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Physiology optimization and stem cell therapy: mutual benefits

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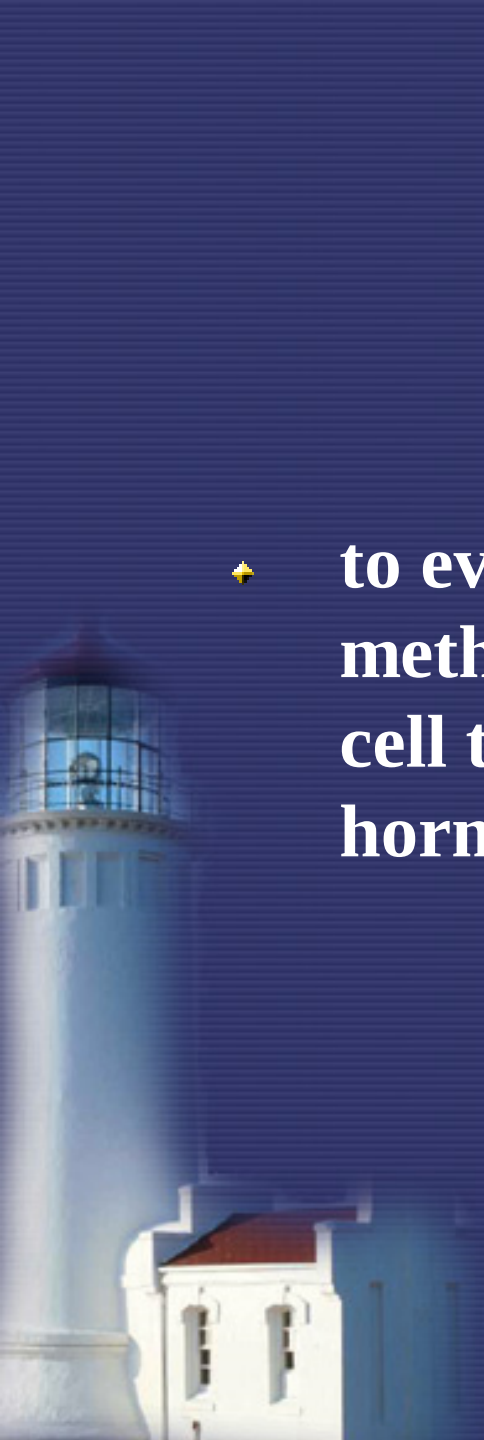
Goal

- **to evaluate the possible role of a multimodal method of physiology optimization in stem cell therapy and stem cell therapy in hormonorestoration**



What happens during aging?

Body transitions

Is it reasonable to assume that stem cells alone placed in this “rotten soup” will work optimally?

How can we refresh the body?

Stem cells act as a rejuvenation and repair system for the body.

What can speed up this reconstructive force?

The answer is a good metabolism.

What is the most powerful force controlling metabolism?

The answer is hormones

We postulate that hormones can significantly improve the function of stem cells.

Hematologic endocrinology

- **feedback regulation mediated by humoral factors is a hallmark of classic endocrinology and also plays a major role in the homeostasis of blood cells**

- **the setting and functioning of the control systems are influenced by hormonal environment; thus, many endocrine disorders have clinically significant hematologic effects[1]**

- **proliferation and maturation of stem cells can be affected by environmental factors, but the main physiologic control of the rate of blood cell formation is exerted at the level of blast transformation, which is mediated by specific factors or hormones[1]**

Stem Cells as units of autopoiesis

- **stem cells can be viewed as first-order autopoietic system, and multicellular organisms can be viewed as second-order autopoietic systems[2]**
- **stem cells represent an essential channel of communication between two levels of autopoiesis, the cellular and the organismal[3]**
- **stem cells are pivotal units between first-order and second-order autopoiesis**
- **stem cells have been shown ability to generate a variety of different cell types. This phenomenon is referred to as stem cell transdifferentiation or plasticity**

A revolution in biology and medicine

- **dogma regarding limitations on the regenerative capacities of adult vertebrates is being cautiously yet enthusiastically revised in the wake of rapidly accumulating discoveries of more types of adult stem cells in mammals, including humans**

- **a review by D. Krause of Yale concluded that "in the [adult] bone marrow, in addition to hematopoietic stem cells and supportive stromal cells, there are cells with the potential to differentiate into mature cells of the heart, liver, kidney, lungs, GI tract, skin, bone, muscle, cartilage, fat, endothelium and brain“[6]**

Bone marrow stem cells (BMSC)

- **hundreds of reports have collectively shown that BMSC can differentiate into various cell types including adipocytes, endothelial cells, epithelial cells, glial cells, hepatocytes, neurons, cardiac muscle cells, skeletal muscle cells and smooth muscle cells[64-66]**

Anti-aging regeneration

- more than a quarter of a century ago, Walter Pierpaoli initiated a series of extraordinary studies that demonstrated in experimental animals the potential for dramatic regeneration associated with changes in the pineal gland and bone marrow

- this appeared to be not only retardation of aging, but also its reversal[6]

- stem cells hold great promise for regenerative medicine because of their ability to self-renew and to differentiate into various cell types[23]

Stem Cells/Hormones – Body Axis

- **stem cells participate during body growth and development, and organ and tissues regeneration**
- **hormones share the same features**

Hormones and stem cells

We hypothesize that hormonorestorative therapy, a core element of *Physiologic Optimization*, is crucial for optimal stem cells function.

- **age-related changes in the production of hormones influence the effect of stem cells**
- **bioidentical steroidal hormones should improve the effectiveness of stem cell therapy**
- **stem cells improve the function of hormones and can increase production of hormones**
- **hormones improve the effect of stem cells by increasing metabolism and by direct effects via stem cell hormone receptors**

Hormones ⟹ Stem Cells

- **DHEA significantly increases the growth rates of human neural stem cells[4]**
  (double effect: on whole body physiology and on stem cells directly)
- **DHEA regulates neurogenesis in the hippocampus and modulates the inhibitory effect of increased corticoids on both the formation of new neurons and their survival[5]**
- **studies have shown that DHEA, IL-10 and IL-4, and melatonin all possess potential regenerative and stem cell-activating properties[6]**
- **the 5-HT re-uptake inhibitor (SSRI) fluoxetine and the adrenal hormone DHEA both increase the proliferation of progenitor cells[7]**

Hormones ⟹ Stem Cells

- the delayed healing of cutaneous wounds in aged individuals may in part reflect the decline in circulating levels of DHEA and estrogens
- based on animal models, aromatase inhibitors may adversely affect cutaneous wound healing in the acute setting
- postmenopausal patients who take aromatase inhibitors as an adjunct to breast cancer therapy may, therefore, be at increased risk of delayed wound healing[8]

Hormones ⟹ Stem Cells (cont.)

- progesterone enhances oligodendrogenesis and myelin protein production which may constitute fundamental steps for repairing traumatic injury inflicted to the spinal cord[9]
- progesterone receptors are highly expressed in human amnion-derived mesenchymal cells[10]
- progesterone has demonstrated neuroprotective and promyelinating effects in lesions of the peripheral and central nervous systems, including the spinal cord[11]

Hormones ⟹ Stem Cells (cont.)

- spinal cord trauma leads to neuronal degeneration, astrogliosis, demyelination, and proliferation of oligodendrocyte-precursor cells. It is now widely accepted that progesterone brings neuroprotection to lesions of the peripheral and central nervous system.[12]
- allopregnanolone (APalpha) induced a significant increase in proliferation of neuroprogenitor cells derived from the rat hippocampus and human neural stem cells derived from the cerebral cortex[13]
- data indicate that APalpha significantly increased neurogenesis in dentate gyrus. APalpha may serve as a neurogenic/regenerative therapeutic for restoration of neurons in victims of Alzheimer's disease.[13]

Hormones ⟹ Stem Cells (cont.)

- hypotestosteronemia is associated with a low number of circulating progenitor cells (PCs) and endothelial PCs (EPCs) in young subjects with hypogonadism. Testosterone treatment is able to induce an increase in these cells through a possible direct effect on the bone marrow.[14]
- normal testosterone levels are necessary to restore the responsiveness of EPCs to phosphodiesterase-5 (PDE5) inhibitors, suggesting that testosterone positively modulates PDE5 in bone marrow[15]
- testosterone acts directly on many embryonic tissues; it induces the development and further their differentiation[16]

Hormones ⟹ Stem Cells (cont.)

- 5 beta-androgens (5 beta-DHT and 5 beta-androstanediol) act specifically on bone marrow tissue, suggesting that marrow stem cells have a unique 5 beta steroid receptors[17]

- the findings that androgens regulate mesenchymal cell differentiation, as well as body composition, lipid profile and bone metabolism, lead to the logic behind the use of testosterone replacement therapy in aging men with late onset hypogonadism[18]

Hormones ⟹ Stem Cells (cont.)

