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A Physiologic Approach to the Optimization of Stem Cell Therapy

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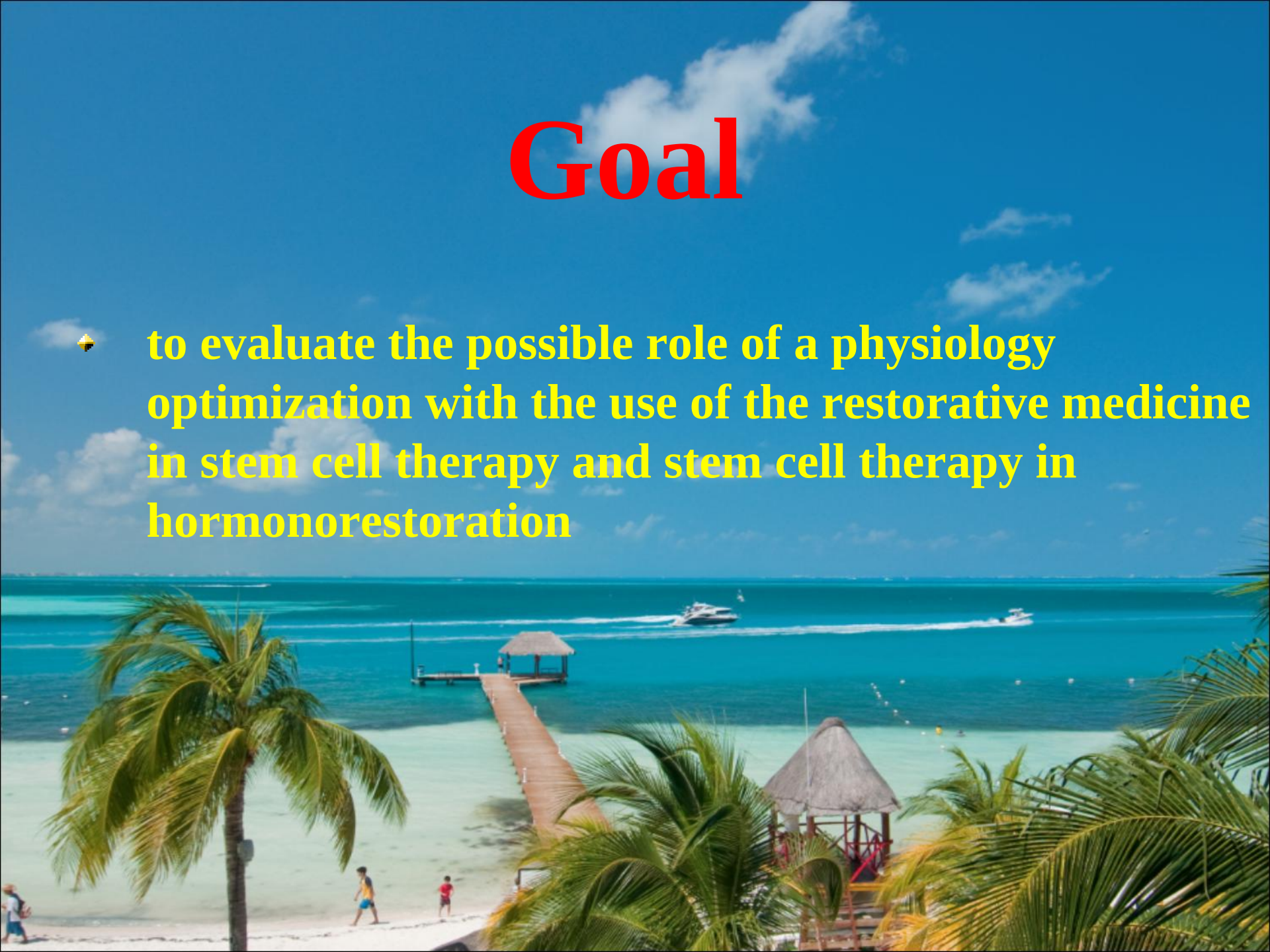
Goal

- to evaluate the possible role of a physiology optimization with the use of the restorative medicine 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**

Stem Cells/Hormones – Body Axis

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

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]**

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]**

- **DHEA increases the proliferation of progenitor cells[7]**

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]
- results of Greek study indicate a high incidence of gonadal dysfunction due to target organ failure in hematopoietic stem cell transplantation recipients[27]

