalienable rights, those rights being life, liberty and property, for which the civil government has been established to protect and preserve.

15

Socialism

"Positive" Law

The state becomes the Sovereign rather than God and the individual exists for the state and puts his confidence in the state. The law becomes whatever those in power or in the majority proclaim it to be. Higher law is denied.

16

Free Enterprise Capitalism

View of Civil Government

Civil government should preserve and protect the unalienable rights of life, liberty and property; maintain law and order to prevent coercion of the weak by the strong; enforce voluntary contracts; define property rights and enforce those rights; provide a monetary system.

17

Socialism

View of Civil Government

Government performs whatever actions those in power choose. Constitutional guarantees may be redefined or eliminated for the betterment of the state.

18

Examples of Socialization of Medicine State

- State Boards of Medicine and Pharmacy
- Medicaid (Federal – State Cooperation)
- HPV Vaccine Mandate – Texas
- Insurance Mandates
  - Massachusetts
- Insurance coverage mandates

19

– Federal

- Food and Drug Administration (FDA) - 1938
- Drug Enforcement Agency (DEA) – 1970
- Health & Human Services (HHS) – 1979 – Formerly HEW
- Medicare/Medicaid – Administered by the Health Care Financing Administration (HCFA) - 1965
- Health Maintenance Organization Act (HMO) - 1973
- Emergency Medical Treatment and Active Labor Act (EMTALA) - 1996

20

– Federal continued

- Clinical Laboratory Improvements Amendments (CLIA) - 1988
- Medicare Prescription Drug, Improvement and Modernization Act - 2003
- Health Insurance Portability and Accountability Act (HIPAA) - 1996
- National Provider ID – (NPI)
- Pay for Performance (P4P) initiatives

21

Safe Drug Compounding Act of 2007

- Sponsors – Senators Kennedy, Burr, Roberts
- Federalizes the practice of Pharmacy and Medicine
- FDA would determine what compounded preparations could be made by a pharmacy or made or prescribed by a physician (Allergy doses are compounded preparations)
- Contact your Senators and Congressmen using Project FANS (Freedom for Access to Natural Solutions) www.projectfans.org

22

Features of Medical Care in US

- Dramatic scientific improvements
- Huge increase in spending
- Rising dissatisfaction over the quality of service by the consumers

23

Comparison with other Technological Advances

- Previous technological advances since the Industrial Revolution - railroads, telephones, electricity, automobiles, radio, television, computers - resulted in decreased costs for the technology as a percentage of national income.
- Medical advances have resulted in increased costs as a percentage of national income, 20% of GDP.

24

Reason for Differences

- In non medical technological advances the ideas, initiative, financing, production and distribution were provided from private sources with government providing a regulatory role.
- In medical care the government plays the leading role in these areas.

25

Cause of Increased Spending

- Third party payments by insurance, employers or government
- "Nobody spends somebody else's money as wisely or as frugally as he spends his own." -Milton Friedman, Nobel Laureate

26

Law of Supply and Demand

- "Free" medical care leads to an infinite demand. Since there is no price to determine the allocation of goods and services there will inevitably be shortages leading to bureaucratic rationing.
- Prime Example – Canadian Socialized Medicine

27

Effects of Socialism on Medicine

- Growth of State Expenditures
- Growth of Federal Expenditures
- Undermining of physician/patient relationship
- Decline in physician income
- Decline in admissions to medical school
- Increase in physicians leaving profession
- Decline in quality of patient care

28

Medical Expenditure Analysis

- 1960 - 21 % of personal medical care expenditures were paid by the government
  - 24% by insurance companies
  - 55% were paid by consumers out of their own pockets.
- 2007 - 50% of all medical expenses paid by government
  - 35% by insurance companies & HMOs
  - 15% of care out of pocket

29

Gammon's Law

- British physician, Max Gammon formulated the Theory of Bureaucratic Displacement.

"In a bureaucratic system the increase in expenditures will be matched by a fall in production. Bureaucratic systems act like black holes in the economic universe, simultaneously sucking in resources and shrinking in terms of emitted production."

30

Personal Example

- Birth of Mary Beth Hotze - 1969 at St. David's Hospital in Austin
  Total Cost - $500 (Cash, no insurance)
  - $250 for three days hospitalization
  - $250 for the obstetrician

Adjusted for inflation - $2500 in 2007.

Comparison - The total cost of a delivery today, including hospital and doctor, has increased 6 times, to approximately $15,000.

Why the increase? Gammon's Law

31

Bureaucratization of Medicine

- Third party payment has led to the bureaucratization of medical care.
- Rather than voluntary exchange of goods and services between patients and physicians a bureaucrat is inserted to determine whether or not the physician/patient interaction is "covered."
- The physician is effectively employed by the insurance company or the government.

32

The Meaning of Insurance

- Historical Meaning – The sharing of risks in order to protect oneself against catastrophes, not minor, regularly occurring expenses, eg. home and car insurance
- Current Meaning in Medicine – The provision of both minor and major medical care, eg. routine exams and medications

33

Solution and Action Steps

- Join and support American Academy of Physicians & Surgeons - www.AAPSonline.org, Foundation for Economic Education - www.FEE.org, Cato Institute - www.cato.org.
- Review State Board Rules for alternative & complementary medicine exemptions (Texas State Board (Standard 200.1-200.3), Minnesota State Board)
- Encourage the use of Health Savings Accounts -HSA
- Opt out of Medicare
- Eliminate Managed Care Contracts and Medicaid
- Obtain uncovered entity status regarding HIPAA
- Establish fee-for-service, cash based practice
- Write editorials and submit to local papers
- Lobby your state and national legislators

34

Staying Out of Trouble When Prescribing BHRT

Protecting Yourself & Your Patients

Presented by

George Juetersonke, DO

Level II BHRT Symposium

Staying Out of Trouble

3 June 2007
George Juetersonke DO

The Medical Community Responds

"THE STANDARD OF CARE"

Position Statement North American Menopause Society

Position Statement NAMS

- Primary indication: symptoms
- Progestogen indication: endometrial protection
- ET EPT considered for osteoporosis
- Not for dementia after age 65
- Not for prevention CHD, stroke