- endothelial progenitor cells (EPCs) may have an important role in vascular homeostasis and repair
- premenopausal females had the highest level of circulating EPCs
- the level of EPCs was lowest in postmenopausal females, and increased significantly with HRT on average by 25.5%
- this observation is in line with the hypothesis that the hormonal status in females modulates the cardiovascular risk and that circulating EPCs could be involved in this phenomenon[19]

It is important to remember that:

diminished bioavailability of zinc in older mammals may represent one of the major factors for the involution of the thymus and consequent cellular immunological dysfunction. Zinc induces several cytokines, predominantly IL-1, IL-6 and TNF-alpha, and therefore, has an immense immunoregulative capacity.[20]

Stem Cells ⟹ Hormones

- stem and progenitor cells normalized the level of testosterone, decreased the concentrations of gonadotropic hormones, reduced hyperplasia of Leydig cells and the number of chromaffin granules, and restored normochromism of Leydig cells nuclei in animals with experimental cryptorchism[21]

- adipose tissue-derived and bone marrow-derived mesenchymal cells develop into different lineages of steroidogenic cells by forced expression of steroidogenic factor 1 and could be a promising regeneration therapy for patients with steroid insufficiency[22]

Stem Cells ⟹ Hormones

- the positive effect of conditioned medium of mesenchymal stem cells on the in vitro maturation and subsequent development of mouse oocyte was registered

- the production of estrogen progressively increased approximately 1-fold every other day during organ culture, while a dramatic 10-fold increase in progesterone was observed 17 h after human chorionic gonadotropin stimulus at the end of culture[83]

Stem Cells ⟹ Hormones

- embryonic stem cell (ESC) could restore the erectile function of neurogenic ED in rats, and adipose tissue-derived stem cells (ADSC) could do so as well. The eventual goal is to use ADSC to treat male infertility and testosterone deficiency[23]

- adult bone marrow cells, in a favorable testicular environment, differentiate into somatic and germ cell lineages. This clinically finding raises the possibility for treatment of male infertility and testosterone deficiency through the therapeutic use of stem cells[24]

Stem Cells ⟹ Hormones (cont.)

- majority of girls with sickle cell disease had complete gonadal failure and most of the boys had spontaneous puberty but germinal epithelial failure after hematopoietic stem cell transplantation[25]

- mesenchymal stem cells or marrow stromal cells represent a useful source of stem cells for producing steroidogenic cells that may provide basis for their use in cell and gene therapy[26]

Stem Cells ⟹ Hormones (cont.)

- results of Greek study indicate a high incidence of gonadal dysfunction due to target organ failure in hematopoietic stem cell transplantation recipients[27]
- gonadal dysfunction was not reported by any of the patients prior to their underlying illness
- hypergonadotrophic hypogonadism was observed in 97% of female and 19% of male patients
- Leydig cell strain (normal testosterone, high luteinizing hormone levels) was evident in 32% and spermatogenesis damage (high follicle-stimulating hormone levels) in 68% of the male population

Stem Cells ⟹ Hormones (cont.)

- osteopenia and osteoporosis are common complications of bone marrow and peripheral blood stem cell transplantation. Bone loss occurs in 50% to 60% of patients treated with the most common preparatory regimens.

- the major causes of transplant-related bone loss are primary hypogonadism (low estrogen and testosterone), secondary hyperparathyroidism due to low serum calcium, and post transplant steroid therapy[28]

Stem Cells ⟹ Hormones (cont.)

- 95 consecutive autologous stem-cell transplant recipients (47 men and 48 women) aged 16 to 55 years were analyzed[29]
- 3 months after the transplant, IGF-1 values were below the normal range in 56%
- 93% of women in reproductive age experienced precocious ovarian failure
- 85% of men showed high FSH
- 37% of men showed low testosterone levels

Stem Cells ⟹ Hormones (cont.)

- adrenal insufficiency occurred in 30% of patients during the peritransplant period after corticosteroid withdrawal
- transient subclinical hyperthyroidism was found in 16% of patients
- transient "low T(3)" syndrome was revealed in 31% of patients

Stem Cells ⟹ Hormones (cont.)

- **12 months after the transplant, IGF-1 values were still low in 38% of patients**
- **menstrual cycles resumed in 4 women**
- **FSH, LH, and estradiol levels improved in 10 patients**
- **testosterone was low in only two men (4%).**
- **seminal analysis revealed azoospermia in 91% of examined men**

Stem Cells ⟹ Hormones (cont.)

- subclinical hypothyroidism was found in 11 patients (12%); eight of them had previously received radiotherapy for the upper half of the body

- this study documents frequent endocrine disorders during the first year after autologous stem-cell transplant. Despite a tendency to improve, in more than half of the cases, the complications persisted for more than 1 year.[29]

Hormones ⟺ stem cells

- **the neurosteroids progesterone and its metabolite 3alpha-hydroxy-5alpha-pregnan-20-one (3alpha,5alpha-THP) promote neurogenesis and show anti-neurodegenerative properties**

- **post-mitotic neuron-like cells (NT2-N) produced neurosteroids may contribute to the encouraging results of NT2-N transplants in animal models of neurodegenerative diseases[30]**

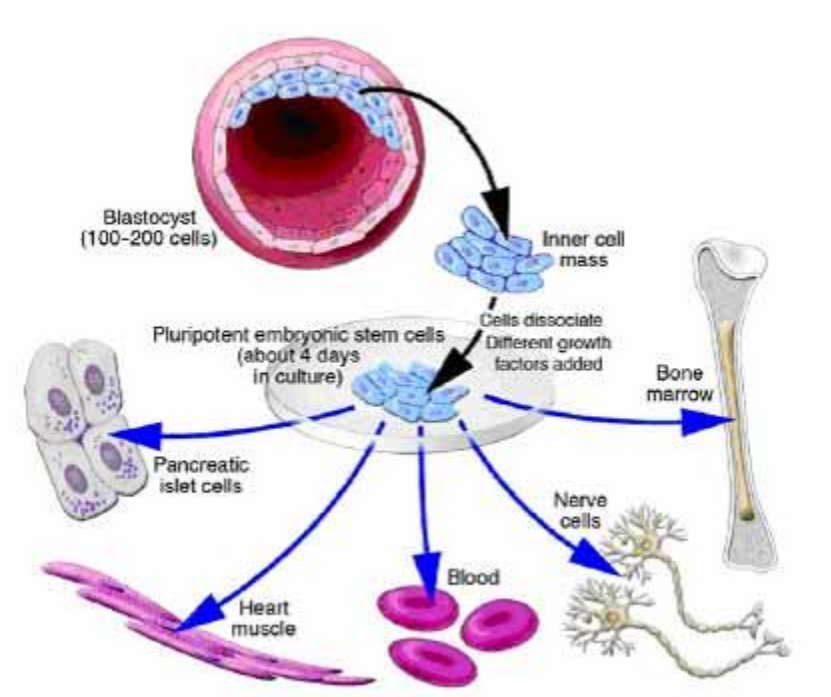
- **commonly observed form of anemia in the elderly (termed unexplained anemia) usually caused by renal insufficiency, inflammation, *testosterone deficiency, and stem cell proliferative decline*[31]**

Similarity of stem cells and HT:

- **stem cell therapy works on very basic mechanisms and levels**

- **it is the same situation with hormonorestorative therapy.**

The example is a normalization of cholesterol in case of hypercholesterolemia.



Stimulation and Restoration of Stem Cell Function

- **targeted nutritional and hormonal therapies may help promote wellness and fight the diseases associated with aging through optimizing stem cell production and function**

Restoration and Stimulation of Stem Cell Function

- **studies have shown that specific nutrients and hormones can encourage the growth or proliferation of stem cells in one's body, thus promoting regeneration and healing**

- **the researchers found a dose-related effect of blueberry, green tea, catechin, carnosine, and vitamin D3 on the proliferation of human bone marrow. Combinations of these nutrients stimulated bone marrow proliferation by as much as 83%, compared with only 48% in a control group, which received a growth factor medicine called granulocyte colony-stimulating factor.[32]**

Restoration and Stimulation of Stem Cell Function (cont.)

- **study revealed that docosahexaenoic acid (DHA) plays a crucial role in supporting normal brain function, including learning and memory, and may exert its effects by triggering the differentiation of neuronal stem cells to produce new neurons in the brain.[33]**

Restoration and Stimulation of Stem Cell Function (cont.)

