Halting the Aging Process

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From: beautyanalysis.com
From: Pilates Reforming NY
The Seven Acts of Life

*Jacques:* All the world's a stage,
    And all the men and women merely players;
    They have their exits and their entrances,
    And one man in his time plays many parts,
    His acts being seven ages. At first, the infant,
    Mewling and puking in the nurse's arms.
    Then the whining schoolboy, with his satchel
    And shining morning face, creeping like snail
    Unwillingly to school. And then the lover,
    Sighing like furnace, with a woeful ballad
    Made to his mistress' eyebrow. Then a soldier,
    Full of strange oaths and bearded like the pard,
    Jealous in honour, sudden and quick in quarrel,
    Seeking the bubble reputation
    Even in the canon's mouth. And then the justice,
    In fair round belly with good capon lined,
    With eyes severe and beard of formal cut,
    Full of wise saws and modern instances;
And so he plays his part. The sixth age shifts
Into the lean and slippered pantaloon
With spectacles on nose and pouch on side;
His youthful hose, well saved, a world too wide
For his shrunk shank, and his big manly voice,
Turning again toward childish treble, pipes
And whistles in his sound. Last scene of all,
That ends this strange eventful history,
Is second childishness and mere oblivion,
Sans teeth, sans eyes, sans taste, sans everything.

(As You Like It, Act II, Scene VII, lines 139-166)
Function Changes During the Life Cycle

- Increasing function
- Stable function
- Decreasing function

Lifespan in Years

Function

0 20 40 60 80 100

Mild
Moderate
Severe
Function Changes During the Life Cycle: Extending Lifespan

- Increasing function
- Stable function
- Slow decreasing function

Cognitive function
Vascular function
Immune function
Bone function
Reproductive function
Athletic performance

Lifespan in Years

Increasing lifespan
Mild
Moderate
Severe

0 20 40 60 80 100
Function Changes During the Life Cycle: Extending Lifespan and Healthspan

Increasing function

Increase stable function

Delay decreasing function

Lifespan in Years

Cognitive function
Vascular function
Immune function
Bone function
Reproductive function
Athletic function

Mild
Moderate
Severe

Increasing Lifespan and Healthspan
How and Why Do We Age?

• The Reproductive-Cell Cycle Theory of Aging

The hormones that regulate reproduction in mammals act in an antagonistic pleiotrophic manner to control aging via cell cycle signaling; promoting growth and development early in life in order to achieve reproduction, but later in life, in a futile attempt to maintain reproduction, become dysregulated and drive senescence.

Provides a credible reason for why and how aging occurs at the evolutionary, physiological and molecular levels

How we can halt the aging process
Commonly Accepted Definition of AGING -

‘a progressive decrease in functional ability over time’

Which function?
A Better Definition of AGING

- complex molecular reactions

Blair - 3 days old

December, 2002
The Rate of Aging is Synonymous with the Rate of Change (of Function)

Stop all chemical reactions, no change would occur over time and aging would be halted.

Blair - 3 days old

Thursday, September 23, 2010

Aging = any change in an organism over time
The Rate of Aging is Synonymous with the Rate of Change (of Function)

Stop all chemical reactions, no change would occur over time and aging would be halted.

Aging = any change in an organism over time

Blair - 3 days old

Thursday, September 23, 2010
The Rate of Aging is Synonymous with the Rate of Change (of Function)

Change = Aging

Rate of Change = Rate of Aging

What is the major change in an organism over time?
Major Organismal Changes Throughout Life – Aging Occurs Throughout the Life Cycle

Three major cellular events: cell division, cell differentiation, cell death
Mitogenesis, Differentiation and Apoptosis are the Major Changes in an Organism over Time

- Single cell to a multi-billion cell organism
- **Major change** – cell division (mitogenesis), cell development (differentiation), cell death (apoptosis)
- Aging = change = cell division, development and death = ?

Whatever controls cell division, differentiation and death must therefore control aging
Reproductive Hormones Regulate Cell Growth, Development and Death

- **Human Chorionic Gonadotropin (hCG)**
- **Luteinizing Hormone (LH)**
  - LH (male and female)
  - LH (adult male)
  - LH (adult female)

Gestation, Infancy, Childhood, Puberty, Adult-reproductive period, Senescence

Mitogenicity Index
Hypothalamic-Pituitary-Gonadal Axis: The Reproductive Axis

Feedback mechanisms keep axis in balance during reproductive period.

