TURNING DOWN THE HEAT ON MENOPAUSE

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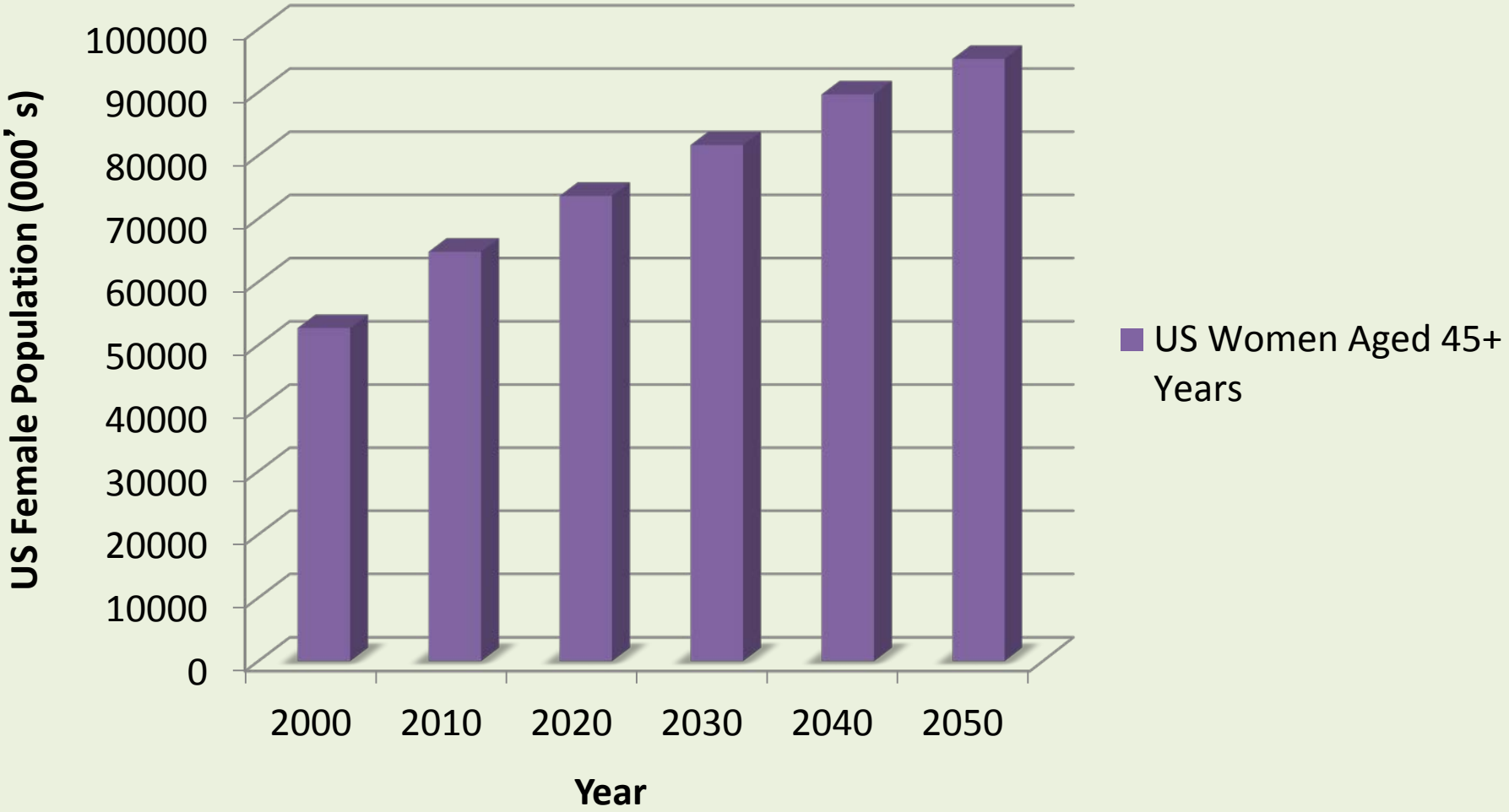
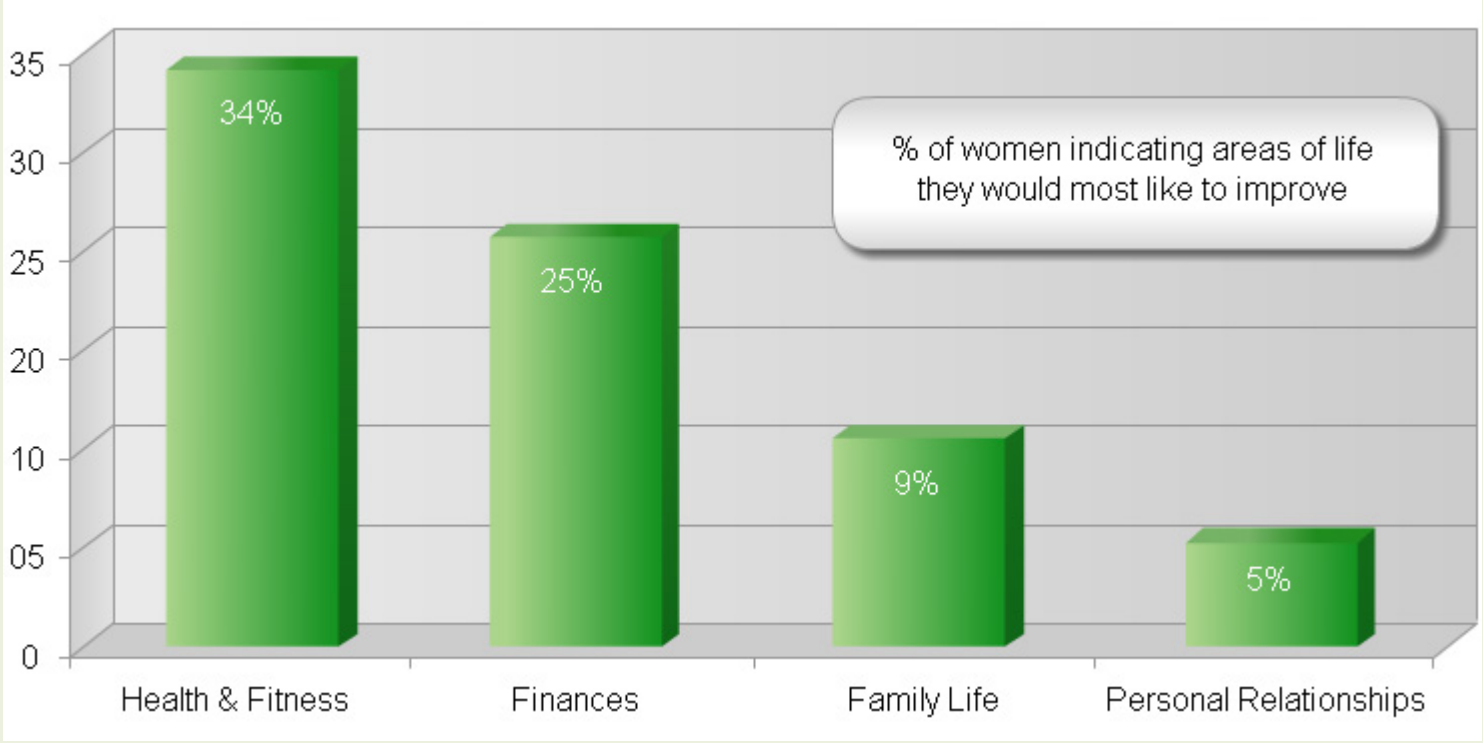
U.S. Census Bureau, 2004



