24 Hour Urine Steroid Testing

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O’Sullivan’s Rule

• “If you don’t know what’s wrong with your patient before you send them to the specialist, you won’t be any farther ahead after they come back”
  – John O’Sullivan MD

• If you don’t understand the lab test you are using, you won’t understand the patient any better after their test results come back.
Why do we test hormone levels?

- Endogenous hormones
  - Not making enough?
  - Making too much?
  - Lack of balance between several hormones may cause symptoms of hormone deficiency or excess
  - e.g. symptoms of high testosterone but testosterone level is normal

Endogenous Hormone Production

- **To a first approximation**, when people are making their own hormones, any of the popular testing modalities (serum, blood spot, saliva, urine) are able to identify significant hormone deficiency or hormone excess
- There is no gold standard way to measure hormones
- Each testing modality has its advantages and pitfalls
24 Hour Urine Collection

- Body runs according to a repeating rhythm
- Capture output during one complete cycle
- Wake up, empty bladder, e.g. 7 AM
- Collect all urine for next 24 hours, including when you wake up at night
- Empty bladder at 7 AM and add to the collection
- Mix well and send us a small fraction of the total collection
Mass Balance/Distribution

Sometimes we want to know: $A + B + C + D + E + F + G + H + I + J + K$

Sometimes we need to look at: $J/G$ and $(F + E)/G$
Hormone Testing and Hormone Supplementation

- We have this notion that hormone replacement simply involves restoring hormone levels to younger levels
- Target metaphor

We would like hormone replacement to go like this: test, supplement, retest, adjust “sliders” i.e. dose based on test results
• The numbers don’t mean the same thing in all situations
• Endogenous hormone ≠ Supplemented hormone
• Transdermal ≠ oral ≠ subcutaneous pellet ≠ patch ≠ troche ≠ injection ≠ vaginal
• Cream ≠ gel ≠ oil

• Hormone levels don’t always “line up”
  • e.g. low testosterone symptoms ↔ low serum total testosterone ↔ low serum bioavailable testosterone ↔ low salivary testosterone ↔ low urine testosterone

Why is it like this?
This stuff is complicated!!

• Reality Check:
  – There is no “Theory of Everything” for lab testing
  – There is no model that links all types of testing together, under all circumstances
Appropriate Use of Post-Supplementation Testing

- Troubleshooting when therapy isn’t working or stops working
- Absorption/formulation/compliance issues
- Metabolites: where are the parent hormones going from a biochemical standpoint?

- If we know this, we may avoid long term problems such as cancer, osteoporosis
- Don’t look to hormone testing to guide 10-20% dose adjustments

**FIGURE 1: CIRCULATION OF HORMONES**
**Conjugation**

- Conjugates are hormones that have extra bits stuck on them to render the molecules water-soluble
  - Extra bits (incomplete list):
    - Sulphate
    - Sugar e.g. glucuronide
    - Glutathione
    - Sulfonyl methane
- Conjugates are made in the liver and in many other tissues (e.g. skin, kidneys, breasts, gut mucosa)
- Conjugates may be considered as storage forms
- If overall hormone production is low or high, the level of conjugates should also be low or high
Oral hormone administration often results in the formation of conjugates and metabolites.

This is what we’d like to see

This is what we get

Estrogen Metabolism

Estradiol → Estrone

Estrone Sulphate (E1S) > 50%

4 hydroxyestrone

16 Hydroxyestrone

Only about 10% of an ingested dose of estradiol remains as estradiol

Estriol

Most of an oral dose of estradiol or estrone is rapidly converted to estrone and estrone metabolites and conjugates.
Inefficient! Hormone bound to SHBG or other carrier protein.
Serum vs Urine Testing

- Serum testing measures unconjugated hormones (unless specifically stated e.g. DHEAS)
- Urine testing measures conjugated hormones (unless specifically stated e.g. urinary free cortisol)
- **Serum and urine tests are looking at two different pools of hormone!**