LH, FSH, GnRH – mitogenic hormones
Sex steroids, activins – differentiative hormones

Receptors for these hormones are expressed in all tissues of the body.
Feedback mechanisms keep axis in balance during reproductive period

LH, FSH, GnRH – mitogenic hormones
Sex steroids, activins – differentiative hormones

Receptors for these hormones are expressed in all tissues of the body
Endocrine Dyscrasia in Women and Age-related Diseases

Dyotic Signaling: decreased sex steroid signaling, but increased gonadotropin, GnRH and activin signaling
Endocrine Dyscrasias in Men and Age-related Diseases

Dyotic Signaling: decreased sex steroid signaling, but increased gonadotropin, GnRH and activin signaling
The Balance Between Mitogenic and Differentiation Hormones Dictates Cell Fate

Mitogenic Signals
hCG/LH/FSH
GnRH

Differentiation Signals
Sex steroids
Activins

Cellular Homeostasis

Aberrant Cell Division and Death/Dysfunction

Equilibrium becomes dysregulated, initiating dyosis which drives senescence

Endocrine dyscrasia
Consequences of HPG Dysregulation

Aberrant re-entry of cells into the cell cycle

Tissues with differentiated cell types
- Brain – neurons – Alzheimer’s disease
- Heart – endothelial cells/cardiomyocytes – CHD

Tissues with totipotent stem cell types
- Lung, liver, colon, reproductive tissues – cancer
- Vasculature – SMC/endothelial cells – stroke
- Bone – osteoclasts/osteoblast – osteoporosis
Consequences of HPG Dysregulation: Endocrine Dyscrasia

Global and pervasive deterioration in bodily function — explains why we develop our age-related diseases

Rate at which degenerative changes occur depends on how dysregulated the HPG axis becomes

Organs involved is dependent upon the influence of both environmental and genetic factors

These factors determine who will age faster and who will age slower

But, we all eventually die
Leading Causes of Death in the USA

Table 1. Leading causes of death in the US

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>All Ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Deaths</td>
<td>2,426,264</td>
</tr>
<tr>
<td>Diseases of the heart</td>
<td>631,636</td>
</tr>
<tr>
<td>Malignant Neoplasms (Cancer)</td>
<td>559,888</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>137,119</td>
</tr>
<tr>
<td>Chronic Lower Respiratory Disease</td>
<td>124,583</td>
</tr>
<tr>
<td>Accidents (unintentional injuries)</td>
<td>121,599</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>72,449</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>72,432</td>
</tr>
<tr>
<td>Influenza and Pneumonia</td>
<td>56,326</td>
</tr>
<tr>
<td>Osteoporosis/low bone mass</td>
<td></td>
</tr>
<tr>
<td>Dementia/cognitive loss</td>
<td></td>
</tr>
</tbody>
</table>

Osteoporosis/low bone mass 55% by 50 years of age
Dementia/cognitive loss 45% by 85 years of age

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Evidence for the Reproductive-Cell Cycle Theory of Aging

1. Epidemiological evidence
2. Clinical evidence
3. Experimental evidence

This evidence provides clues as to how to halt the aging process that leads to our age-related diseases
Age-related Reproductive Endocrine Dyscrasia Initiates Senescence and Age-related Diseases

Epidemiological Evidence (>10 studies)

- Disease risk in women with later menopause:
  - ↓ cardiovascular disease
    - ↓ calcifications in the aorta
    - ↓ atherosclerosis
  - ↓ dementia/cognitive decline
  - ↓ osteoporosis/bone fractures
  - ↓ colorectal and breast cancer
  - ↑ uterine and ovarian cancer

The longer the HPG axis is in balance, the less likely you are to develop an age-related disease
Age-related Reproductive Endocrine Dyscrasia Initiates Senescence and Age-related Diseases

Epidemiological Evidence (>16 studies)

- Disease risk in women with early reproductive endocrine dyscrasia (oophorectomy or natural):
  - ↑ cardiovascular disease (fatal and non-fatal)
  - ↑ stroke
  - ↑ dementia/cognitive decline/Parkinsonism
  - ↑ osteoporosis/bone fractures
  - ↑ lung cancer
  - ↑ depression and anxiety
  - ↓ breast and ovarian cancer