- **powerful method to support stem cell proliferation and function is through optimizing hormone levels. Using bioidentical hormones, it is possible to restore deficient adult hormones to youthful levels.**
- **stem cell-enhancing effects have been noted with both growth hormone and estradiol replacement therapy[34,35]**
- **animal studies have shown that estrogen and growth hormone enhanced the action of stem cells in cardiac repair[36,37]**
- **a study in men aged 60-75 years old found that testosterone replacement therapy increased muscle mass by stimulating stem cells in muscle[38]**

Nutraceuticals Known to Optimize Adult Stem Cells[32,33,39-46,55]

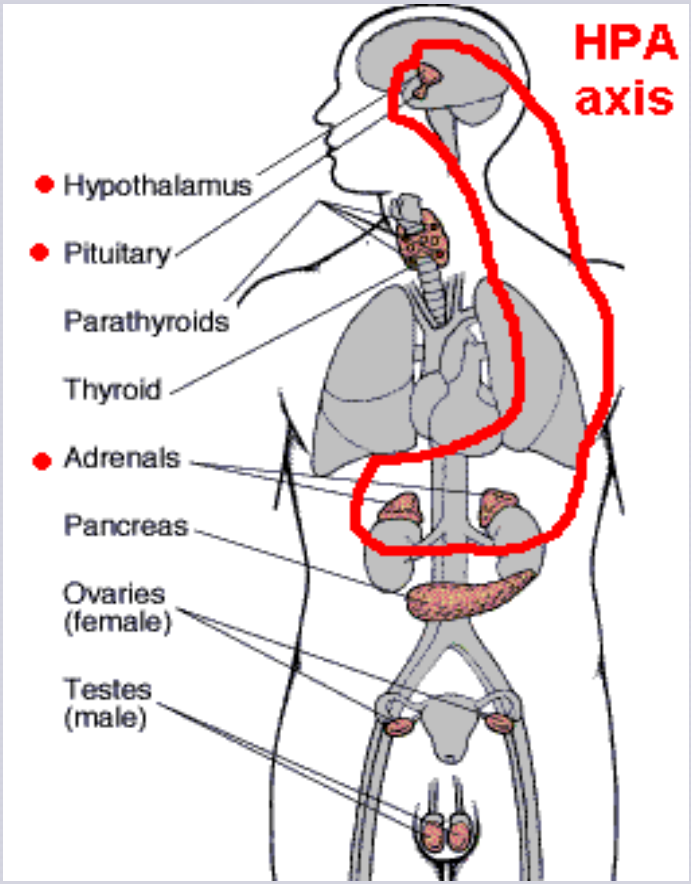
- blueberry
- green tea
- catechin
- carnosine
- vitamin D3
- resveratrol (found in red wine)
- omega-3 fatty acids
- panax notoginseng saponins
- folic acid
- salvianolic acid B/vitamin C
- vitamin B1
- vitamin K
- vitamin B3
- choline
- beta-carotene

Hormones Known to Optimize Adult Stem Cells[4-19,34-38,47]

- **growth hormone**
- **estradiol**
- **testosterone**
- **5 beta-androgens (5 beta-DHT and 5 beta-androstanediol)**
- **DHEA**
- **allopregnanolone**
- **progesterone**
- **melatonin**

The team-work of our glands

In most organs of the body, old cells are continually being replaced by new ones. If too many new cells are produced, however, it can lead to overgrowth and tumor formation. Too few cells, on the other hand, can result in organ degeneration. It is therefore crucial that exactly the right number of cells are produced.



Team work

Bones are perfect example

- bone is a dynamic tissue that is constantly being reshaped by osteoblasts, which build bone, and osteoclasts, which resorb bone
- osteoblast cells tend to decrease as individuals become elderly, thus decreasing the natural renovation of the bone tissue[48]
- osteoblasts are mononucleate cells that are responsible for bone formation. Osteoblasts arise from osteoprogenitor cells located in the periosteum and the bone marrow
- osteoprogenitors are differentiated under the influence of growth factors and hormones

Testosterone, growth hormone, progesterone, estrogens, vitamin D, vitamin K, calcium, magnesium, potassium, sodium, etc – bone physiology players

Aging

- high cholesterol
- myocardial infarction
- type II diabetes
- hypertension
- congestive heart failure
- fatigue
- insomnia
- depression, anxiety
- fibromyalgia
- migraine
- cataract
- macular degeneration
- bone loss
- skin changes
- loss of muscle mass
- weight gain
- arthritis
- memory loss
- poor immunity
- menopause
- andropause, ED
- cancer
- Alzheimer's disease
- Parkinson disease

Potential Clinical Applications of stem cells:

- myocardial infarction, CHF
- stroke
- traumatic brain injury
- diabetes
- learning defects
- spinal cord injury
- osteoarthritis
- rheumatoid arthritis
- bone marrow transplantation
- wound healing
- autism
- macular degeneration
- baldness
- blindness
- deafness
- missing teeth
- muscular dystrophy
- Crohn's desease
- amyotrophic lateral sclerosis
- ED, male infertility
- anti-aging
- cancer
- Alzheimer's disease
- Parkinson disease

As you can see anti-aging and stem cell doctors "play on the same field".

Patients try:

Exercise
Drugs
Hormones
Supplements
Vitamins
Plastic surgery
Stem Cell Therapy
etc.

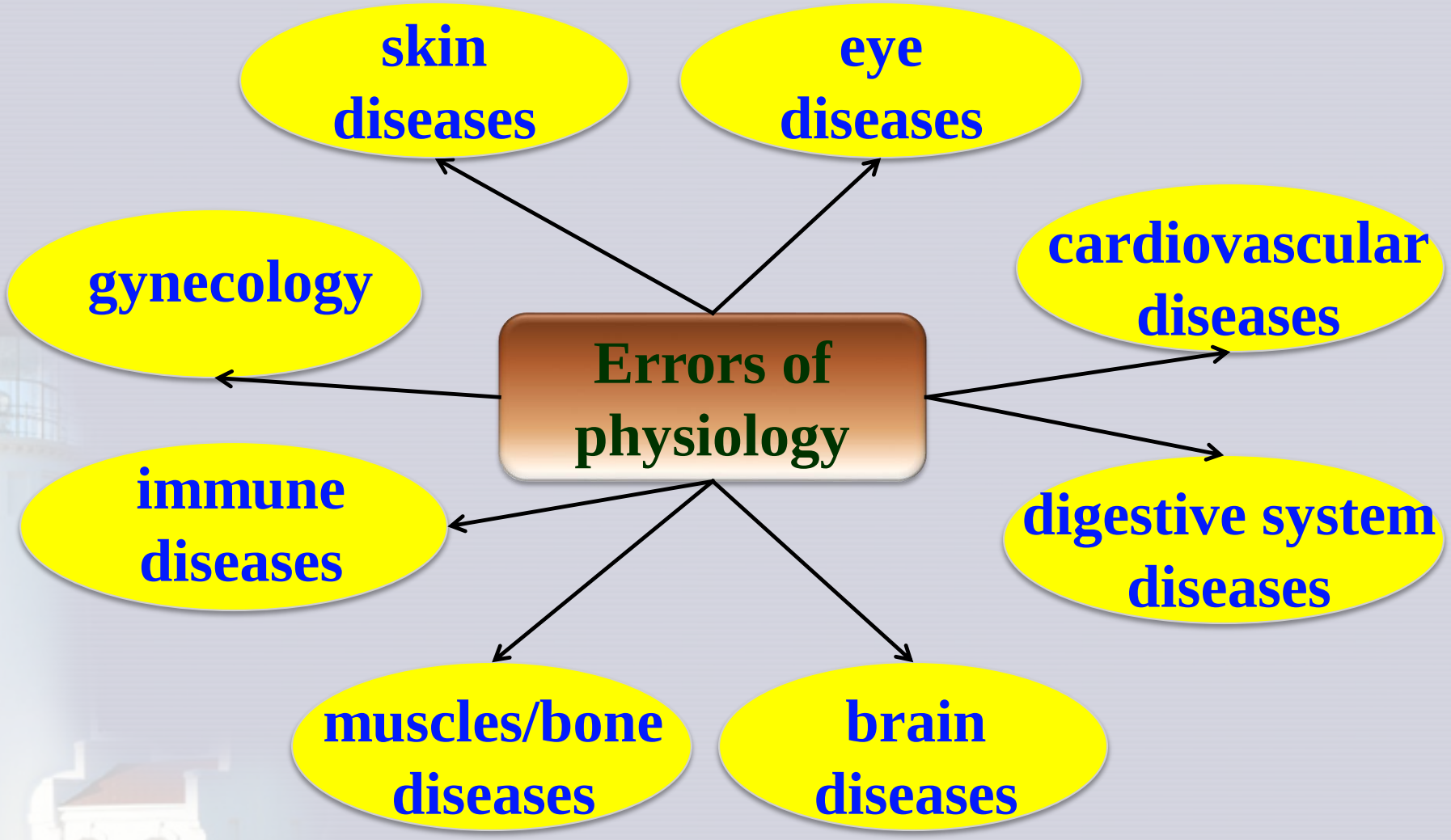
What is the optimal option for the patient and what can we do?

What Causes Disease?