NAMS continued

- WHI, HERS data cannot be extrapolated to women younger than 50
- Use lower than standard doses of ET EPT
- Non-oral may offer benefits but long term risks unknown

NAMS continued

- Breast cancer increases with EPT beyond 5 years
- Cancer risk is small 6/10,000
- No mortality difference between users and non users
- CEE no increased risk (WHI arm)

NAMS continued

- ET EPT goals depends on individual women and quality of life
- Extended use OK provided woman is aware of risk and benefits and is supervised
- Comprehensive exam necessary for RX

NAMS continued

- Specific compounds, dose and route of administration *may* have different outcomes

BUT current clinical trial results should be *generalized* to all agents within same family *including bioidentical products*

ACOG Committee Opinion Ob Gyn 2005;106:1139-40

1. Compounded products have not undergone testing for safety, efficacy or quality assurance regarding purity, potency and quality

ACOG Committee Opinion

2. Salivary or Blood/Serum Testing. HT does not belong to a class of drugs with an indication for individualized dosing.

Individualized dosing only for nonlinear pharmacokinetics, renally eliminated, not metabolized first pass liver, or clearly defined therapeutic or toxic concentrations

ACOG Committee Opinion

- Salivary hormones are not biologically meaningful
- Large within patient variability
- Levels depend on diet, time of day, mode of administration

ACOG Committee Opinion

3. There is no scientific evidence to support increased *efficacy or safety* for Bio identical hormones

Bio identical hormones should be considered to have the same safety issues as those approved by the FDA.

ACOG Committee Opinion

4. Bio identical hormones should have the same class labeling (Back Box Warnings) reflective of the WHI as do the FDA approved estrogens and progestogens

What is the treatment for Menopause?

1. Nothing
2. Antidepressants, antihypertensives etc.
3. Hormone substitution
4. Hormone replacement
5. SERMS

Answer

Whatever the patient chooses together with their physician after being fully informed of the benefits and risk of all the options

Wouldn't anything else constitute abuse?

Summary

1. No trial is perfect
2. Evidence-based medicine demands recommendations based on studies relevant to the patient being seen.
3. Ideal but not practical. There never will be adequate randomized controlled trials covering all populations, eventualities and drug regimens
4. We see patients, not populations
5. WHI does not apply to most of the patients we see

The Controversy Is Dead, Long Live the Controversy!

- Irrational exuberance vs irrational backlash
- Science can help us understand the biological differences among women, their unique mental and physical vulnerabilities and help us develop strategies tailored for their individual needs.

WHI is not the end of HT,

nor is it the beginning of the end,

it is the end of the beginning.

Informed Consent

- Increase you and your patient's comfort level
- Recommended by major malpractice insurance company!
- Gyns do not require consent..
- *Should you consider it?*

Wyeth in Court

- 4,500 lawsuits filed for breast cancer
- Linda Reeves first to be settled September 2006
- Linda admits she did not read PI,
- Wyeth cleared
- 4,499 left to go……..

Consent Basic Elements

1. Treatment Alternatives
2. Risk of Therapy
   be both specific *and* vague
3. Benefits of Therapy
4. Monitoring of Therapy
5. Consent and agreement to review consent at time of refill

Malpractice Alert

Cancer, especially breast most common missed diagnosis!

Breast Management Pearls

1. Nobody knows their breasts better than their owner
2. Team effort
3. Low risk does not mean no risk
4. Tenderness does not always mean benign
5. Hands can't tell
6. If you can't find it or resolve it refer it.

7. Share the risk
8. If you have a lump take a chunk
9. Mammos can't always tell
10. Use mammo to rule cancer in *not* out
11. If you order it look at it
12. Never assume, get direct confirmation

13. Don't know if not written down
14. Assume it is cancer until proven otherwise
15. If you cannot get a definitive diagnosis have patient follow up every two months. Have patient notify you of any changes.

Formula for Management

1. Identify breast problem
2. Develop plan
3. Discuss, use team approach
4. Document, document
5. Evaluate tests ordered
6. Tracking system
7. Reminder system for patients to follow up

Informed Refusal

- Patients have the right to refuse any and all medical treatment and diagnostic procedures
- US courts have increasingly affirmed the right of patients to reject treatment even if it means that they will die

Ovarian cancer: Can we make the clinical diagnosis sooner? Smith LH et al. 2005

- Diagnosis delayed by 4 to 12 months
- GI work up 61 %
- Pelvic work up 25 %

Key Target Symptoms Ovarian Cancer

1. Abdominal pain
2. Abdominal bloating/swelling
3. Urinary urgency
4. Gastrointestinal symptoms
5. Pelvic pain

Management: Consider Ovarian cancer first in differential diagnosis

- Pelvic trans vaginal ultrasound
- CA 125

Then proceed with GI work up

Uterine Cancer

- Unusual vaginal bleeding or discharge
- Trouble urinating
- Pelvic pain
- Pain during intercourse

Common Signs and Symptoms of Pulmonary Embolism

- Unexplained shortness of breath
- Chest pain that gets worse with a deep breath, coughing, or chest movement
- Increased heart rate

General, less-specific signs and symptoms

- Anxiety or feelings of dread
- Lightheadedness
- Fainting
- Sweating

Signs and Symptoms of DVT

- Swelling of the leg or swelling along the vein in the leg.
- Pain or tenderness in the leg. Feeling of increased warmth in the area of the leg that is swollen or that hurts.
- Red or discolored skin on the affected leg.