"http://www.census.gov/ipc/www/usinterimproj/"

Top Priority: Better Health



Data Source: Legato, MA, et al., "Women's perception of their general health, with special reference to coronary artery disease: Results of a national telephone survey, Journal of Women's Health" Vol. VI, No 2, 1997.

Better Health Means… PREVENTION!!!!

- ✓ Better conventional options to prevent disease
- ✓ Better integration of quality of life issues into conventional health care
- ✓ Better quality of life meaning less frailty and disease driven life
- ✓ Ideal Body Weight

Why Is Hormone Therapy Important?

- HRT as standard of care
- Quality of life
- Quality of care
- Aging population
- Cost of healthcare
- Sea of misinformation and fear

Menopause / Andropause Population

Menopause	Andropause
▪ 52 million women will reach menopause in the next decade. ▪ Half will live a third of their life beyond menopause. ▪ Only 20% (7 million) of these women currently utilize hormonal therapy (non- hysterectomized women); 55% of users do not stay on therapy beyond 6 months.	▪ 60 million men over the age of 50 in the US. ▪ More than 30% will live another three decades. ▪ Low testosterone and hypothyroidism are rampant in this population and rarely diagnosed. ▪ Treatment with testosterone is rarely a first line therapy .

Solutions for better health leading to “TRUE PREVENTION”

- Providers must return to Patient Centric Medicine
- Focus on patient and his/her individual needs
- Use information from testing solely to integrate into individual clinical picture
- Become the patient’s partner and advocate
- Represent only the patient’s interest
- Be aware of personal bias and ego and eliminate them from relationship with patient
- Integrate human identical hormones into the practice of prevention and medicine in general

Women's HRT History

1900

1889 Merck manual – Ovariin – oral powder derived from dried cow's ovaries – as treatment for "climacterica"

1910

1920

1922 Allen and Doisy discover estrogen and identify the ovarian cycle and the hormones involved.

1930

1936- Schering in Germany and Richter in Hungary develop oral contraceptives.

1939 Allen and Doisy *Sex and Internal Secretions* (estrogen can cause cancer).

1940

Nobel Prize Adolph Butenandt for estrogen from pregnant mare's urine – Schering.

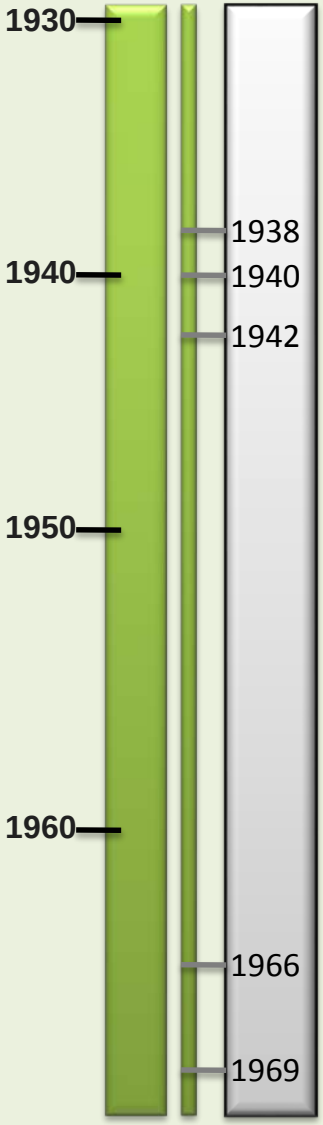
1942 Ayerst brings Premarin to the market.

1950

1951- Madeline Gray's book "*The Changing Years*" propels Premarin

1960

Different Non-Human-Identical Estrogens



1938 Nature – DES – Inexpensive – Charlie Dodds.

1940 Jo. of NCI - Shimkin - Stilbestrol causes breast cancer in males and females.

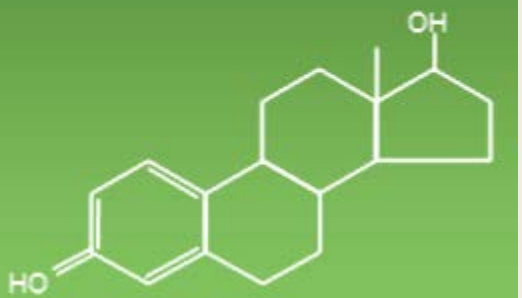
1942 McKenna gets FDA approval for Premarin in spite of data about Endometrial cancer available.