Disease can be caused by one of four factors:

- Genetics/Congenital
- Infections
- Trauma
- Acquired physiologic errors

Errors of Physiology are the Root Cause of Disease



The Main Principle:

ONE CAUSE…

and

ONE SOLUTION!

or

One Disease, One Treatment Approach

Method of Restorative Medicine

- **restorative medicine treats the errors of physiology by restoring the body's hormones and nutrients to optimal levels**

Conventional Medicine

vs

Physiologic Medicine

1

One Thing
"Single Mode"

Many Things
"Multimodal"

Conventional Medicine vs Physiologic Medicine

1

Conventional Medicine

Lipitor | Xanax | Boniva | Viagra | Ambien | Topomax | Lisinopril | Toprol | Cyclosporin

Physiologic Medicine

Testosterone | Estrogens | DHEA | Progesterone |Pregnenolone | Thyroid | Melatonin | Vitamin D3 | Magnesium | Zinc | Vitamin E | Saw Palmetto | and others…

Many

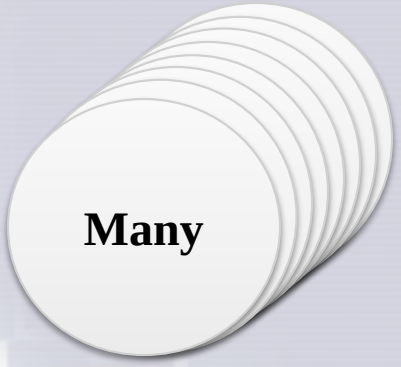
Question

What are you deficient in?

Conventional Medicine *VS.* Physiologic Medicine

Physiologic Medicine

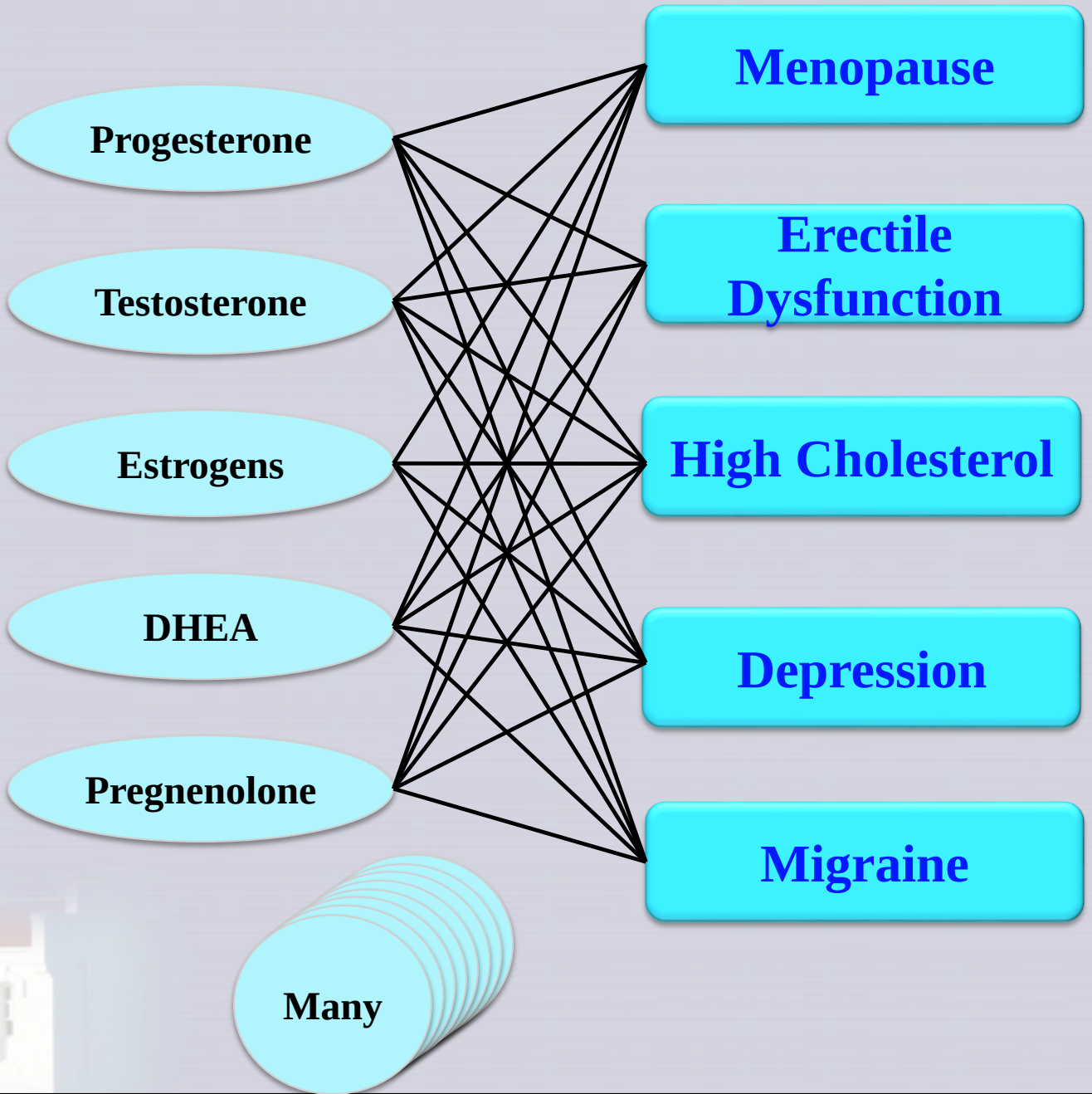
Testosterone | Estrogens | Progesterone | DHEA | Pregnenolone | Thyroid | Melatonin | Vitamin D3 | Zinc | Magnesium | Vitamin E | Vitamin C | 5-HTP | MSM | Saw Palmetto | and others…



Balancing Your Physiology:

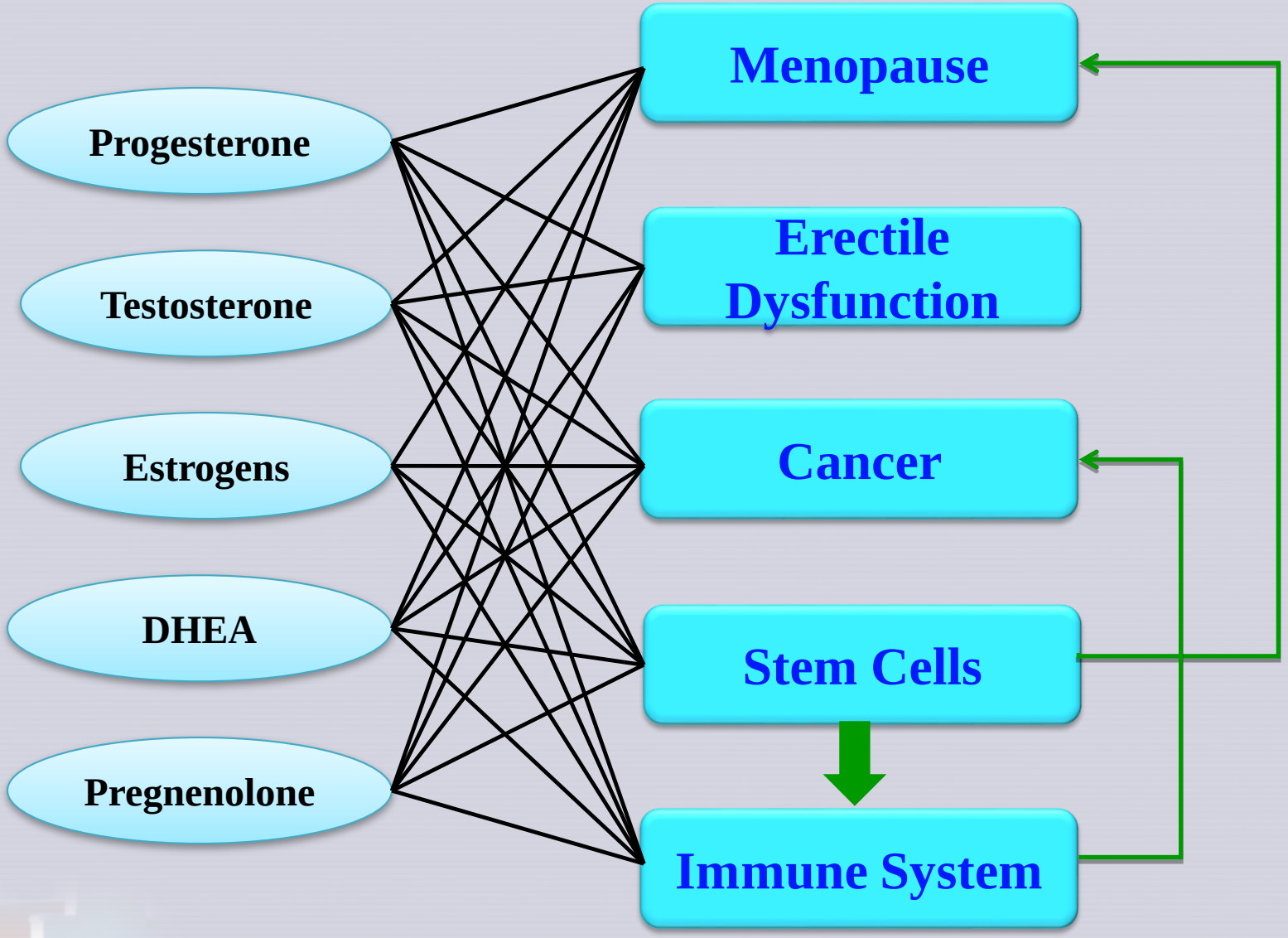
Physiologic Medicine

Cause - Solution



Physiologic Medicine

Cause - Solution



Hypercholesterolemia

↓

Coronary Heart Disease

↓

Hormonorestorative Therapy

Hypercholesterolemia

↓

Coronary Heart Disease

↓

Stem Cells Therapy

Hypertension

↓

Congestive Heart Failure

↓

Hormonorestorative Therapy

Hypertension

↓

Congestive Heart Failure

↓

Stem Cells Therapy

Example of Stem Cell Therapy effect

- retrospective, questionnaire-based study showed an overall improvement in well-being when it was used for anti-aging purpose[49]

- clinical trial on patients with diabetes type II shown:

✓ statistically significant decrease in the fasting blood sugar and the level of hemoglobin A1C

✓ statistically significant decrease in triglyceride levels

✓ improvement in kidney function and a statistically significant decrease in creatinine levels[50]

Example of Stem Cell Therapy effect

- **the resulting meta-analysis concluded that Bone Marrow-derived Stem Cells (BMCs) therapy consistently improves cardiac performance parameters (LVEF, LVESV, and LVEDV) when compared to placebo, even after the establishment of primary intervention. It is also safe to use and prevents the development of recurrent MI and HF[56]**

- **the cardiac stem/progenitor cells isolated by a combined clonal selection and surface marker approach possessed multiple stem cell features important for cardiac regeneration[57]**

Example of Stem Cell Therapy effect

- **both bone marrow-derived mesenchymal stem cells (BMSCs) and adipose tissue-derived stem cells (ASCs) are multipotent and may be induced by 5-azacytidine to differentiate into cardiomyocytes. ASCs may be a better candidate as a novel source of cell therapy in sinus bradycardia disorders than BMSCs[58]**

Stem cells – steroidopenia - cholesterol?

- **steroidogenic factor 1 (SF-1)/adrenal 4 binding protein is an essential nuclear receptor for steroidogenesis, as well as for adrenal and gonadal gland development**

- **SF-1 can transform long-term cultured mouse bone marrow mesenchymal cells (BMCs) into ACTH-responsive steroidogenic cells[22]**

Stem cells – steroidopenia - cholesterol? (cont.)

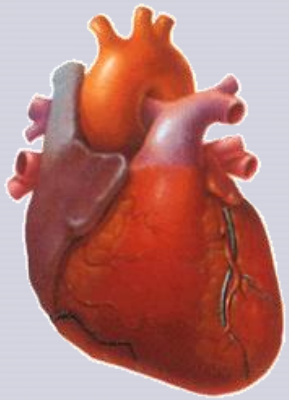
- steroidogenic property of adipose tissue-derived mesenchymal cells (AMCs) was rather different from that of BMCs, especially in steroidogenic lineage
- AMCs were much more prone to produce adrenal steroid, corticosterone rather than gonadal steroid, testosterone, whereas the contrary was evident in BMCs
- such marked differences in steroidogenic profiles between AMCs and BMCs were also evident by the changes of steroidogenic enzymes[22]

Cholesterol - stem cells

- **hypercholesterolemia associated with enhanced stem cell mobilization[59]**

- **hyperlipidemia is common in the first 2 years after allogeneic hematopoietic stem cell transplantation (HSCT)[60]**

Hypercholesterolemia



Hormonorestorative therapy - definition

In 1996 we employed the term hormonorestorative therapy (HT) into our practice for the regimen that was used for our patients.

Hormonorestorative therapy is the multi-hormonal therapy with the use of a chemically identical formula to human hormones and is administered in physiologic ratios with dose schedules intended to simulate the natural human production cycle and allows to restore the optimal level of hormones.

One of the most significant age-related events is an alteration in amplitude and pulsatile pattern of hormone release.[51] Hormone restoration should provide a serum hormone profile similar to that found in normal physiology.

Basic Hormonorestorative therapy

HT includes a combination of several bio-identical hormones:

- pregnenolone
- dehydroepiandrosterone (DHEA)
- triestrogen (women)
- progesterone
- testosterone
- Armour thyroid
- melatonin
- hydrocortisone
- aldosterone

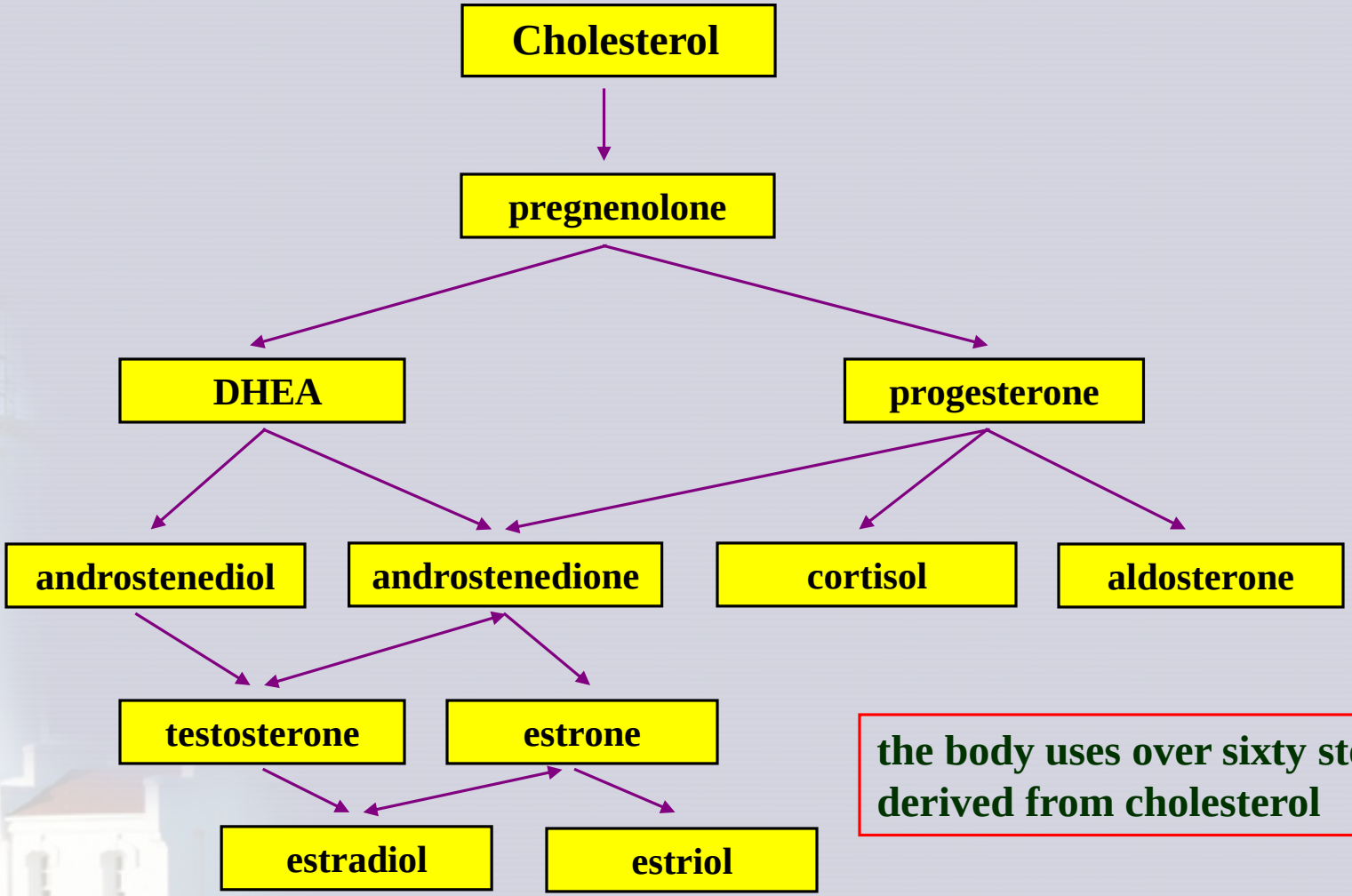
Vitamin D-3 is a part of optimization therapy for cholesterol

The goal of hormonorestorative therapy:

to restore vital forces that control the optimal physiology to treat the patient, not the illnesses that have befallen them