Diagnosis Codes

- V15.81 Non compliance with treatment
- V62.6 Refusal of treatment due to religious reasons or conscience
- V64.2 Procedure not carried out because of patient's decision
- V58.69 Long term use of medications
- 995.20 Unspecified adverse effect of drug, medicinal and biological substance (due) to correct medicinal substance properly administered

Diagnosis

- Justify time for extended visit by coding 4 diagnoses if possible, (max # that fit)
- Do NOT bill Medicare for an OV that is used to prescribe Bio identical HRT or for salivary testing
- A9370 code for OV non covered service
- Principal Insurance will not pay for an OV if BHRT was Rx

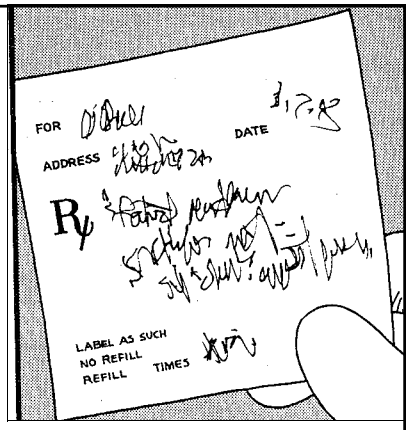
Colorado Statutes : TITLE 12-22-123. Labeling

- The purpose for which the anabolic steroid is being prescribed shall appear on the label
- FHU for hormone use
  or
- HRT Hormone replacement therapy

Three Rules to Prescribing

1. Keep it simple
2. Print / write it clearly
3. Avoid confusing abbreviations

The Scary thing is that doctors who write like this are out there doing surgery



0.1 Always use leading zeros

0.5 mg not .5 mg 0.5 not .5

2 Never never use trailing zeros

0.5 mg not .50 mg, not 0.50

5 mg not 5.0 mg, not 5.00 mg

DrugnameDose run together

Estradiol.5 mg Estriol2mg
Mistaken as Estradiol 1.5 not 0.5
Mistaken as Estriol 12 mg not 2 mg
EstrONE = E1 E1.5 mg, 0.5 mg E1
EstraDIOL = E2 E2.5, 0.5 mg E2
EsTRIOL = E3 E3.5, 0.5 mg E3
Leave lots of SPACE
E2 0.5 mg E3 0.5 mg Better yet
Write Estradiol 0.5 mg

Biest/P4/T 1.25/100/0.625

Biest/P4/T/DHEA 1.25/100/0.625/5

Biest 1.25 mg Prog 100 mg Test 0.625 mg per 2ml gel

Numericaldoseunit run together

The m is sometimes mistaken for a zero
10mg vs 10 mg

100ml vs 100 ml

Implementing Strategies to Optimize Your Patient's Longevity & Health

Presented by

Terry Grossman, MD

Implementing Strategies to Optimize Patient's Longevity

Terry Grossman M.D.
Frontier Medical Institute
Denver CO

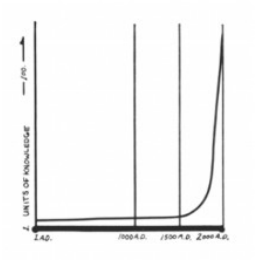
The idea of living to 100 has gone mainstream.

Time Magazine Cover Story
August 30, 2004

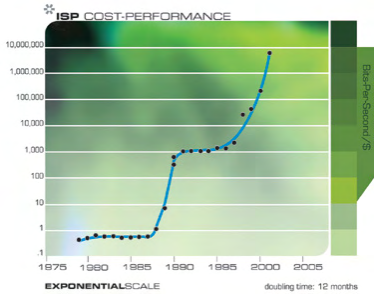
Ray Kurzweil - *The Law of Accelerating Returns*

- Change is accelerating *and* the rate at which change is occurring is accelerating as well
- This leads to exponential growth in exponential growth
- We Are Living in “Double Exponential Times”

Knowledge – Exponential Growth



ISP Cost Performance – Double Exponential Growth



Rate of Progress Is Accelerating

- **100 years of progress (1900 – 2000) now takes 20 years (2000-2020)**

Frontier Medical Institute

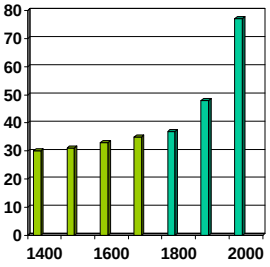
Frontier Medical Institute

Google

Frontier Medical Institute

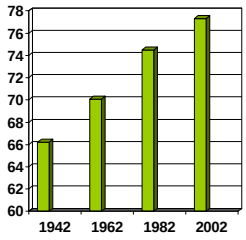
Double Exponential Growth

- **100 more yrs in 14 years (2020 – 2034)**
- **Then in 7 years (2034 – 2041)**
- **Then in 3½ years (2041 – 2044)**
- **Then in 1¾ years (2044 – 2046)**
- **By 2050, 2000 years of progress**
- **And by 2100, 20,000 yrs of progress**
  - at the current rate of progress



Life Expectancy Europe

Europe 1400 - 2002



Life Expectancy U.S.A. 1942 - 2002

Life Expectancy Increasing

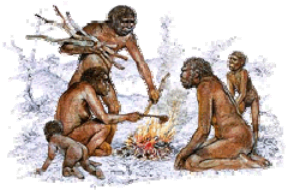
- **Life expectancy 2003 – 77.5 years**
- **Life expectancy 2004 – 77.9 years**

Life Expectancy Increasing Exponentially

- **Currently increasing at 3-5 additional months every year**
- **Within 25 years we may be increasing lifespan by 12 or more months every year**

(Biological) Evolution is NOT on Our Side

- **Biological evolution took place in an era of scarcity**
  - (Biological) Evolution favored a limited life span
  - The very old just used up limited material resources



Biological vs. Technological Evolution

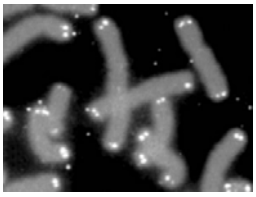
- **Biological Evolution**
  - The Fat Insulin Receptor (FIR) Gene
  - Designed to help us absorb and store as many fat calories as possible
- **Technological Evolution**
  - FIRKO (Fat Insulin Receptor Knockout)
  - Reprogram Our Biochemistry for life extension

Biological vs. Technological Evolution

- **Biological Evolution**
  - Telomere Shortening
  - Designed to guarantee shortened lifespan
  - Humans < 124 years
- **Technological Evolution**
  - Telomerase
  - Allows cells to indefinitely

Telomeres

- **End caps at ends of chromosomes**
- **Shortens each time chromosome reproduces**
- **Telomerase → immortality**
- **Telomere shortening guarantees finite life span**
- **Humans – 124 yrs**