1966 Robert Wilson Feminine Forever (Searle, Ayerst and Upjohn sponsor his Research Foundation.

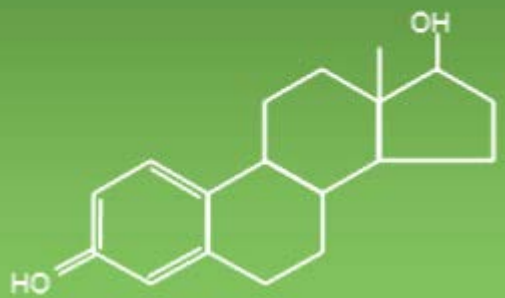
1969 David Reuben - *Everything you always wanted to know about sex.*

Estrogen (Estradiol)

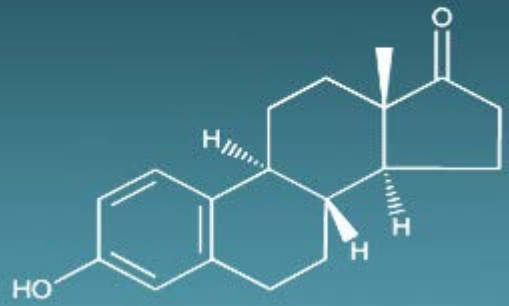
Natural Bioidentical Estradiol



Human Estradiol



Premarin



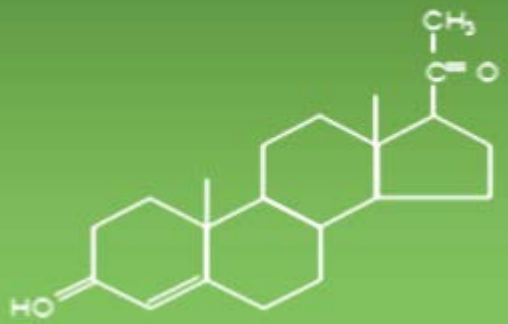
CEE (Premarin) is composed of 200 molecules.

Only 3 of them are similar to human estrogen:

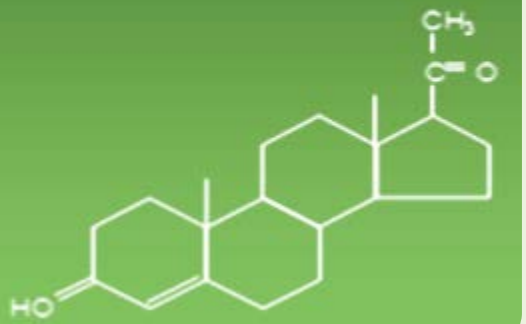
Equilin, Equilenin and Estrone

Progesterone

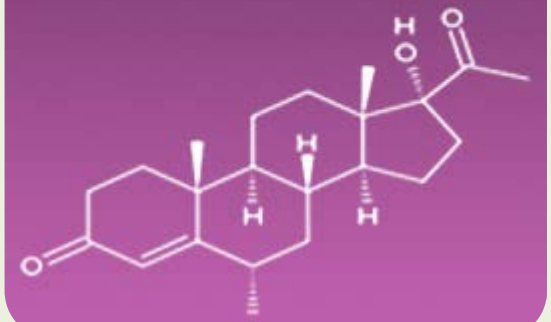
Natural Progesterone



Human Progesterone



MPA – Medroxyprogesterone 17-Acetate



Review of W.H.I. Study

Summary:

- 16,608 women ages 50-79 (avg age 63). → Avg 13.4 years post-menopause.
- Multi-year study compared synthetic (CEE + MPA) HRT: Premarin, Provera, Prempro vs. placebo.
- Only oral medications were administered (no transdermal).
- Trial ended in 2002 (3 years early) due to consistent presence of results linking synthetic HRT to increased risk for CVD, stroke and VTE.

Limitations:

- Average age of study population was 63 and 10+ years post-menopause.
- Did not include bioidentical hormones.
- Did not include transdermal formulations.
- Did not address confounding factors (advanced age, smoking, chronic illnesses, etc.)
- Results nontransferable to bioidentical hormone therapies (BHRT) or to younger, healthier women.

It was clear that the trial had shown physicians something highly important about the perils of starting older postmenopausal women (qualifier No. 1) on pills (No. 2) containing equine estrogens (No. 3) plus MPA (No. 4).