- most diseases represent a manifestation of a long established derangement of vital forces
- the derangement of the vital force had happened due to a deficit of the surveillance control system resulting in an abnormality of hormonal metabolism
- **the vital force is hormonal health and physiological balance**

Metabolism of Cholesterol
(simplified version)



the body uses over sixty steroids derived from cholesterol

New hypothesis of the etiology and pathogenesis of hypercholesterolemia: (hormonodeficit hypothesis of hypercholesterolemia)[52]

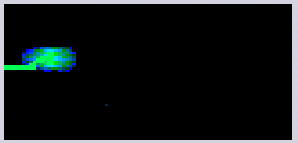
- this hypothesis implies that hypercholesterolemia is the reactive consequence of enzyme-dependent down regulation of steroid hormone biosynthesis and their interconversions

- in short, hypercholesterolemia is the compensatory mechanism for declined production of steroidal hormones

Note!
We believe that:
- a high cholesterol level is a consequence of a low production of steroid hormones
- a low cholesterol level is a cause of a low steroid hormones production

Material and Method:

- we retrospectively analyzed the results of two studies that included 155 patients with hypercholesterolemia[53,54]



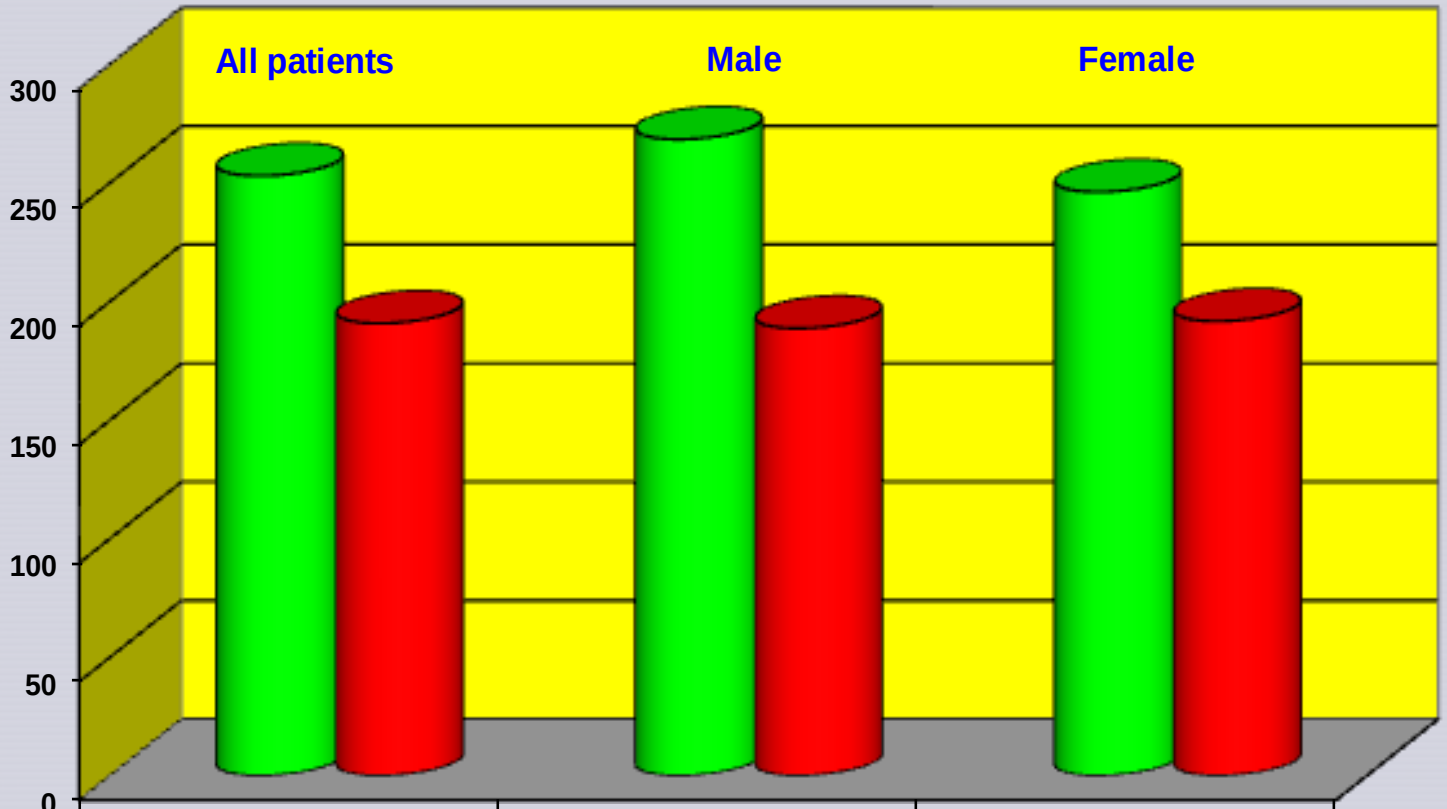
Material and Method:

- we analyzed 112 patients with hypercholesterolemia[53]
- mean age – 54.2 (from 22 to 81yr)
- male to female ratio – 1:2.3 (34-78)
- follow up duration – 3-144 months

Results:

- acute morbidity of HT was zero
- the mean serum TC decreased from 252.9 mg/dL before treatment to 190.7 mg/dL after intervention (dropped 24.6%)
- serum TC normalized in 71 patients (63.4%)
- 41 patients (36.6%) still have serum TC levels slightly higher then normal

Total Cholesterol Before and After Hormonorestorative therapy



	1	2	3
Before Treatment	252.9	268.3	246.1
After Treatment	190.7	188.6	191.6

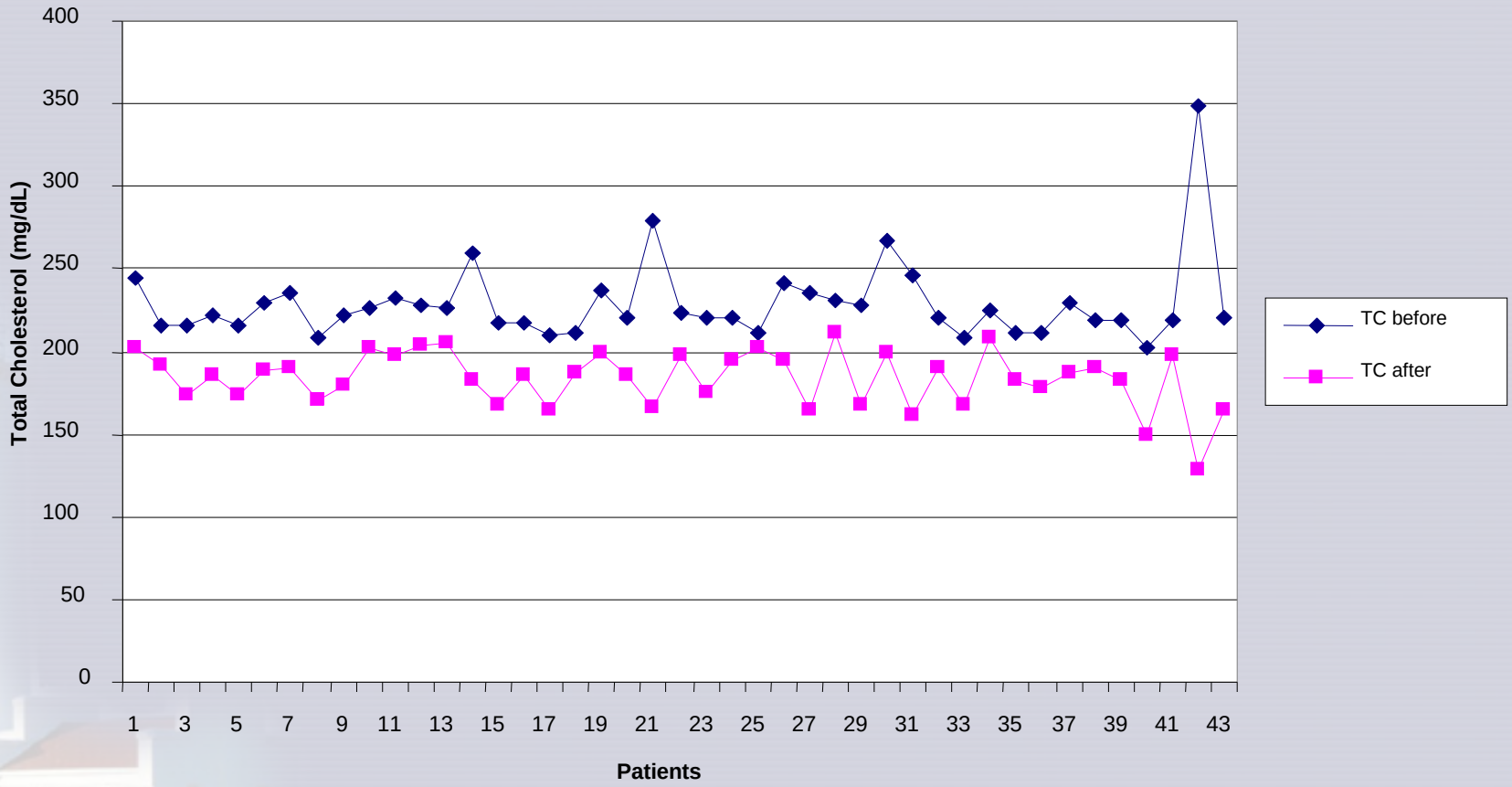
Correction of Steroidopenia[54]