Jeanne Calment

1875 – 1997

122 years, 164 days

The Rules Have Changed

- ***Biological*** **evolution took place in a world of scarcity**
- ***Technological*** **evolution is taking place in an era of abundance**

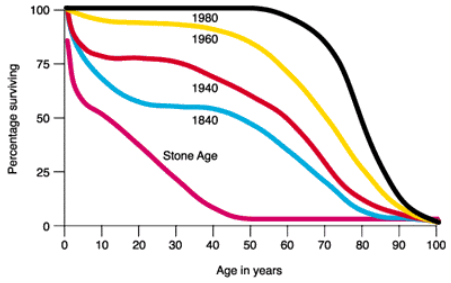
Old View of Aging

New View of Aging

Bob Delmonteque -- Age 84

Getting Older Without "Aging"

Squaring the Curve



Life

Metabolism → Damage → Disease

Eating

Exercise

Heart Disease

Cancer

Diabetes

Antiaging Medicine

Conventional Medicine

Living → Aging → Dying

Prevention

Early Detection

Treat Disease

After It Occurs

It is Possible to Grow Older Without Aging

Most Common Diseases of Old Age

- **Arthritis** **50%**
- **High blood pressure, heart** **32%**
- **Diabetes** **11%**

- **Hearing loss** **32%**
- **Decreased vision** **26%**

Human bodies are not breaking down the way they used to

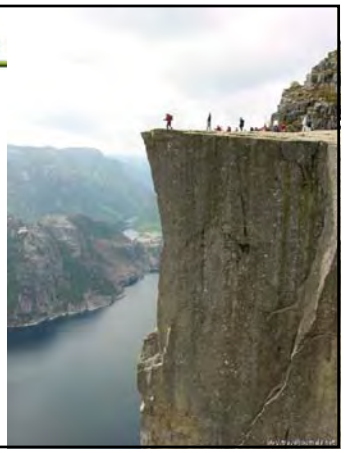
"Many chronic ailments like heart disease, lung disease and arthritis are occurring an average of **10 to 25 years later** than they used to. There is also less disability among older people today, according to a federal study that directly measures it."

New York Times, July 30, 2006

People Don't Get Sick Overnight

- The leading causes of death (heart disease, cancer, stroke, diabetes, kidney disease, liver disease) do not happen suddenly (although they appear to).
- They are the end result of decades-long processes.

- **You can assess where you are personally** in the progression of these processes
- **And stop (and reverse)** the lethal march towards these diseases



Most degenerative diseases have no symptoms until. . . It is too late.

- **2/3 of cardiac patients receive their first warning by suffering a heart attack**

Two Very Important Tools

- **Prevention**
  - Don't allow disease a foothold
- **Early Detection**
  - If unable to prevent completely, detect disease while it's still curable
  - Use new, non-invasive tests for cardiovascular disease, cancer and other diseases that didn't exist a few years ago

Disease Prevention

- **Diet & Calorie Reduction**
- **Exercise**
- **Stress Management**
- **Nutritional Supplementation**
- **Detoxification**
- **Care of the Brain**

Diet

- **Four sources of calories**
  - Carbohydrates
  - Proteins
  - Fats
  - Alcohol

Carbohydrates

- **Good Carbohydrates**
  - Whole grains (brown rice)
  - Beans, Lentils
  - Vegetables (green, above ground)
  - Fruits (melons and berries best)

Carbohydrates

- **Bad Carbohydrates**
  - Sugars, sweets
  - Refined flour products
  - Bread
  - Vegetables (root, below ground)
  - Fruit juices
  - Tropical fruits (bananas, pineapple, papaya)

Excess Weight – A Very Big (and Expensive) Problem

- **64 percent of US adults age 20 years and over (120 million) are overweight**
- **30 percent of adults age 20 years and over are obese (30 percent above ideal weight)**
  - 34% of women
  - 28% of men
- **Extra weight costs the nation about $100 billion in annual medical bills**

The NEW ENGLAND JOURNAL of MEDICINE

A Potential Decline in Life Expectancy in the United States in the 21st Century

"From our analysis of the effect of obesity on longevity, we conclude that the steady rise in life expectancy during the past two centuries may soon come to an end."

Olshansky SJ et al. NEJM 352:1138-1145 3/17/2005

Soft Drinks

- **Largest part of sugar consumption**
- **Average American drinks 53 gallons of soft drinks/ yr**
- **Equal to 565 cans/ year**
- **Has doubled in the past 30 years**

We Associate Sugar With Love

- Names for people we love
- Special holidays in celebration of sugar
- So people think sugar is a good thing

Longevity Rule #1

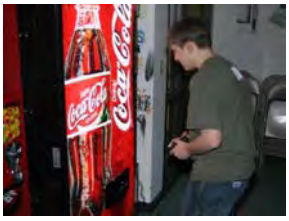
- Eat less sugar
- And foods that turn into sugar quickly

(Biological) Evolution Big Problem #1

- We are genetically programmed to crave sugar

What Are We Teaching Our Kids?

- One out of six elementary school children is now overweight



Public Health Recognizes Sugar As a Health Problem

- WHO (2003): "Diet, Nutrition and the Prevention of Chronic Diseases"
- Suggests people worldwide cut the total calories they get from simple sugars from 25 percent to less than 10 percent
- Advice was ignored by the US FDA due to pressure from sugar lobby

Health Problems from Sugar

Sugar causes metabolic problems in two ways

#1: Sugar is very easily converted into fat

#2: Eating Sugar causes Insulin levels to rise very quickly → metabolic syndrome

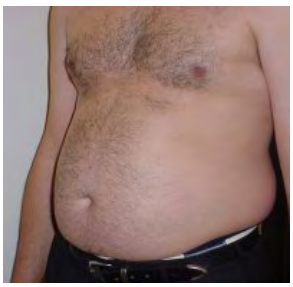
Metabolic Syndrome

- Excess amounts of sugar and high glycemic foods for too long
- Tissues become resistant to insulin
- “Normal" levels of insulin don’t lower blood sugar
- Pancreas needs to excrete increasing amounts of insulin to bring blood sugar levels down.