Also, if you are sulphate deficient or lack cofactors for glucuronidation, that type of conjugate won't appear in urine as much.
Standard Urine Hormone Testing Measures Conjugates

- e.g. mix of conjugated estrogens
- estrone-3-sulphate: 12 mcg/L
- estrone-3-glucuronide: 8 mcg/L
- "urinary estrone": 20 mcg/L

Hydrolysis destroys information

Conjugated hormone

Unconjugated hormone

Hydrolysis destroys information

- Serum
  - hormone bound to albumin
  - free unconjugated
  - free conjugated
  - albumin

Urine

- This form may reflect what's going on in a specific tissue
- This form is heavily influenced by factors affecting the liver

A urinary hormone level is not the same as a serum hormone level e.g. urine "estradiol" is not the same as total serum estradiol
A urinary hormone level is not the same as a salivary hormone level. e.g., urine "estradiol" is not the same as salivary estradiol.
Urine Steroids Hormone Profile Webinar

November 21, 2012

Dr. George Gillson, MD, PhD

17-ketosteroids

Progestogens

17-hydroxysteroids

Mineralocorticoids

Estrogens

Estrogen Metabolism

Estradiol

Estrone

Estrone Sulphate (E1S)

4 hydroxyestrone

2 hydroxyestrone

16 Hydroxyestrone

Estriol
<table>
<thead>
<tr>
<th>Urinary Estrogens</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>5.3</td>
</tr>
<tr>
<td>Estrone</td>
<td>15.0</td>
</tr>
<tr>
<td>Estriol</td>
<td>11.1</td>
</tr>
<tr>
<td>16OH estrone</td>
<td>7.3</td>
</tr>
<tr>
<td>4OH estradiol</td>
<td>1.2</td>
</tr>
<tr>
<td>4OH estrone</td>
<td>3.1</td>
</tr>
<tr>
<td>2OH estradiol</td>
<td>3.6</td>
</tr>
<tr>
<td>2OH estrone</td>
<td>37.6</td>
</tr>
<tr>
<td>4methoxyestradiol</td>
<td>0.2</td>
</tr>
<tr>
<td>4methoxyestrone</td>
<td>0.5</td>
</tr>
<tr>
<td>2methoxyestradiol</td>
<td>0.7</td>
</tr>
<tr>
<td>2methoxyestrone</td>
<td>8.0</td>
</tr>
</tbody>
</table>


**Estrogen Quotient**

- EQ = E3/(E1 + E2)
- Studies by Henry Lemon indicated that in populations with a low incidence of breast cancer, **urinary** EQ > 1
- Caucasians normally have a urinary EQ <1 and are at increased risk for breast cancer relative to other races (e.g. Japanese eating traditional diet)
- Lemon postulated:
  - if the urinary excretion of estriol (E3) can be increased relative to the other estrogens, this will decrease the risk of breast cancer (make EQ >1)
<table>
<thead>
<tr>
<th>Urinary Estrogens</th>
<th>Adlercreutz</th>
<th>Xu</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Total</td>
<td>% of Total</td>
<td></td>
</tr>
<tr>
<td>Estradiol (E2)</td>
<td>7.6</td>
<td>5.3</td>
</tr>
<tr>
<td>Estrone (E1)</td>
<td>21.7</td>
<td>15.0</td>
</tr>
<tr>
<td>Estriol (E3)</td>
<td>13.4</td>
<td>11.1</td>
</tr>
<tr>
<td>EQ</td>
<td>0.46</td>
<td>0.55</td>
</tr>
</tbody>
</table>

EQ = E3/(E1 + E2)

EQ = 11.1/(15 + 5.3) = 0.55


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**Estrogen Quotient**

- Ways to increase urinary estriol levels include:
  - Iodine supplementation
  - Sea vegetables
  - Estriol!
- Caveats:
  - Iodine supplementation may be beneficial with respect to breast cancer for reasons which have nothing to do with estriol
  - Many interventions thought to reduce the risk of breast cancer also reduce urinary estriol excretion, e.g. indole-3-carbinol
Estradiol