- we analyzed 43 patients
- mean age - 58.4 years
- 12 males and 31 females

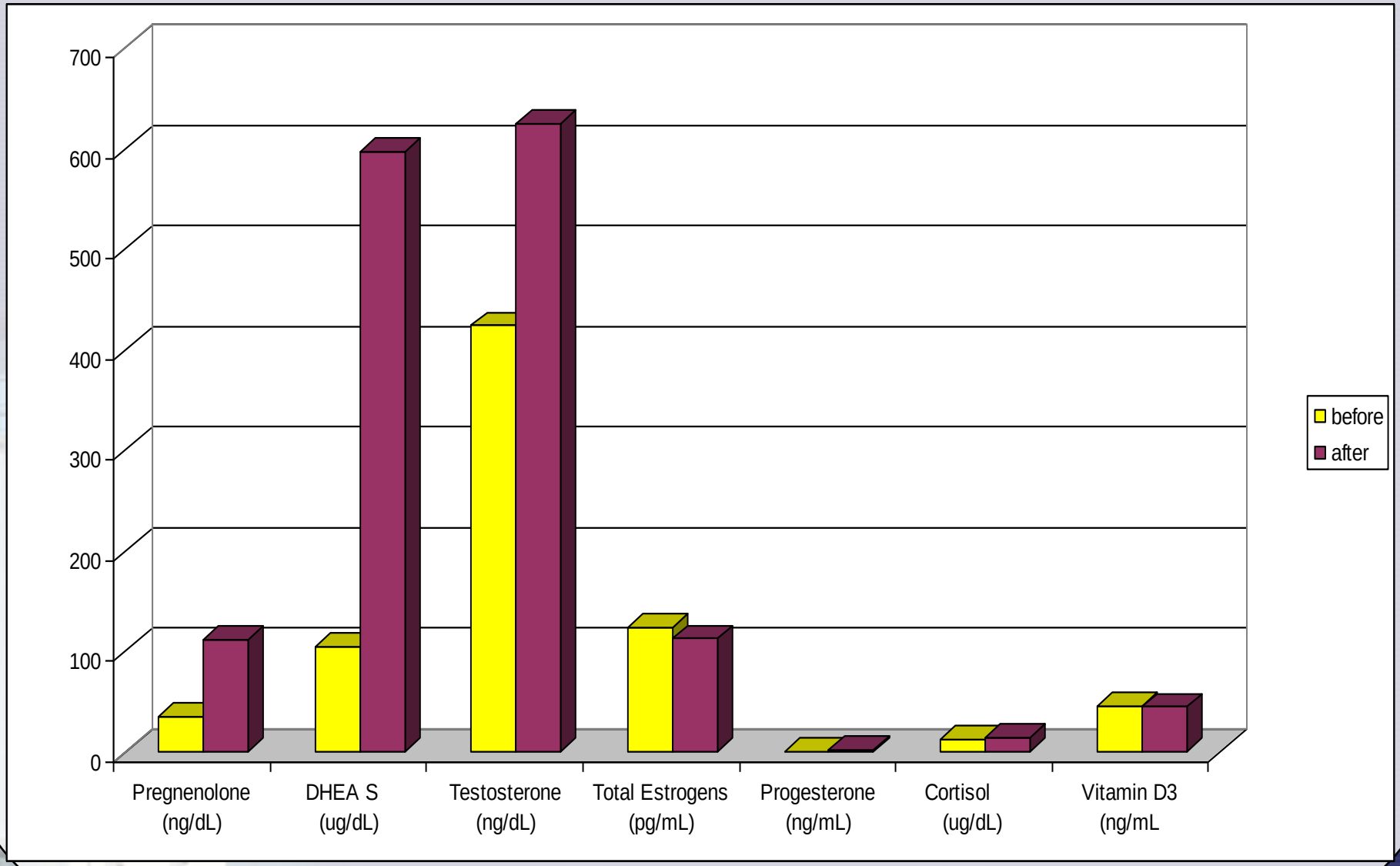
Results:

- the mean serum TC decreased from 228.8 mg/dL before treatment to 183.7 mg/dL after intervention (dropped 19.7%)
- 7 patients still had cholesterol levels ranging from 202 mg/dL to 211 mg/dL but all of these patients had a beneficial drop in TC
- HT was associated with statistically significant elevations in pregnenolone, DHEA Sulfate, testosterone, progesterone, but not in total estrogen, cortisol, or vitamin D-3 in both men and women

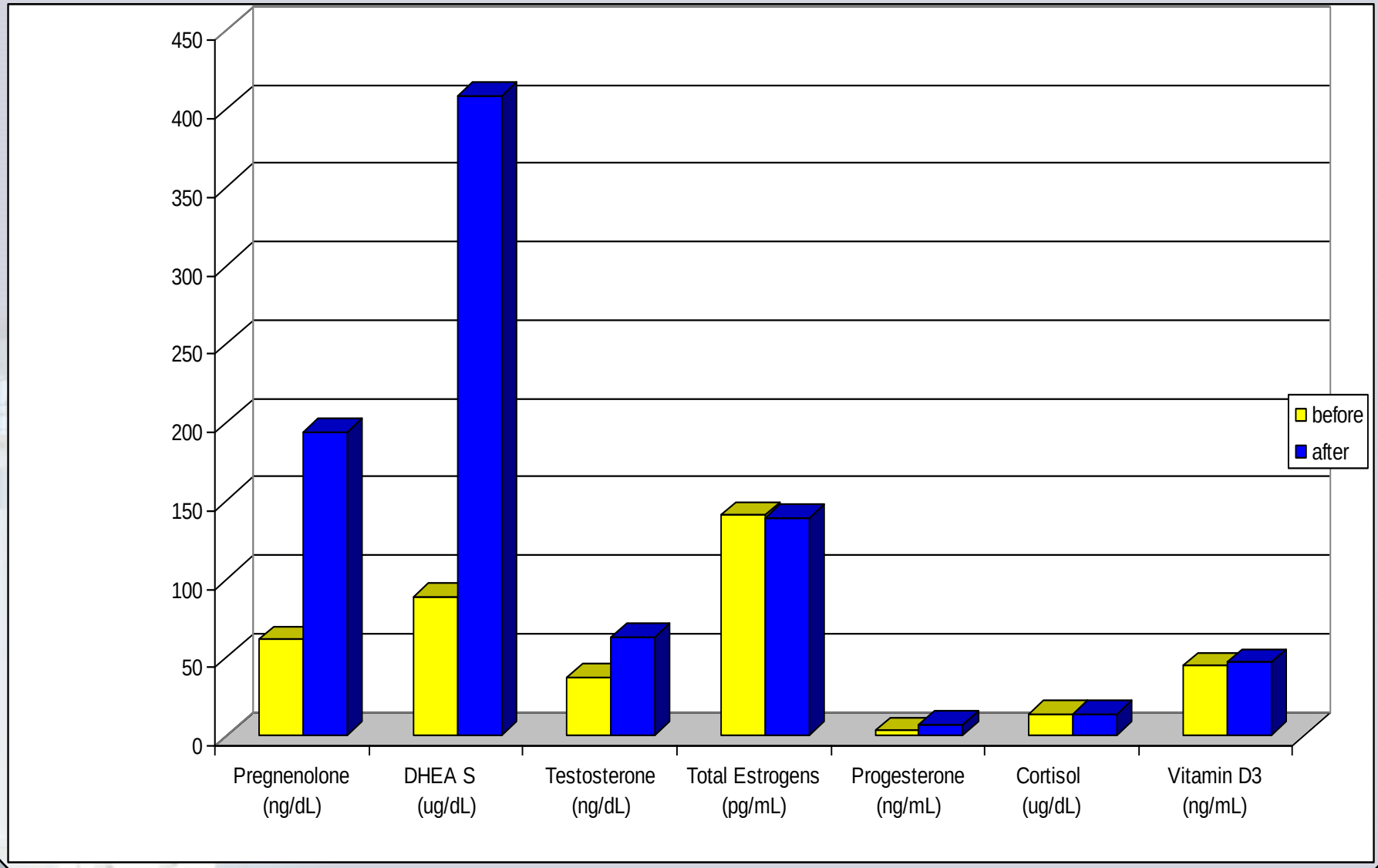
Total Cholesterol Before and After Hormonorestorative therapy