Earlier endocrine dysrasia is associated with earlier onset of age-related disease
Age-related Reproductive Endocrine Dyscrasia and Age-related Diseases

Experimental Evidence

Positive relationships between age-related diseases and decreased circulating sex steroids and increased gonadotropins in both men and women

- Coronary heart disease
- Stroke (except women)
- Alzheimer’s disease/dementia/cognitive loss
- Osteoporosis/bone fractures
- Cancer
- Obesity, metabolic syndrome/diabetes mellitus II
- Frailty (men)

The more dysregulated your HPG axis, the more likely you are to develop age-related diseases
Hormone Replacement Therapy

- The most compelling evidence for endocrine dyscrasia as promoting age-related diseases comes from HRT studies.

- Sex steroids used to supplement those sex steroids no longer produced by the gonads.

- Women: estrogen, progesterone, or both given to women after menopause to replace the hormones no longer produced by the ovaries (~50 years of age).

- Men: testosterone given to men with hypogonadism to replace testosterone no longer produced by testes.

- Sources vary:
  - Physiologically (bio)identical human hormones
  - Unphysiological hormones - hormones extracted from horse urine plus synthetic analogs.
Age-related Reproductive Endocrine Dyscrasia and Age-related Diseases

Clinical and Epidemiological Evidence

Supplementation with **physiological** sex steroid post-menopause and during andropause delays the onset, decreases the incidence and often improves the course of age-related diseases

- Alzheimer’s disease/dementia/cognitive loss
- Coronary heart disease
- Stroke* (except women)
- Osteoporosis/bone fractures
- Obesity, metabolic syndrome/diabetes mellitus II
- Cancer*
Estradiol Halts Cognitive Decline and Enhances Cognition

- Estradiol study, elderly women, 5 years
  - No estradiol - 16% developed AD
  - Estradiol - 1.7% developed AD

- Other studies
  - Women who suffered only moderate memory problems from Alzheimer's disease improved their memory while on HRT
Compelling Evidence that Sex Steroids are Important for Brain Health

- Why are we not all taking human estradiol and progesterone post-menopause to supplement for the loss of these hormones with aging?

- And testosterone during andropause in men to supplement for the loss of these hormones with aging?
Unphysiological Sex Steroids and Disease Risk

1. Women Health Initiative Studies
   - Human versus non-human sex hormones
   - Non-human sex hormones developed initially for treatment of menopausal symptoms (profit from patented sex steroids)
   - Analogs/non-human forms developed for human use
   - Long-term use led to health issues

2. Risk of cancer, stroke, AD and heart disease
1. Women’s Health Initiative Studies

Horse-derived and synthetic analogs:

- **PREMARIN** – conjugated equine estrogens (estrone sulfate)
- **PREMPRO** – CEE plus medroxyprogesterone acetate

Let’s compare estradiol with CEE.....
Clinical and Observational Studies of Natural and Unnatural Sex Steroids on Cognitive Outcome

- **17β-estradiol:**
  - 100% of studies show improvement in cognition in AD subjects
  - 80% of studies show improvement in cognitive performance in healthy older women

- **Conjugated equine estrogens:**
  - ~50% of studies show a delay in onset and halting of the progression of AD
  - ~50% of studies show an improvement in cognitive performance in healthy older women
  - One study, the Women’s Health Initiative – Memory Study (WHIMS) showed that women taking CEE (Premarin) or CEE with medroxyprogesterone (Prempro) were more likely to show cognitive **decline**

- Different forms of estrogen vary in their effects, and side effects, on the brain and other tissues
Undoing the ‘Scientific’ Damage

Natural Forms of Sex Steroids
Undoing the ‘Scientific’ Damage

Natural Forms of Sex Steroids
Undoing the ‘Scientific’ Damage

Progesterone

Testosterone

Natural Forms of Sex Steroids
Undoing the ‘Scientific’ Damage

Natural Forms of Sex Steroids

Progesterone

Testosterone

Major differences in biological action
Undoing the ‘Scientific’ Damage

Natural Forms of Sex Steroids

**Progesterone**

**Testosterone**

Synthetic/Animal Forms of Sex Steroids

**Medroxyprogesterone (MPA)**

Biologically – we might expect major differences, and we do
Undoing the ‘Scientific’ Damage