 Estrone

 Estrone Sulphate (E1S)

 4 hydroxyestrone

 Accumulates in breast tumour cells
 Irreversibly damages DNA
 Damages oncogenes

 2 hydroxyestrone

 16 hydroxyestrone

 Estriol


 Estrone

 4-Hydroxyestrone

• Supplementation with antioxidant/detox-supporting nutrients may reduce formation of 4-hydroxyestrone:
  – Lipoic acid, curcumin, Vit A,C,E, green tea, Selenium, N-acetylcysteine

 4-Hydroxyestrone

 Estrogen-GSH conjugates

 GSTP

 Estrogen quinones

 GSH (glutathione)

 Harmful DNA adducts
Ways to Increase Glutathione

- SAMe
- Natural food sources of methionine: beans, eggs, fish, garlic, lentils & lean red meats & onions
- Whey protein e.g. Immunocal
- N-acetylcysteine (NAC)
- Lipoic acid
- Milk thistle
- Liposomal glutathione

Estrogen Oxidation

- Estradiol
- Estrone
  - CYP1B1
  - CYP3A5
- Estrone Sulphate (E1S)
  - CYP1A2
  - CYP3A1
  - 4 hydroxyestrone
    - CYP1A2
    - 2 hydroxyestrone
    - CYP3A4
    - CYP1A1
- 16 Hydroxyestrone
  - Estriol

4OHE1 / 2OHE1 may be a useful marker for assessment of breast cancer
A ratio > 0.15 may be associated with breast cancer
There is some shaky literature suggesting that 16OHE1 is a bad actor for breast cancer. A low ratio: 2OHE/16OHE1 may increase future risk of breast cancer.

2-16 Ratio

- All research was based on an immunoassay measuring: (2OHE1 + 2OHE2 + 2OHE3) / 16OHE1
- Cutoff was > 2, i.e. ratio greater than 2 implied reduced risk of breast cancer
- The data never had strong statistical significance, and were really only applicable to premenopausal women
- We never got a handle on the “flavour” of the numerator
- Mostly 2OHE1? 2OHE2? A balance of the two?
- Is one flavour worse than another?

- Newer methods (GCMSMS and LCMSMS) measure 2OHE1 / 16 OHE1 or 2OHE2 / 16OHE1
2-16 Ratio

- Reasoning used to derive a new cutoff is not valid
- The prospective studies should be repeated with new methodology

Methyl Donors and Estrogens

Proper breakdown of estrogens demands an adequate supply of methyl donors.
Reference Ranges

- Derived from clinically normal individuals
- Males > 21 yrs of age
- Follicular, luteal phase cycling females
- Postmenopausal females
- Female patients on hormones are referenced to unsupplemented luteal ranges
- Male patients on testosterone are referenced to the unsupplemented range

Reference Ranges

- Data from clinically normal people are modelled using a statistics program
- That allows us to calculate the percentile for a given result:
- Where in the “herd” does our patient sit?
Highest 2.5%

Lowest 2.5%

68% of the results from a normal population are in here, between the 16th and the 84th percentile

This is roughly equivalent to +/- 1 Standard Deviation on a bell curve
Catabolic and Anabolic Ratios

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Range</th>
<th>0%</th>
<th>20%</th>
<th>40%</th>
<th>60%</th>
<th>80%</th>
<th>100%</th>
<th>Total</th>
<th>Range Applied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total 17-Hydroxysteroids</td>
<td>4.550</td>
<td>2,500 - 5,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>51%</td>
<td>Lateral</td>
</tr>
<tr>
<td>Total 17-Ketosteroids</td>
<td>5.200</td>
<td>2,200 - 7,400</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>66%</td>
<td>Lateral</td>
</tr>
</tbody>
</table>

Anabolic: Catabolic Ratio

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Range</th>
<th>0%</th>
<th>20%</th>
<th>40%</th>
<th>60%</th>
<th>80%</th>
<th>100%</th>
<th>Total</th>
<th>Range Applied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anabolic 17KS / Catabolic 17HS</td>
<td>0.96</td>
<td>0.72 - 1.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>34%</td>
<td>Lateral</td>
</tr>
</tbody>
</table>