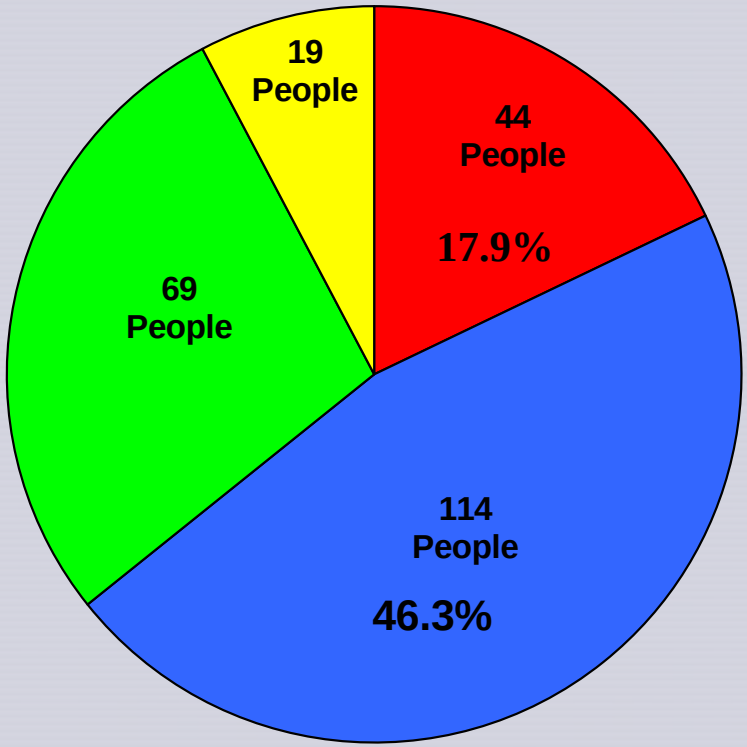
Steroid hormone levels in males before and after Hormonorestorative Therapy



Steroid hormone levels in females before and after Hormonorestorative Therapy



Average distribution of cortisol range



246 patients:

men: 158

women: 88

- **percentage of people with high cortisol (over 22.4) is 7.7%**
- **majority of patients (46.3%) had less than optimal level**

Dzugan SA, Scipione A, Vandenbroeke M, Kuznetsov AS. Cortisol production in relationship to age. The Health of Donbass. 2006;2:73-75.

Depression

- **DHEA, a steroid prominent in the blood and cerebral environment of humans, but which decreases markedly with age and during major depressive disorder, regulates neurogenesis in the hippocampus and modulates the inhibitory effect of increased corticoids on both the formation of new neurons and their survival[5]**

Depression (cont.)

- DHEA increases the proliferation of progenitor cells in the adult hippocampus and also has antidepressant activity[7]
- DHEA can be a useful adjunct therapy for depression since altered neurogenesis has been linked to the onset or recovery from depression

Nociceptive system

- **neurosteroids are steroids produced within the nervous system and involve in important neurophysiological processes**

- **neuroanatomical and neurochemical results demonstrate the occurrence of neurosteroidogenesis in nociceptive pathways and strongly suggest that neurosteroids may control pain mechanisms[61]**

Collagen metabolism

- **DHEA can increase procollagen synthesis and inhibit collagen degradation by decreasing matrix metalloproteinases (MMP)-1 synthesis and increasing tissue inhibitor of matrix metalloprotease (TIMP-1) production in cultured dermal fibroblasts**

- **DHEA was found to inhibit ultraviolet (UV)-induced MMP-1 production and the UV-induced decrease of procollagen synthesis[62]**

Aged skin

- **DHEA induced the expressions of transforming growth factor-beta1 and connective tissue growth factor mRNA in cultured fibroblasts and aged skin[62]**

Crohn's disease

- several promising therapies such as stem cell transplantation and hormonal therapies that includes growth hormone and dehydroepiandrosterone are the novel therapies for Crohn's disease[63]

Spinal cord trauma

- it is now widely accepted that progesterone brings neuroprotection in lesions of the peripheral and central nervous system

- progesterone effects on oligodendrogenesis and myelin proteins may constitute fundamental steps for repairing traumatic injury inflicted to the spinal cord[12]

- when spinal cord injury is produced at the thoracic level, several genes become sensitive to progesterone in the region caudal to the lesion site[11]

Spinal cord trauma (cont.)

- progesterone treatment increased the mRNA of brain-derived neurotrophic factor (BDNF) and BDNF immunoreactivity in perikaryon and processes of motoneurons, whereas chromatolysis was strongly prevented

- progesterone-induced BDNF might regulate, in a paracrine or autocrine fashion, the function of neurons and glial cells and prevent the generation of damage

- progesterone restored myelination, according to measurements of myelin basic protein (MBP) and mRNA levels, and further increased the density of NG2+-positive oligodendrocyte progenitors[11]

Parkinson's Disease

- **mesenchymal stem cells can be considered as an ideal source for replacing lost cells in degenerative diseases like Parkinson's. Hence, the use of these cells in the differentiation of dopaminergic neurons becomes significant and thrives as a therapeutic approach to treat Parkinson's disease.[89]**

- **The results obtained suggest that progesterone and estradiol should be useful in producing higher proportions of dopamine neurons from embryonic stem cells in the treatment of Parkinson's disease.[90,91]**

Ligaments and degenerative joint disease

- **The use of autologous bone marrow aspirate concentrate (BMAC) or adipose-derived progenitor cells (ADPC) with platelet-rich plasma (PRP) combination shows promise for the treatment of early partial cranial cruciate ligament (CCL) tears in dogs[85]**

- **innovative therapy for degenerative joint disease (DJD) combines the potential chondrogenic differentiation of MSCs inside equine adipose tissue with the proliferative effect of growth factors present in platelet rich plasma (PRP)[88]**

Pterygium

- **proliferation of pterygium fibroblasts can be suppressed by progesterone due to inhibitory effect on cholesterol esterification[84]**

AMD

- **Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) are promising technologies that can potentially provide an unlimited source of cells for cell replacement therapy in the treatment of retinal degenerative disorders such as age-related macular degeneration (AMD), Stargardt disease, and other disorders[86]**

Insulin Dependent Diabetes Mellitus

- **Mesenchymal stem cells (MSC) seems to have a specific and beneficial characteristics due to their in vivo as well as in vitro potential to mimic a pancreatic endocrine phenotype and immune-regulatory actions. MSC have the capacity to tweak endogenous tissue and cells of immune system and have been proven as secure and efficacious cell-based regenerative therapy, to treat diverse autoimmune, degenerative diseases and tissue injuries.[87]**

Endothelial dysfunction

- **endothelial dysfunction seems to be the first step of the atherosclerotic process**

- **in the past few years, it has been demonstrated that injured endothelial monolayer is restored by a premature pool of circulating progenitor cells (PCs) and a more mature one of circulating endothelial PCs (EPCs)[14]**

Endothelial dysfunction (cont.)

- endothelial progenitor cells (EPCs) are bone marrow-derived cells required for endothelial repair
- circulating EPC concentration is low in conditions characterized by endothelial dysfunction
- EPCs are also reduced in hypogonadal men and testosterone treatment restores their concentration[15]

ED, male infertility

- bone marrow stem cells (BMSC) are the best-studied adult stem cells (ASC) and have the potential to treat a wide variety of diseases, including erectile dysfunction (ED) and male infertility[23]

- BMSC were able to improve the erectile function of aged rats[67]

- embryonic stem cells (ESC) could restore the erectile function of rats whose cavernous nerves were experimentally damaged[68]

ED, male infertility (cont.)

- ESC could form male germ cells in vitro[69]
- ESC-derived germ cells were able to generate offspring mice[70]
- BMSC could differentiate into male germ cells[71-73]

adipose tissue-derived stem cells

- several studies demonstrated that ADSC have adipogenic and osteogenic potential[77-81]
- ADSC could also differentiate into chondrocytes and myocytes[82]
- there are hundreds ADSC-related articles were published last few years[23]
- the list of ADSC-differentiated cell types now includes endothelial, epithelial, muscle (cardiac, skeletal, and smooth), Schwann cells, hepatocytes and neurons

ADSC – clinical application

- in 2004 the successful application of adipose tissue-derived stem cells (ADSC) in repairing the cranial defects of a 7-year-old girl who suffered severe head injuries due to an accidental fall was reported[74]

- in 2006 and 2007, two separate papers reported the successful application of ADSC for cosmetic surgeries, primarily breast augmentation, on more than 70 patients[75,76]

Conclusion

- changes in delicate hormonal balance may trigger a cascade of molecular events that can ultimately lead to both aging and serious diseases that need to be addressed

- hormonorestorative therapy as a part of a multimodal method of physiology optimization can be a very effective adjuvant method to stem cell therapy

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