Natural Forms of Sex Steroids

**Unlike progesterone, medroxyprogesterone:**

- DOES NOT protect against glutamate-induced neuronal toxicity (Nilsen et al., 2006, *Gynecol Endocrinol*.; Jodhka et al., 2009, *Endocrinology*)

- DOES NOT protect against the neurodegeneration induced by traumatic brain injury (Wright et al., 2008; *Brain*)

- DOES prevents neurogenesis (Nilsen and Brinton, 2003, *PNAS*; Brinton, 2009)
Undoing the ‘Scientific’ Damage

Natural Forms of Sex Steroids

**Progesterone**

**Testosterone**

**17β-estradiol**

Synthetic/Animal Forms of Sex Steroids

**Medroxyprogesterone (MPA)**
Undoing the ‘Scientific’ Damage

Natural Forms of Sex Steroids

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Chemical Structure</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td><img src="image1" alt="" /></td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td><img src="image2" alt="" /></td>
<td></td>
</tr>
<tr>
<td>17β-estradiol</td>
<td><img src="image3" alt="" /></td>
<td></td>
</tr>
<tr>
<td>Medroxyprogesterone (MPA)</td>
<td><img src="image4" alt="" /></td>
<td></td>
</tr>
<tr>
<td>Estrone sulfate</td>
<td><img src="image5" alt="" /></td>
<td>Major estrogen from horse urine found in Premarin</td>
</tr>
</tbody>
</table>

Synthetic/Animal Forms of Sex Steroids

Biologically – major differences in function
Undoing the ‘Scientific’ Damage

Natural Forms of Sex Steroids

Progestosterone

Testosterone

17β-estradiol

CEE – different signaling pathways?
- major CEE = estrone sulfate
- contain ~ 15 different estrogens
- excretory products
- decreased ER binding
- conjugation - hormonal inactivation to limit signaling (sulfation or glucuronidation)

Estrone sulfate

Major estrogen from horse urine found in Premarin

Biologically – major differences in action
We need to be supplementing our body with sex steroids that are physiologically relevant!

For Women: 17β-estradiol and progesterone

For Men: testosterone and progesterone

No study has ever shown a negative cognitive outcome from the use of human sex steroids.
2. Cancer Risk for Hormone Replacement Therapies (HRT)

- There is an indisputable increase in the risk of breast, uterine and ovarian cancer with CEE and estradiol supplementation.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Usage (years)</th>
<th>Incidence (/1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CEE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>&gt;10</td>
<td>3-6</td>
</tr>
<tr>
<td>Ovarian</td>
<td>&gt;10</td>
<td>3-11</td>
</tr>
<tr>
<td>Uterine</td>
<td>&gt;10</td>
<td>7-15</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>~23/1000</td>
<td></td>
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<td><strong>Estradiol</strong></td>
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<tr>
<td>Breast</td>
<td>&gt;10</td>
<td>1-13</td>
</tr>
<tr>
<td>Ovarian</td>
<td>&gt;10</td>
<td>1-3</td>
</tr>
<tr>
<td>Uterine</td>
<td>&gt;10</td>
<td>1-5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>~12/1000</td>
<td></td>
</tr>
</tbody>
</table>

~1-2 women per 100 will develop a reproductive cancer
Cancer Risk for Hormone Replacement Therapies (HRT)

- But estradiol replacement therapy decreases the risk of other diseases: heart disease, AD, stroke, osteoporosis, diabetes mellitus II, etc.

- Does the risk of cancer from HRT outweigh the risk from developing other diseases of aging?
2. Cancer Risk for Hormone Replacement Therapies (HRT)

- But HRT decreases the risk of nearly every other disease: heart disease, AD, stroke, osteoporosis, diabetes mellitus II, etc
- Does the risk of cancer from HRT outweigh the risk from developing other diseases of aging?