**17-ketosteroids**

**17-hydroxysteroids**

**Progestogens**

**Mineralocorticoids**

**Estrogens**
Other ratios such as 4OHE1 / 2OHE1 are calculated internally and presented in the commentary.

Result is below the instrumental detection limit.
Both E1 and E2 are < 0.5, so the ratio can only be estimated. This is done in the body of the interpretation.

\[ \frac{2.7}{1} = >2.7 \]

63 y.o. with BMI = 20. No estrogen supplementation, c/o vasomotor symptoms, vaginal dryness.
40 y.o. with BMI = 34.7  No estrogen supplementation
Where is her estrogen?
E2 is stored in adipose tissue in the form of fatty acid esters

60 y.o. male with complaints about erections
17-ketosteroids OK
E2 at 84th percentile
Not forming 2-methoxyestrone well
Zinc, methyl donors

### Urine Steroids Hormone Profile Webinar

**November 21, 2012**

**Dr. George Gillson, MD, PhD**

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#### Symptoms

- Nerve Flashes
- Night Sweats
- Low Sex Drive
- Fatigue
- Insomnia
- Low Blood Sugar
- Allergies
- Headaches
- Weight Gain/West

#### 57 y.o. male

- **Symptoms:** Myalgia, fatigue, allergies
- **Results:**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>%</th>
<th>0%</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>dehydroepiandrosterone (DHEA)</td>
<td>7.1</td>
<td>30–1,000</td>
<td>22%</td>
<td>71%</td>
<td>95%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>androsterone (AND)</td>
<td>1.5</td>
<td>1.8–6.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>testosterone (T)</td>
<td>1.4</td>
<td>19–69</td>
<td>15%</td>
<td>55%</td>
<td>85%</td>
<td>99%</td>
<td>100%</td>
</tr>
<tr>
<td>estradiol (E2)</td>
<td>1.3</td>
<td>1.6–6.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T:estradiol</td>
<td>19</td>
<td>138–320</td>
<td>6%</td>
<td>7%</td>
<td>7%</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>T:estrone</td>
<td>34</td>
<td>180–400</td>
<td>9%</td>
<td>9%</td>
<td>9%</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>T:androsterone</td>
<td>34</td>
<td>180–400</td>
<td>9%</td>
<td>9%</td>
<td>9%</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>dehydroepiandrosterone (DHEA)</td>
<td>7.1</td>
<td>30–1,000</td>
<td>22%</td>
<td>71%</td>
<td>95%</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Sum of Estrogens:** 5.3

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#### 51 y.o. female

- **Symptoms:** Myalgia, fatigue, allergies
- **Results:**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>%</th>
<th>0%</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>cortisol</td>
<td>24</td>
<td>20–82</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tetrahydrocortisol (THF)</td>
<td>100</td>
<td>350–1,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aldosterone (ALD)</td>
<td>250</td>
<td>110–290</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>corticosterone (CORT)</td>
<td>64</td>
<td>62–180</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tetrahydrocortisol (THE)</td>
<td>1,100</td>
<td>1,100–3,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**17 Hydroxyprogesterone Metabolites**

- **Results:**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>%</th>
<th>0%</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>pregnanediol (PD)</td>
<td>540</td>
<td>400–1,500</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tetrahydrocortisol (THF)</td>
<td>67</td>
<td>37–118</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total 17-Hydroxyprogesterone = THF + PD**

- **Results:**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>%</th>
<th>0%</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>total 17-hydroxyprogesterone (THP)</td>
<td>2,000</td>
<td>2,000–5,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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#### Uric Acid