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

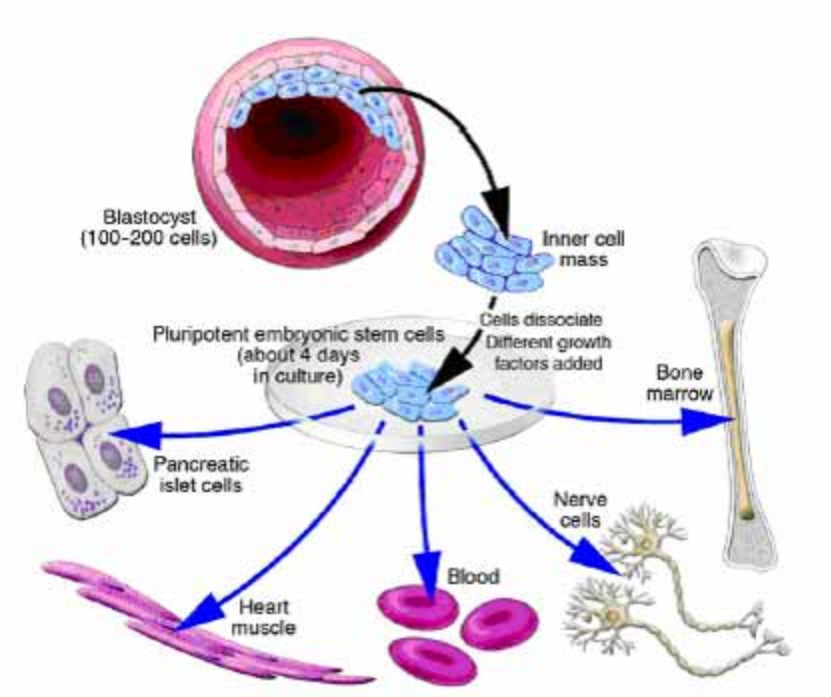
Stem Cells ⟹ Hormones (cont.)

- **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]



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]**

Restoration and Stimulation of Stem Cell Function (cont.)

- **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**
- **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**

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 therapy doctors "play on the same field".

Hypercholesterolemia

↓

Coronary Heart Disease

↓

Hormonorestorative Therapy

Hypercholesterolemia

↓

Coronary Heart Disease

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Stem Cells Therapy

Hypertension

↓

Congestive Heart Failure

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Hormonorestorative Therapy

Hypertension

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Congestive Heart Failure

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Stem Cells Therapy

Conventional Medicine vs Physiologic Medicine

Conventional Medicine

Single mode

Crestor | Zoloft | Fosamax | Viagra | Ambien | Imitrex | Cyclosporin | Atenolol |