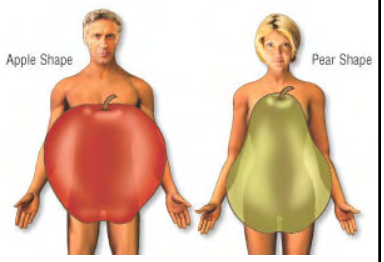
Metabolic Syndrome

- **Very common** – 25 percent of adults
- **To diagnose need 3 of the following 5:**
  - BP > 135/85 (no Rx)
  - Waist circumference >40” (men), >35” (women)
  - Fasting glucose >99
  - Triglycerides >150
  - HDL-cholesterol <40 (men), <50 (women)

Metabolic Syndrome – Body Type



- **Normal**
  - Men: Celery
  - Women: Hourglass
- **Metabolic Syndrome**
  - Men and Women: Apples



Metabolic Syndrome Speeds AGING

- **Increases risk of**
  - Heart disease
  - Cancer
  - Alzheimer's disease
  - Diabetes
  - High blood pressure

Treatment of Metabolic Syndrome

- Completely avoidable with proper diet and weight control
- Diet: avoid sugar and high glycemic foods
- Weight loss: smaller fat cells need less insulin

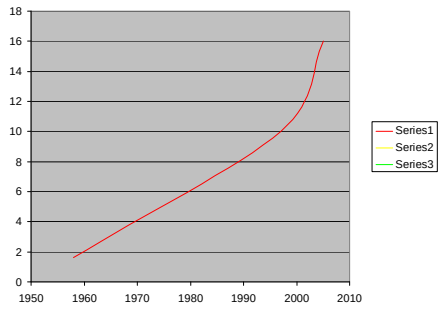
Eventually pancreas “wears out” and can’t keep up with producing the large amounts of insulin needed day after day →Type II Diabetes

Increase in Type II Diabetes – U.S.

- **1.6 million in 1958**
- **10 million in 1997**
- **16 million in 2005**
- **800,000 new cases diagnosed each year**

- **Type 2 diabetes reduces life expectancy by 15 years**
  - Lancet July 1, 2006, Vol. 368, No. 9529: 29-36

Incidence Type 2 Diabetes – US



Longevity Rule #2

- **Keep insulin levels low**

Proteins

- **Good Protein**
  - Fish, seafood (low mercury best)
  - Skinless poultry
  - Lean red meat (buffalo)
  - Non-fat dairy
  - Vegetable protein (soy-based foods – tofu, soy milk)

Proteins

- **Bad Protein**
  - Fatty red meat
  - Egg yolks
  - Full fat dairy

Fats

- **Good Fats**
  - Fat from fish and fish oil
  - Olive Oil
  - Avocado
  - Nuts, Seeds
- **Bad Fats**
  - Deep fried foods
  - Vegetable oils
  - "Fake" or "trans" fats (margarine)

(Biological) Evolution Big Problem #2

- **We are genetically programmed to crave fat**

What Are We Teaching Our Kids?

- **Fast food outlets in their schools**

Alcohol – Good & Bad

- **Good alcohol**
  - Red wine
  - High in phytonutrients, resveratrol
- **Not so good alcohol**
  - Beer
    - Causes fat – high in amylose
  - Distilled spirits (hard liquor) – high glycemic

Caloric Restriction

- **Restricting calories extends life in animal experiments**
  - Only proven method to extend animal lifespan
- **Also extends** health span
- **Excess weight shortens life**

Okinawa

- **Okinawans live longer than any people on earth**
- **Men 78 yrs**
- **Women 86 yrs**
- **Not due to genetics, but due to lifestyle**

Okinawa Elders

- **Okinawan elders are thin**
  - BMI 18-22 (lean <23)
- **Follow traditional lifestyle**
  - Remain physically active
  - Eat low calorie, high complex carbohydrate diet
- **"Hara hachi bu" – Stomach 80% full**

Okinawan Elders

Not Just Long Life – Healthy Live

97 year old karate master

Younger Okinawans

- **Younger Okinawans**
  - Adopting "modern" diets and lifestyles
  - BMI 26 – similar to US and highest in Japan

Compare to U.S. – Land of Bad Lifestyle Choices

- **Leading cause of death in US – Poor lifestyle choices**
- Half of US Deaths Caused by Easily Preventable Risk Factors
  - #1 – Tobacco (18.1%)
  - #2 – Bad Diet and Lack of Exercise (16.6%)
    - JAMA 9 Mar 2004

MacDonald's "Big Mac" Hamburger

A Better

"Big Mac"

"Caloric restriction without the restriction"

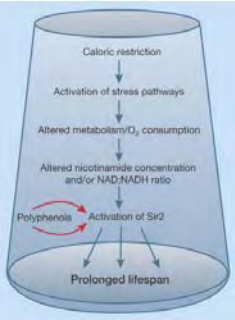
- **CR - Mimetics**
- **Drugs that simulate caloric restriction in the body**
- **FIRKO mouse model**
- **Resveratrol – red wine extract**

Resveratrol

- **Extract of red wine**
- **Mimics the effects of caloric restriction**

Sir2 Enzyme

- **Yeast**
- **Fruit flies**
- **Worms**
- **Mice**
- **Humans?**



Longevity Rule #3

- **Reduce calories**
- **(Or take a CR-mimetic like resveratrol)**

Exercise – Physical Activity

- **Three Types Needed for Optimal Health**
  - Aerobic Training
  - Weight Training
  - Flexibility Training

(Biological) Evolution Big Problem #3

- **We are genetically programmed to prefer rest to exercise whenever possible**

What Are We Teaching Our Kids?

- **AHA recommends that all school aged children get 30 minutes of PE every day**
  - 8% of elementary schools
  - 6.4% of middle/junior high schools
  - 5.8% of senior high schools

Aerobic Training

- **60-80% of MPHR (220-age) for 30 minutes 3-5 times a week**
- **At 40 years old, HR 108 – 144**
- **At 60 yrs old, HR 96 – 128**

Aerobic Training More Important than Lowering Cholesterol for Preventing Heart Attacks

- **25,000 executives**
- **Lowest 20% of physical fitness a greater risk factor for heart attack than cholesterol > 240**
- **Low fitness caused 3x as many CVD deaths as high cholesterol**
  - M Wei et al. JAMA. 1999 Oct 27;282(16):1547-53.