- **Uric Acid:** 5 mg/dL

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#### Liver Function Tests

- **Aspartate Transaminase (AST):** 30 IU/L
- **Alkaline Phosphatase (ALP):** 15 IU/L
- **Alanine Transaminase (ALT):** 25 IU/L
- **Total Bilirubin:** 0.5 mg/dL
- **Direct Bilirubin:** 0.1 mg/dL
- **Total Protein:** 7.5 g/dL
- **Albumin:** 4.0 g/dL
- **Creatinine:** 0.8 mg/dL
- **Glucose:** 80 mg/dL

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#### Thyroid Function Tests

- **TSH:** 4.0 mIU/L
- **T4:** 1.0 mg/dL
- **T3:** 1.5 ng/dL

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#### Other Tests

- **Complete Blood Count (CBC):**
  - Hemoglobin: 14 g/dL
  - White Blood Cells: 8,000/μL
  - Platelets: 250,000/μL

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#### Follow-up

- **Treatment Plan:**
  - 3 mg of dexamethasone 12-hourly
  - 10 mg of prednisone 8-hourly

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#### Notes

- **Diagnosis:** Adrenal insufficiency
- **Recommendations:**
  - Increase dietary intake of sodium chloride
  - Monitor blood pressure closely

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#### References

54 y.o. female BMI 38, waist 42”, MetS
anxiety, problems sleeping, acne, increased facial hair

### Cortisol/Cortisol Metabolites

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Range</th>
<th>%ile</th>
<th>Range Applied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>58</td>
<td>26 - 72</td>
<td></td>
<td>Post</td>
</tr>
<tr>
<td>Tetrahydrocortisol (THF)</td>
<td>1.100</td>
<td>415 - 1.000</td>
<td>71%</td>
<td>Post</td>
</tr>
<tr>
<td>allo-Tetrahydrocortisol (aTHF)</td>
<td>1.300</td>
<td>120 - 350</td>
<td>85%</td>
<td>Post</td>
</tr>
<tr>
<td>Cortisolone</td>
<td>110</td>
<td>56 - 140</td>
<td>100%</td>
<td>Post</td>
</tr>
<tr>
<td>Tetrahydrocortisone (THE)</td>
<td>3.200</td>
<td>1,400 - 2,000</td>
<td>72%</td>
<td>Post</td>
</tr>
</tbody>
</table>

### 17-Hydroxyprogesterone Metabolites

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Range</th>
<th>%ile</th>
<th>Range Applied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone (P)</td>
<td>600</td>
<td>140 - 530</td>
<td>71%</td>
<td>Post</td>
</tr>
<tr>
<td>Tetrahydrodecoxyallopregnane (THD)</td>
<td>64</td>
<td>29 - 96</td>
<td>85%</td>
<td>Post</td>
</tr>
</tbody>
</table>

### Total 17-hydroxysteroids + ATP + P3 + THE + THF + THS

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Range</th>
<th>%ile</th>
<th>Range Applied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total 17-hydroxy steroids</td>
<td>6,300</td>
<td>2,200 - 4,300</td>
<td>71%</td>
<td>Post</td>
</tr>
</tbody>
</table>

### 17-Ketosteroids

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Range</th>
<th>%ile</th>
<th>Range Applied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydroepiandrosterone (DHEA)</td>
<td>110</td>
<td>10 - 100</td>
<td>70%</td>
<td>Post</td>
</tr>
<tr>
<td>Androstenedione (AISON)</td>
<td>6.3</td>
<td>0.8 - 2.8</td>
<td>95%</td>
<td>Post</td>
</tr>
<tr>
<td>Testosterone</td>
<td>3.8</td>
<td>0.74 - 4.1</td>
<td>80%</td>
<td>Post</td>
</tr>
<tr>
<td>Dihydrotestosterone (DHT)</td>
<td>1.5</td>
<td>0.2 - 1.7</td>
<td>75%</td>
<td>Post</td>
</tr>
<tr>
<td>3-alpha-androstenediol</td>
<td>1G</td>
<td>0.5 - 0.9</td>
<td>95%</td>
<td>Post</td>
</tr>
<tr>
<td>Estriol (E3)</td>
<td>1,300</td>
<td>400 - 1,000</td>
<td>73%</td>
<td>Post</td>
</tr>
<tr>
<td>11-ketotestosterone (11KET)</td>
<td>150</td>
<td>52 - 400</td>
<td>50%</td>
<td>Post</td>
</tr>
<tr>
<td>11-hydroxyetiocholanolone (11HE)</td>
<td>64</td>
<td>70 - 510</td>
<td>50%</td>
<td>Post</td>
</tr>
<tr>
<td>Androstanolone (AISO)</td>
<td>2,300</td>
<td>350 - 1,100</td>
<td>95%</td>
<td>Post</td>
</tr>
<tr>
<td>11-hydroxyandrosterone (11HMA)</td>
<td>49</td>
<td>11 - 50</td>
<td>95%</td>
<td>Post</td>
</tr>
<tr>
<td>11-hydroxyandrostenedione (11HMA)</td>
<td>1,300</td>
<td>160 - 400</td>
<td>95%</td>
<td>Post</td>
</tr>
</tbody>
</table>
Do whatever it takes to increase GH and decrease inflammation