The New York Times Magazine, "The Estrogen Dilemma," April 12, 2010

Different Molecules Affect the Human Body Differently

Fitzpatrick LA et. al.	Comparison of regimens containing oral micronized progesterone or medroxyprogesterone acetate on quality of life in postmenopausal women: a cross sectional survey.	J Womens Health Gen Based Med 2000;9(4):381-7
Lippert T, Seeger H, Mueck A.	Pharmacology and toxicology of different estrogens.	G Endo.2001;15:26-33
Schindler A, Compagnoli C.	Classification and pharmacology of progestins.	Maturitas 2003;46:S7-16
Stanczyck FZ.	All progestins are not created equal.	Steroids 2003;68:879-90
Schindler A.	European Progestin Club. Differential effects of progestins.	Maturitas 2003;46:S3-5
Jernstrom H, Bendahl P.	A prospective study of different types of hormone replacement therapy use and the risk of subsequent breast cancer: the Women's Health in the Lund Area (WHILA) study (Sweden).	Cancer Causes Control 2003;14:673-80
Schindler A.	European Progestin Club. Differential effects of progestins.	Maturitas 2003;46:S3-5
Zegura B, Guzic-Salobir B.	The effects of various menopausal hormone therapies on markers of inflammation, coagulation, fibrinolysis, lipids, and lipoproteins in healthy postmenopausal women.	Menopause 2006;13(4):643-50
Ribot C, Tremollieres F.	Hormone replacement therapy in postmenopausal women. All treatments are not the same.	Gynecol Obstet Fertil 2007;35:1-10

2011-INTERNATIONAL MENOPAUSE SOCIETY TAKEAWAYS ON FEMALE HORMONES

- **No “class” effect**
- **HRT more help than harm**
- **Window hypothesis**
- **17-beta estradiol and micronized progesterone preferable active hormones to use in HRT**

KEEPS

- 727 women mean age was 52,
- Within three years of the start of menopause, and stringent standards of health.
- 3 treatment groups.
  - Oral Premarin and Prometrium for the first 12 days of the month.
  - Trans dermal Climara estradiol patches and cyclical Prometrium.
  - Placebo patch or pill and placebo Prometrium.

KEEPS results

North American Menopause Society (NAMS) 2012

-Neither Premarin nor Estradiol affected systolic or diastolic pressure significantly (in contrast to WHI where the higher dose, older women and sole use of synthetic hormones DID)

-Oral Premarin increased HDL, decreased LDL and increased TG

-TD- estradiol improved insulin sensitivity (lowered insulin resistance) following insulin and glucose levels as “HOMA-IR”

-No detectable effects on progression of atherosclerosis assessed via carotid ultrasound and a non-significant trend toward less accumulation of coronary artery calcium (CAC)

-Improvement in hot flashes, night sweats, mood, sexual function, and bone density with HT not placebo

-No significant differences in adverse effects (breast cancer, endometrial cancer, myocardial infarction, TIA, stroke or venous thromboembolic disease) were found among groups.

- Absolute number of events was so small that definitive conclusions could not be drawn.

What if anything have we learned from KEEPS

- Risk-to- benefit ratio favors HT for symptoms
- Confirmed the risk of adverse events from HT very small
- Outweighed by the many proven quality-of-life benefits

KEEPS

Question:

What if improved quality of life leads to less disease and healthy aging?

DANISH STUDY-BMJ-Oct. 2012

- 16 year randomized study
- 1006 healthy women
- 45-58 year old (average 50)
- Women with intact uterus: 17 beta-estradiol and norethisterone acetate/ Hysterectomized women: unopposed 17 beta-estradiol
- Excluded pre-existing diseases (cancer or cardiac disease)
- Endpoint was death, admission to hospital for heart failure or MI

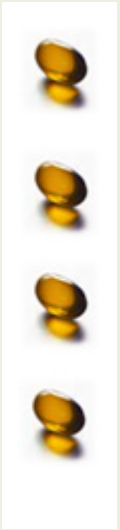
Danish Study Outcome

- 10 years of randomized treatment
- Women receiving HT early after menopause
  - significantly reduced risk of mortality
  - significantly reduced risk of heart failure
  - Significantly reduced risk of myocardial infarction
  - No increase in risk of cancer,
  - No increase in risk of thromboembolism
  - No increase in risk of stroke