Basic Aerobic Prescription

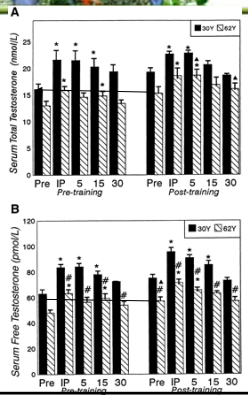
- **Try for 30 minutes every day**
- **Heart rate at 60 – 80 percent of MPHR**
- **Jogging, racquetball, tennis, cycling, biking**
- **Evaluate for risks**

Weight Training

- **More important as you get older**
- **Do in addition to aerobic exercise**

Weight Training – Secret to Healthy Aging

- **Increases levels of anti aging hormones**
  - Testosterone
  - Growth hormone
  - DHEA



• Strength Training increases testosterone levels in 60 yr olds to 30 yr old levels

• Kraemer WJ et al. Effects of heavy-resistance training on hormonal response patterns in younger vs. older men. J Appl Physiol. 1999 Sep;87(3):982-92.

Flexibility Training

- **Tendons and ligaments shorten with age**
- **Make part of your aerobics & weight training**
- **More important AFTER than before**

It's never too late to get fit

- **Study of 10,000 individuals of <u>all ages</u>**
- **Least fit who improved their fitness over 5 year period → Cut their risk of death from CVD in half**
  - SN Blair. JAMA. 1995 Apr 12;273(14):1093-8.

Longevity Rule #4: Exercise (Almost) Every Day

1) **Aerobic Exercise: 30 minutes a day**
   1) Do aerobic exercise to stay alive
2) **Weight Training: 15 – 45 minutes 1 – 3 times a week**
   1) Do weight training to stay young
3) **Flexibility Training: After each of the above**
   - Do flexibility training to not hurt – and to be able to keep doing 1) and 2) above

Stress

Manage Stress

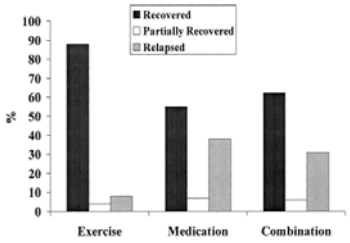
- **Hobbies**
- **Massage**
- **Vacations & mini-vacations**
- **Supplements**

EFT – Emotional Freedom Technique

- **Uses acupressure to bring about emotional healing**

www.emofree.com

Alpha Stim



Babyak M et al. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. Psychosom Med. 2000 Sep-Oct;62(5):633-8.

Longevity Rule #5

- **Control stress**

Nutritional Supplements

Nutritional Supplements

- **Most chemical reaction in the body require enzymes**
- **Many enzymes require two co-factors:**
  - A vitamin co-factor
  - A mineral co-factor

RDA vs. ONA

- **RDA – Recommended Dietary Allowance**
- **ONA – Optimal Nutritional Allowance**

National Institutes of Health

- Calcium and Vitamin D reduce risk of osteoporosis
- Selenium reduces risk of prostate, lung and colon cancer
- Vitamin E reduces risk of heart disease (women)
- Vitamin A and zinc reduce stomach cancer risk
- Zinc, beta-carotene, vitamins C and E help prevent macular degeneration

A Basic Anti Aging Program

- Multiple Vitamin/ Mineral
- EPA/ DHA
- Anti aging antioxidants

Longevity Rule #6

- Take basic nutritional supplements

Detoxification

"We've got to pause and ask ourselves – how much clean air do we need?" Lee Iacocoa

Detoxification

- **Eat organic produce**
- **Free range beef/ poultry**
- **Sweat more**
  - Exercise, saunas
- **Watercress, pomegranate juice**
- **Drink more water**

Drink Ionized Water

- Most people chronically dehydrated
- Need ½ oz per pound body weight
- Like taking antioxidants when drinking water

Lymphatic Detoxification

Rebounders

Saunas

Longevity Rule #7

- Reduce & remove toxins

Care for Your Brain

Care for Your Brain

- **"Use it or lose it" – stay mentally active**
  - Take a class
  - Learn something entirely new – a new language
- **New hobbies to stimulate your "right brain" – art, sculpture, photography, writing**
- **Avoid excessive stress**
  - Stress destroys memory
- **Nutritional supplements**

Supplements for Your Brain

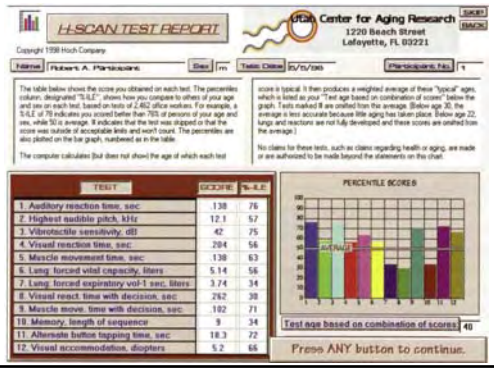
- **Vinpocetine**
- **Phosphatidylserine**
- **Phosphatidylcholine**
- **Ginkgo biloba**

Early Detection of Disease – How Practitioners Can Help Patients

Perform Extended Medical Evaluations

- **Don't rely on the standard "Annual physical"**
- **Use the latest diagnostic tools and tests**
- **Emphasis on noninvasive methods**
- **Determine current status and uncover any risks or predispositions to disease so that disease can be prevented as much as possible**

Biological Age Measurement



Cardiovascular Evaluation

- **Almost all adults have Coronary Artery Disease**
- **Cardiovascular Disease is the #1 killer in US -- 43% of all deaths**
- **Executive Physical: Longevity Evaluation**
  - Blood Tests
  - Imaging & Physiological Tests

Don't Accept "Good" Strive for Optimal

- **Total Cholesterol**
  - Good <200 Optimal 160 – 180
- **LDL – C**
  - Good < 130 Optimal < 80
- **HDL – C**
  - Good > 45, optimal > 60
- **Triglycerides**
  - Good < 150, optimal < 70

Homocysteine

- **Independent risk factor for heart disease**
- **Optimal < 7.5**
- **Excellent 7.6 – 9.5**
- **High risk > 15, any age**

C- Reactive Protein (CRP) – measures inflammation

- **Optimal < 1.2**
- **Acceptable 1.2 – 2.5**
- **Decreasing CRP levels associated with 6.5 months of increased life expectancy**
  - Blake CJ et al. Projected life-expectancy gains with statin therapy for individuals with elevated C-reactive protein levels. Am Coll Cardiol. 2002 Jul 3;40(1):49-55.