51 y.o. female on Premarin and Provera

Repeat after me...
“Provera is not progesterone”
“Provera is not progesterone”
“Provera is not progesterone”
Endogenous Progesterone

Topical Progesterone

Pregnanediol glucuronide P2G

Urine

Endogenous Progesterone

Topical Progesterone

Pregnanediol glucuronide P2G

Urine

Endogenous Progesterone

Topical Progesterone

Pregnanediol glucuronide P2G

Urine

-measured P2G after Pg cream
-concluded Pg not absorbed

Urinary PDG did increase after application of progesterone cream to skin, but the person-to-person variability was wide

17 Postmenopausal ♀ (natural or surgical) using Progesterone cream:

<table>
<thead>
<tr>
<th>Pg Cream Dose</th>
<th>P2</th>
<th>Age</th>
<th>Within Luteal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 bid</td>
<td>350</td>
<td>58</td>
<td>No</td>
</tr>
<tr>
<td>“bid”</td>
<td>240</td>
<td>53</td>
<td>No</td>
</tr>
<tr>
<td>25 bid</td>
<td>290</td>
<td>66</td>
<td>No</td>
</tr>
<tr>
<td>60 qid</td>
<td>210</td>
<td>59</td>
<td>No</td>
</tr>
<tr>
<td>20 mg qid</td>
<td>155</td>
<td>58</td>
<td>No</td>
</tr>
<tr>
<td>40 qid</td>
<td>220</td>
<td>42*</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>210</td>
<td>38*</td>
<td>No</td>
</tr>
<tr>
<td>50 bid</td>
<td>600</td>
<td>54</td>
<td>Yes</td>
</tr>
<tr>
<td>50 bid</td>
<td>790</td>
<td>55</td>
<td>Yes</td>
</tr>
<tr>
<td>“bid”</td>
<td>940</td>
<td>78</td>
<td>Yes</td>
</tr>
<tr>
<td>60 qid</td>
<td>730</td>
<td>54</td>
<td>Yes</td>
</tr>
<tr>
<td>50 qid</td>
<td>900</td>
<td>63</td>
<td>Yes</td>
</tr>
<tr>
<td>“sporadic”</td>
<td>900</td>
<td>52</td>
<td>Yes</td>
</tr>
<tr>
<td>80 ± 20</td>
<td>520</td>
<td>52</td>
<td>Yes</td>
</tr>
<tr>
<td>50 qid</td>
<td>2030</td>
<td>53</td>
<td>Yes</td>
</tr>
<tr>
<td>50 bid</td>
<td>830</td>
<td>60</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Postmeno Range: 70-430 mu = 190

Luteal Range: 600-3200 mu = 1560

* hysterectomy/oophorectomy

Urine P2 acts like serum Pg
Supraphysiologic doses of Pg cream (≈200 mg/day) are likely required to produce luteal levels of P2
Some hormone “authorities” have abandoned Pg cream on this basis
• Urine P2G level is likely lower than expected, based on dose, because Pg is hanging up in s.c. fat at site of application and elsewhere

• We know from saliva testing that Pg continues to appear at high levels in saliva for months after stopping Pg cream, so it must be stored somewhere
Urine P2 levels track oral or troche Pg in a more linear way if the saliva that is generated by the troche is swallowed.