NO
Humans: Estrogen Replacement Therapy Decreases Mortality

Consistently show a 20-50% decrease in mortality among estrogen (CEE) users

Paganini-Hill et al., 2006
Higher Age at Menopause Increases Female Post-Reproductive Lifespan

9 studies demonstrate advanced age at menopause - ↑ longevity

Advanced age at last reproduction is associated with improved longevity

~ 2.4% reduced mortality per year increase in age at menarche
Healthy Lifespan Extension Following Ovary Transplantation

40% increase in life expectancy

Rebalancing the HPG Axis Increases Longevity

C. Elegans – Linking Reproduction to Longevity

Rudimentary HPG Axis

Vadakkadath Meethal et al., (2006)
Supressing GnRHR Signaling Extends Longevity

*Ce-GnRHR1*-deletion mutant (RB509) worms by gene silencing significantly decreased reproduction 46%, delayed the commencement of egg laying 24 h, extended egg laying 72 h, increased fat deposition 35% and prolonged lifespan 15%
Suppressing the HPG Axis as a Means to Extend Longevity

Life-extending modalities
  • caloric restriction (fasting, inadequate or inconsistent food supply)
  • cold
  • stress

- all modalities suppress HPG axis hormones
- decrease fertility
- sparing of ovarian and testicular reserves
- offset the reproductive clock to a later time when the environment might be better for reproducing and raising offspring
- suppressing gonadotropins with GnRH agonists halves the risk of death from Alzheimer’s disease
Life Extension Strategies Through Hormone Supplementation or Suppression

1. Modulating Reproductive Parameters
   - later menopause
   - later puberty
   - pregnancy and lactational amenorrhea
   - stress: caloric restriction or cold

   - ~5-20 years
2. Pharmacological solutions

**Hormone replacement therapies (physiological hormones)**
- Sex steroids – 17β-estradiol, progesterone and testosterone
- Currently we cannot replace all hormones lost

**Hormone suppression therapies**
- GnRH agonists and antagonists
- 5-20 years
Reversing Endocrine Dyscrasia as a Means to Extend Longevity
Reversing Endocrine Dyscrasia: Restoring Some Balance to the HPG Axis

It’s not perfect, but it’s the best we can do for now
Summary: Sex Hormones and Age-related Disease Risk

Maintaining sex steroid levels reduces the risk of:

- Alzheimer’s disease
- Stroke
- Coronary heart disease
- Osteoporosis
- Obesity, metabolic syndrome/diabetes mellitus II
- Depression and anxiety
- Menopausal symptoms

Maintaining sex steroid levels increase the risk of:

- Cancer
- Quality of life
- Living longer!
Life Extension Strategies Through Hormone Supplementation or Suppression

3. Replacing gonadal cells

- Ovarian and testicular implants?
- Ovary replacement shown to increase longevity
- Human embryonic stem cell technologies
- Not currently a possibility for humans

- 20-40 years
Restoration of the HPG Axis Extends Lifespan and Healthspan

- Increasing function
- Increase stable function
- Delay decreasing function

Function:
- Cognitive function
- Vascular function
- Immune function
- Bone function
- Reproductive function
- Athletic function

Lifespan in Years:
- 0
- 50
- 100
- 150
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Life and Death is About Balance: Hormonal Balance!

Live Longer Foundation

Laboratory for Aging, Endocrinology and Disease (LEAD)

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Female Hormone Replacement Therapy: What Should I Take?

- **Women**
  - 17β-estradiol (USP) - patch (Climara)
  - progesterone (USP) - Pro Gest (cream), Prometrium (pill)

- **Route?**
  - Varies for hormone

- **Opposed or unopposed?**
  - 17β-estradiol + progesterone
  - decreased uterine cancer

- **Timing, duration and cyclicity?**
  - during menopause – for relief of menopausal symptom
  - post-menopause: window – 5 years versus forever
  - continuous progesterone to avoid breakthrough bleeding
Male Hormone Replacement Therapy: What Should I Take?

- **Men**
  - testosterone (USP) – gel or spray
  - progesterone (USP) - Pro Gest, Prometrium

- **Route?**
  - Transdermal to avoid oral first pass effects through liver

- **Opposed or unopposed**
  - testosterone + progesterone?

- **Timing, duration and cyclicity**
  - Starting at andropause (30 years)
  - Starting when hypogonadal (i.e. low serum T) and phenotypic changes menopause – for relief of menopausal symptom
  - Continuous?