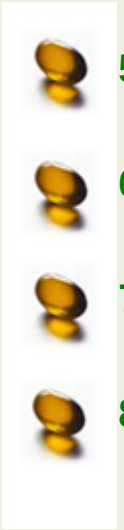
DANISH Study- Limitations

- 2 mg of oral estradiol, (a relatively high dose- our average dose is 1.2 mg estradiol in transdermal form)
- Noresthisterone, an androgenic progestin not used in the US
- Didn't compare different types of estrogens
- Didn't compare different types of progestogens
- Didn't compare routes of delivery.
  - Transdermal estradiol instead vs. oral
  - Micronized progesterone vs. norethisterone acetate

What are the drugs most frequently sold in the US?



1. Antidepressants
2. Birth Control Pills
3. Anti-anxiety Meds
4. Statins



5. Sleeping Pills
6. Blood Pressure Meds
7. NSAIDs
8. Antihistamines

TURNING DOWN THE HEAT ON MENOPAUSE

1. **ESTRADIOL, PROGESTERONE, TESTOSTERONE**
2. **THYROID**
3. **HGH**
4. **GNRH**
5. **HORMONE PRECURSORS**
6. **VITAMINS AND SUPPLEMENTS**
7. **ADRENAL SUPPORT**
8. **DIET**
9. **EXERCISE**
10. **SLEEP**
11. **LIFESTYLE**
12. **INDIVIDUALIZED PROGRAMS**

Bioidentical Estrogen/Progesterone/Combination Preparations

Estrogen	Progesterone	Combinations
✓ 17-BETA ESTRADIOL ORAL (Alora, Climara, Esclim, Estrace) ✓ 17-BETA ESTRADIOL PATCHES (Fempatch, Vivelle-dot, Vivelle, Estraderm) ✓ ESTRADIOL TRANSDERMAL gel- Estrogel, Elestrin ✓ COMPOUNDED ESTRADIOL CREAMS, CAPSULES, TROCHES, SUPPOSITORIES	✓ PROGESTERONE IN PEANUT OIL CAPSULES (Prometrium) ✓ PROGESTERONE VAGINAL GEL (Crinone, Prochieve) ✓ COMPOUNDED CREAMS, CAPSULES, TROCHES, SUPPOSITORIES	✓AVAILABLE ONLY COMPOUNDED OTHERWISE THEY ARE NOT EXCLUSIVELY BIOIDENTICAL

If you are prescribing compounded products you need:

- Know exactly what the patient is getting.
- Different compounders have different ways of making product, practitioner must know what the product looks like.
- No measuring involved – the easier it is to dispense, the more likely the patient will follow your directions.
- Easy dose adjustment within standardization chosen.
- User-friendly.
- Easy for practitioner to follow.
- East for the patient to use.
- If change in formulation, patient will report change in symptomatology and may think hormones do not work.
- Working in physiologic range of treatment presents different approach to therapy

The Use of Compounded Preparations

- Compound hormones individually when you first start to figure out individual patient needs.
- Do not mix hormones initially. Mixing will yield confusing results..
- Verify what is in the transdermal preparation/vehicle/base and read up on side-effects, absorbability, bioavailability.
- Understand the preparation and work with experienced MD as support/mentor at first (200-500 patients is a good start).
- Become an expert in one particular form of distribution.
- Do not skip around from one form to another, you'll never really know anything well.
- Subcutaneous pellets have many problems and are difficult to remove.
- Less is more and less invasive is better.

- **Remember the reason for treatment with hormones is to help patients feel better safely.**

Setting Expectations

- Expect improvement in 3-4 weeks.
- Side effects – very rare.
- Discontinue if patient is fearful.
- Patient must be directly involved in the treatment.
- Patient must feel confident and trust this is the correct course of action for him/her
- BHRT is only part of the picture – use it to make diet, exercise, life changes easier to implement.
- Help abolish cure-all mentality.

Chart review of 300 patients treated at the index practice at 200 W 57 St with E2/MP/T and Lifestyle changes over 3+ years