In general, this is true of any hormone which travels to your stomach: rapid metabolism (within 2 hours of ingestion).

This seems like a whopping big dose, but how much of it actually got a chance to circulate as Pg?

High numbers may not reflect clinical activity.

Like saliva levels after topical Pg, but for a different reason.
Supplementation with progesterone appears to gently nudge the 17-ketosteroid family members toward their luteal means (DHEA excepted).

Progesterone can convert to androstenedione and thence to other members of the androgen family.
DHEA and TESTOSTERONE METABOLITES IN 16 PATIENTS USING TOPICAL TESTOSTERONE ≈ 2 mg/day AND TOPICAL PROGESTERONE 50-100 mg/day

This hormone combination appears to produce high normal to markedly above normal levels of most of the 17-ketosteroid family of metabolites.

TESTOSTERONE and TESTOSTERONE METABOLITES IN PATIENTS USING TOPICAL TESTOSTERONE ≈ 2 mg/day and TOPICAL PROGESTERONE 50-100 mg/day

<table>
<thead>
<tr>
<th></th>
<th>Expected # &gt; 84th %</th>
<th>Observed # &gt; 84th %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testo</td>
<td>2.5</td>
<td>7</td>
</tr>
<tr>
<td>DHT</td>
<td>2.5</td>
<td>7</td>
</tr>
<tr>
<td>ANDL</td>
<td>2.5</td>
<td>9</td>
</tr>
</tbody>
</table>

N = 16
Effect of Estrogen Supplementation on Urinary Estrogens in Postmenopausal Women

<table>
<thead>
<tr>
<th>E2 Dose (avg)</th>
<th>Luteal Endogenous</th>
<th>Postmeno Endogenous</th>
<th>BiEst Topical</th>
<th>BiEst Vaginal</th>
<th>Estrogel Topical</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>850 mcg</td>
<td>500 mcg</td>
<td>1500 mcg</td>
<td></td>
</tr>
<tr>
<td>2-OHE1 ng/mg Cr</td>
<td>7.4</td>
<td>1.7</td>
<td>2.9</td>
<td>8.4</td>
<td>8.6</td>
</tr>
<tr>
<td>16-OHE1 ng/mg Cr</td>
<td>2.3</td>
<td>0.9</td>
<td>1.7</td>
<td>4.5</td>
<td>2.3</td>
</tr>
</tbody>
</table>
Oral Estrogen = Estrogen Overdose

Is this “excess” conjugated estrone exerting a clinical effect? Is it just demonstrating that you are sending much of your ingested dose straight to the toilet?
<table>
<thead>
<tr>
<th>Hormone Therapies</th>
<th>Estrogens (e.g., Premarin, Opis)</th>
<th>Progesterone (e.g. Provera)</th>
<th>Testosterone (e.g. Androderm)</th>
<th>Other Hormone (e.g. Pregnenolone)</th>
<th>Other Hormones (e.g. GnRH analogues)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand Used (e.g., Premarin)</td>
<td>CUSTOM MADE</td>
<td>CUSTOM MADE</td>
<td>CUSTOM MADE</td>
<td>CUSTOM MADE</td>
<td>CUSTOM MADE</td>
</tr>
<tr>
<td>Delivery (e.g., oral, transdermal)</td>
<td>TROCHE</td>
<td>TROCHE</td>
<td>TROCHE</td>
<td>TROCHE</td>
<td>TROCHE</td>
</tr>
<tr>
<td>Dose (in mg)</td>
<td>175 mg</td>
<td>25 mg</td>
<td>1 mg</td>
<td>2 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>Date &amp; Hour of Last Use</td>
<td>10:00 AM</td>
<td>12:00 PM</td>
<td>7:00 PM</td>
<td>10:00 AM</td>
<td></td>
</tr>
<tr>
<td>Number of Times Per Day (e.g., 3x)</td>
<td>2x</td>
<td>2x</td>
<td>2x</td>
<td>2x</td>
<td>2x</td>
</tr>
<tr>
<td>Snorer, Much Odor (e.g., 3x)</td>
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<tr>
<td>Length of Time of Use (e.g., 2x)</td>
<td></td>
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<tr>
<td>Other Medications</td>
<td>Circle One: SMOKER</td>
<td></td>
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<td></td>
<td>NON-SMOKER</td>
</tr>
</tbody>
</table>