Optimal Vs. Good

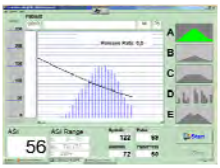
- **What are your chances of having a heart attack if you have these optimal levels?**
- **Essentially zero**

Cardiovascular – Imaging & Physiological Tests

- **Cardiovision Test of Artery Stiffness**
- **Dopplers of carotids and legs**
- **Exercise Treadmill**
- **Ultrafast CT Scan of Heart**

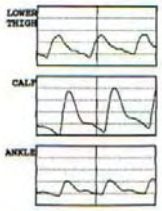
Cardiovision Test

Normal Result



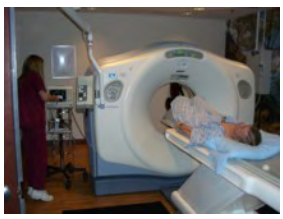
Arteriosclerosis
(Hardening of the Arteries)

Vascular Dopplers

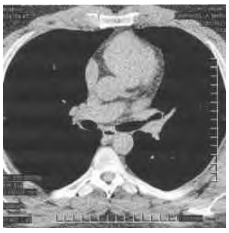


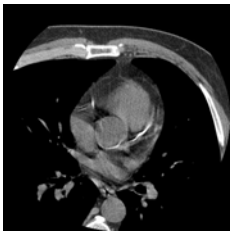
Exercise Treadmill Test

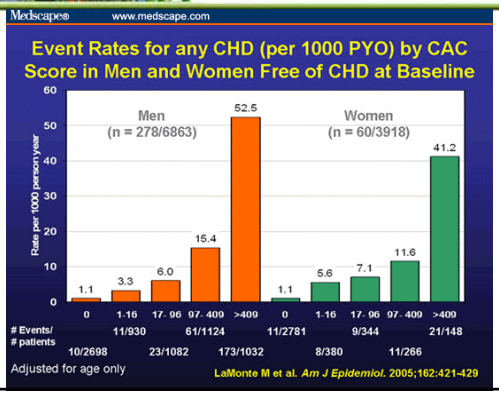
Ultrafast CT Scan of Heart



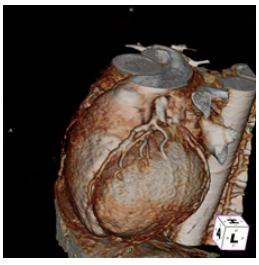
Coronary Calcium Score







CTA (CT Angiogram)



The End of Heart Disease

- **Middle-aged individuals can decrease their risk of heart problems by 57 percent by**
  - Eating right
  - Not smoking
  - Drinking in moderation
  - Maintaining a healthy weight
  - Exercising regularly

Gene Testing

Genomics

- **Don't test for genes that you can't do anything about**
- **Only test for genes that are known to increase risk**
- **And for which the risk can be reduced by lifestyle changes**

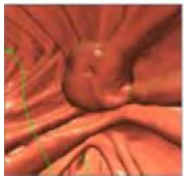
Apo E

- Apo E determines risk of Alzheimer's
- 2, 3 and 4 – two copies
- Apo E2 – protective vs. Alzheimer's
- Apo E3 – most common – 80% of people have 1 copy, 60% have 2 copies – average risk
- Apo E4 – significantly increased risk

Cancer Screening – Early Detection

- **Early Detection improves survival**
- **"Total body" CT scans – not recommended (radiation)**
- **Virtual exams – colonoscopy, bronchoscopy, etc.**

Virtual Colonoscopy



Swallowed Camera

Digestive Analysis

Hormone Testing

- **Estrogen**
- **Progesterone**
- **Testosterone**
- **DHEA**
- **Human Growth Hormone – IGF-1**
  - GH stimulation test
  - IGFBP-3

20 weeks of Bioidentical HRT

March 6
Pre Treatment

July 21 – 20 weeks of treatment

Minerals and Heavy Metals

Heavy Metals

- **Sweat!**
  - Saunas & exercise
- **Chelation**
  - Oral or iv
- **Supplements**
  - Cilanto, garlic, chlorella

Vitamins & Antioxidants

Hepatic Detox Profile


HEPATIC DETOX PROFILE

Frontier Medical Institute

Additional Tests

- **Free radicals**
- **Adrenal stress index**
- **Brain neurotransmitter levels**
- **Tests for Inflammation, methylation and glycation**
- **Body Impedance – body fat and daily calories**

Frontier Medical Institute

CASE PRESENTATION – Patient KT

Initial Longevity Evaluation – May 7, 2001

Follow Up Longevity Evaluation – March 20, 2006

Vital Signs

- **May 7, 2001**
- **Bp 123/84**
- **Weight 143 lb**
- **Body Fat 14.4%**

- **March 20, 2006**
- **BP 111/72**
- **Weight 138 lb**
- **Body Fat 12.8%**

Sugar Metabolism

- **May 7, 2001**
  - Glucose 114
  - Hb A1c 6.1
- **March 20, 2006**
  - Glucose 90
  - Hb A1c 5.7