**Symptoms:** Please indicate the symptoms you are experiencing as 0 (none), 1 (mild), 2 (moderate), 3 (severe). For example if you have moderate allergies you would indicate this by entering the 2 next to allergies. **(0-3 Alleviation):**

- **0: No Symptoms**
- **1: Mild Symptoms**
- **2: Moderate Symptoms**
- **3: Severe Symptoms**

1. **Hot Flashes**
2. **Fatigue**
3. **Insomnia**
4. **Concentration**
5. **Foggy Thinking**
6. **Memory Loss***
7. **Arthritic Pain***
8. **Headaches***
9. **Low Energetic***
10. **Increased Appetite***
11. **Increased Acne***
12. **Increased Sweating***
13. **Increased Hunger***
14. **Increased Weight***
15. **Increased Sleep***
16. **Decreased Libido***
17. **Decreased Energy***
18. **Decreased Sex Drive***
19. **Decreased Appetite***
20. **Decreased Memory***
21. **Decreased Concentration***
22. **Decreased Motivation***

**Cortisol Metabolites**

| Analyte | Result | Range | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % |%
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<tbody>
<tr>
<td>Cortisol</td>
<td>220</td>
<td>28 - 72</td>
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<tr>
<td>Tetrahydrocortisol (THF)</td>
<td>2,200</td>
<td>419 - 1,300</td>
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<tr>
<td>aTetrahydrocortisol (aTHF)</td>
<td>1,200</td>
<td>129 - 300</td>
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<tr>
<td>Cortolone</td>
<td>210</td>
<td>56 - 140</td>
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<tr>
<td>Tetrahydrocortisone (THE)</td>
<td>5,500</td>
<td>1,400 - 2,900</td>
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</tbody>
</table>

**17 Hydroxyprogesterone Metabolites**

| Analyte | Result | Range | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % |%
<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>Tetrahydroxyprogesterone (THP)</td>
<td>260</td>
<td>28 - 96</td>
<td></td>
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<tr>
<td>Progesterone (P)</td>
<td>900</td>
<td>140 - 520</td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

**Pregnenolone (P2)**

| Analyte | Result | Range | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % |%
<table>
<thead>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Pregnenolone</td>
<td>5,000</td>
<td>600 - 3,200</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Saliva hormone level

Urine conjugate level

Serum total hormone level

Topical creams
- Reflects fat stores
- High numbers don’t reflect clinical impact
- Lag dose
- Low numbers may underestimate clinical effect
- Are numbers low because a lot of hormone is being “stashed”? Are numbers low because a lot of hormone is being “stashed”?

Oral
- Can remain close to physiologic levels at physiologic doses
- High numbers reflect rapid, excessive conjugation, not clinical effect
- High numbers reflect formation of metabolites which cross-react with assay

SL/Troche
- Local contamination
- Not valid
- Rapid, excessive conjugation
- Physiologic doses may yield physiologic numbers for low-volume SL
Urine steroid conjugate testing

- Allows us to inspect the “family trees”
- Looks at output over one diurnal cycle
- Quite useful for assessing hormone baselines
- May be useful for identifying situations where there is an unfavourable pattern of metabolites, especially estrogens, at baseline
- Supplemented levels must be interpreted with care
- The minimum dose which gives a good patient response is still the best dose

CONCLUSIONS

Don't let the lab test do all your thinking!

Remember to treat the Patient first!

Just be thankful you're not my dentist