Ultrafast CT Scan Coronary Arteries – May 20, 2006

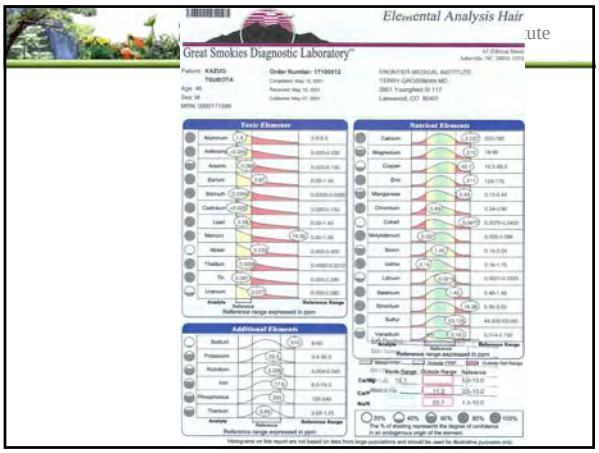
Ranking Guide

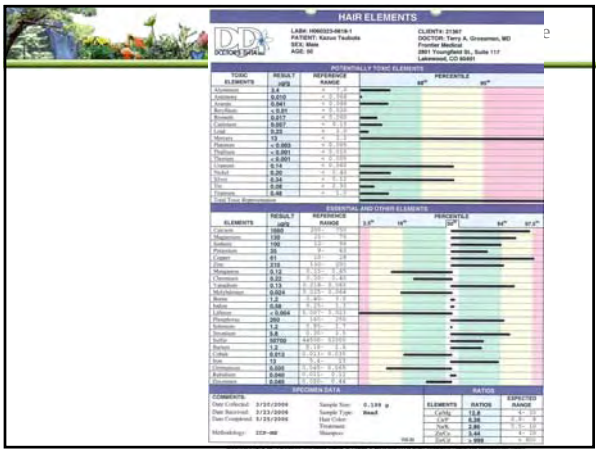
Your score of 0 places you in the 10 percentile rank. That means 90 percent of the r ule at the ages from 46 to 50 will have a higher calcium score than you.

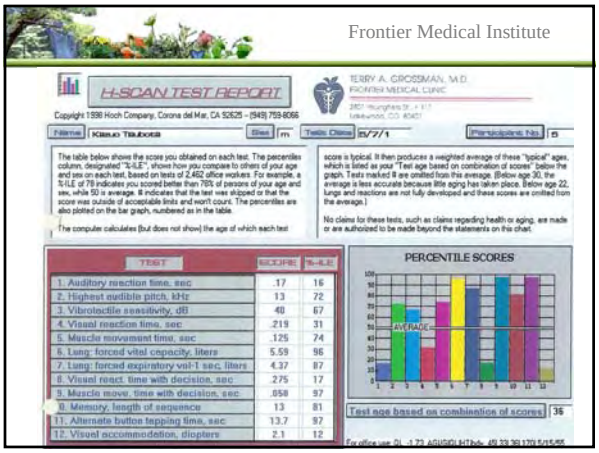
Category Table

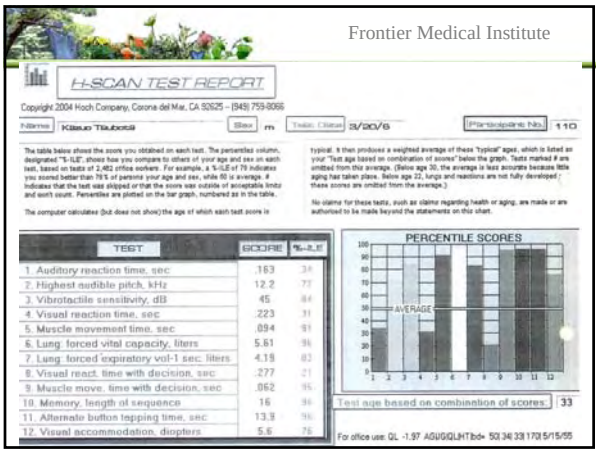
Diagnosis	No identifiable plaque. Very low risk of cardiovascular disease.
Clinical Interpretation	Significant coronary artery disease is very unlikely (95 % negative predictive value).
Recommended Clinical Action	Continue preventative measures, including healthy diet (low in saturated fat and cholesterol), no smoking, and maintain recommended weight.

CORONARY	Volume 130	AJ-130
Left Main Artery (LMA)	0	0
Left Anterior Descending (LAD)	0	0
Left Circumflex (LCX)	0	0
Right Coronary Artery (RCA)	0	0
Posterior Descending Artery (PDA)	0	0
A	0	0
B	0	0
C	0	0
Total	0	0


Elemental Analysis Hair
Great Smokies Diagnostic Laboratory


HAIR ELEMENTS


Frontier Medical Institute
H-SCAN TEST REPORT
TERRY A. GROSSMAN, M.D.
FRONTIER MEDICAL CLINIC
PERCENTILE SCORES



H-SCAN TEST REPORT

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Name: Klaus Tiubotti | Sex: m | Test Date: 3/20/6 | Participant No.: 110

TEST	SCORE	%-ILE
1. Auditory reaction time, sec	.163	34
2. Highest audible pitch, kHz	12.2	77
3. Vibrotactile sensitivity, dB	45	84
4. Visual reaction time, sec	.223	31
5. Muscle movement time, sec	.094	91
6. Lung: forced vital capacity, liters	5.61	96
7. Lung: forced expiratory vol-1 sec, liters	4.19	82
8. Visual react. time with decision, sec	.277	21
9. Muscle move. time with decision, sec	.062	95
10. Memory, length of sequence	16	98
11. Alternate button tapping time, sec	13.9	96
12. Visual accommodation, diopters	5.6	76

PERCENTILE SCORES

AVERAGE

Test age based on combination of scores: 33

For office use: QL -1.97 AGUGIQLHT bd= 50 34 33 17 0 5/15/55

- **May 7, 2001**
  - Chronological Age 45
  - Biological Age 36
- **March 20, 2006**
  - Chronological Age 50
  - Biological Age 33
- **Net Change = 8 years younger**

Longevity Rule #8

- **Get periodic Comprehensive Longevity Health Evaluations**

Leading Causes of Death Today

- **Heart disease – 33 percent**
- **Cancer – 22 percent**
- **Stroke – 8 percent**
- **These could essentially disappear within the next 20 years**

The 21st century is worth living to experience. . .

<u>Why not see all of it?</u>

Terry Grossman, M.D.
Frontier Medical Institute
2801 Youngfield St.
Suite 117
Golden CO 80401
(303) 233-4247

www.fmiclinic.com
terry@fmiclinic.com