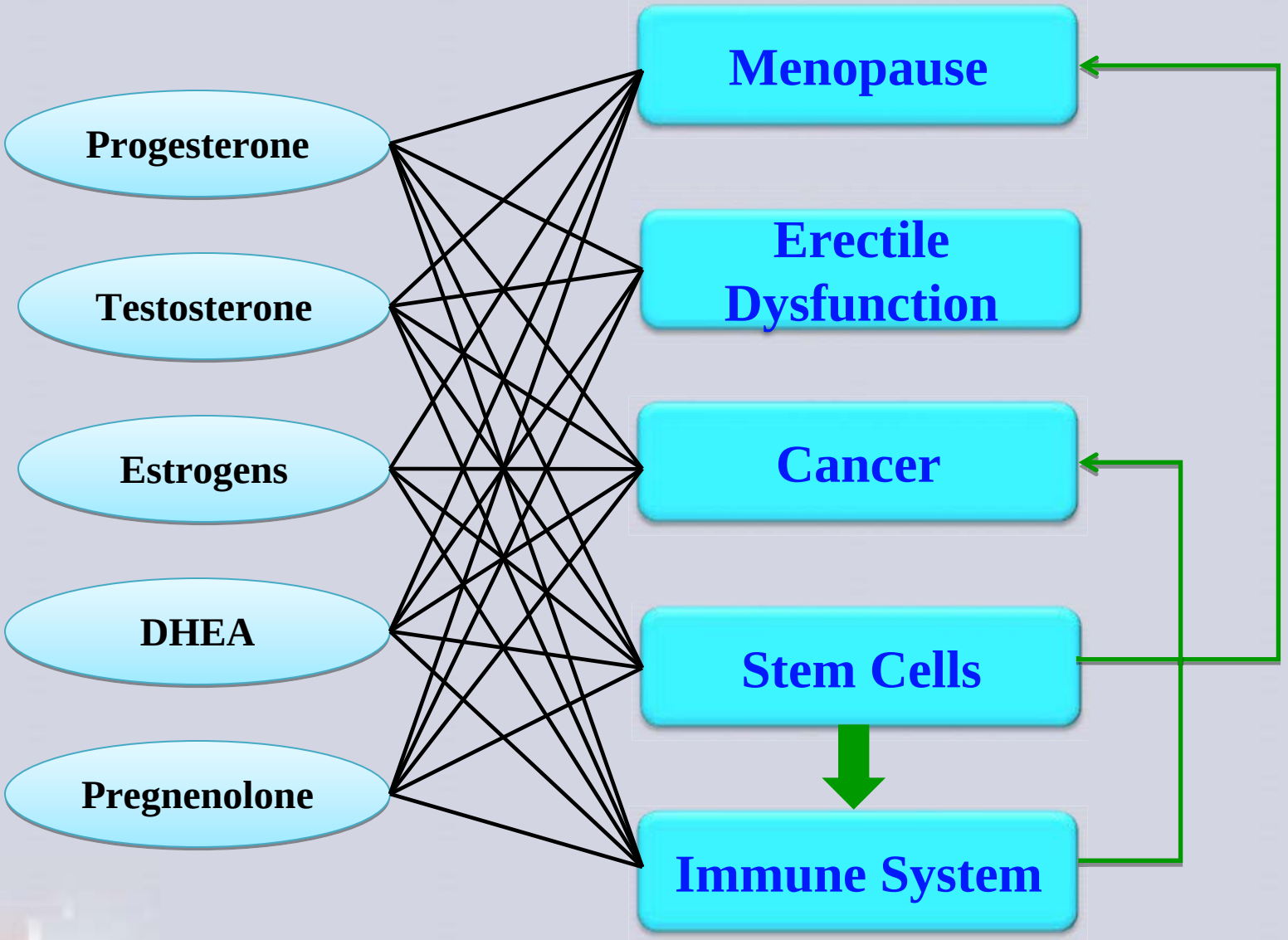
Physiologic Medicine

Multimodal

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

Physiologic Medicine

Cause - Solution



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

Material and Method:

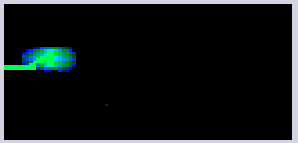
- we retrospectively analyzed the results of two studies that included 155 patients with hypercholesterolemia[53,54]

Basic Hormonorestorative therapy

HT includes a combination of several bio-identical hormones:

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

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



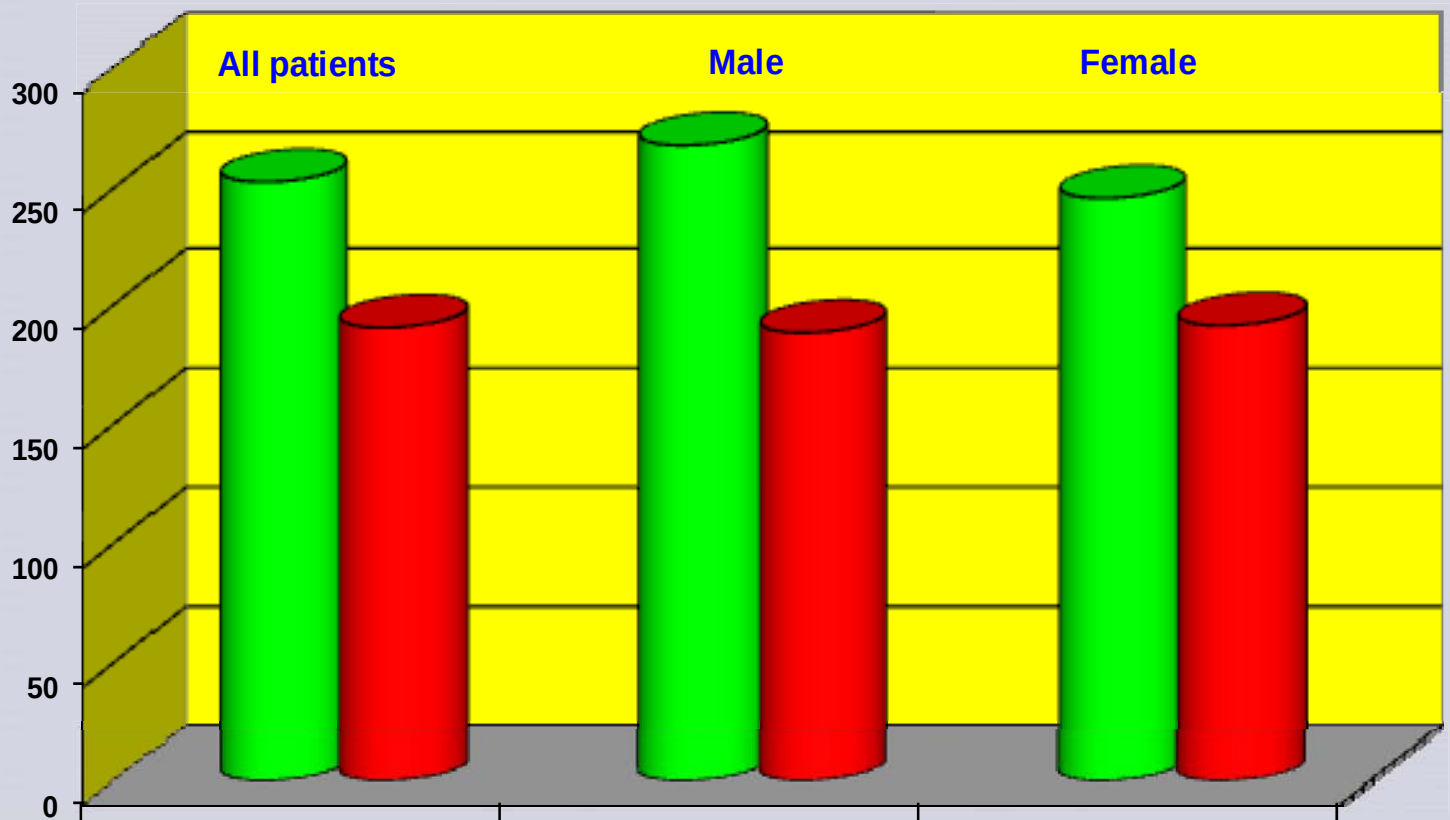
Material and Method:

- 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

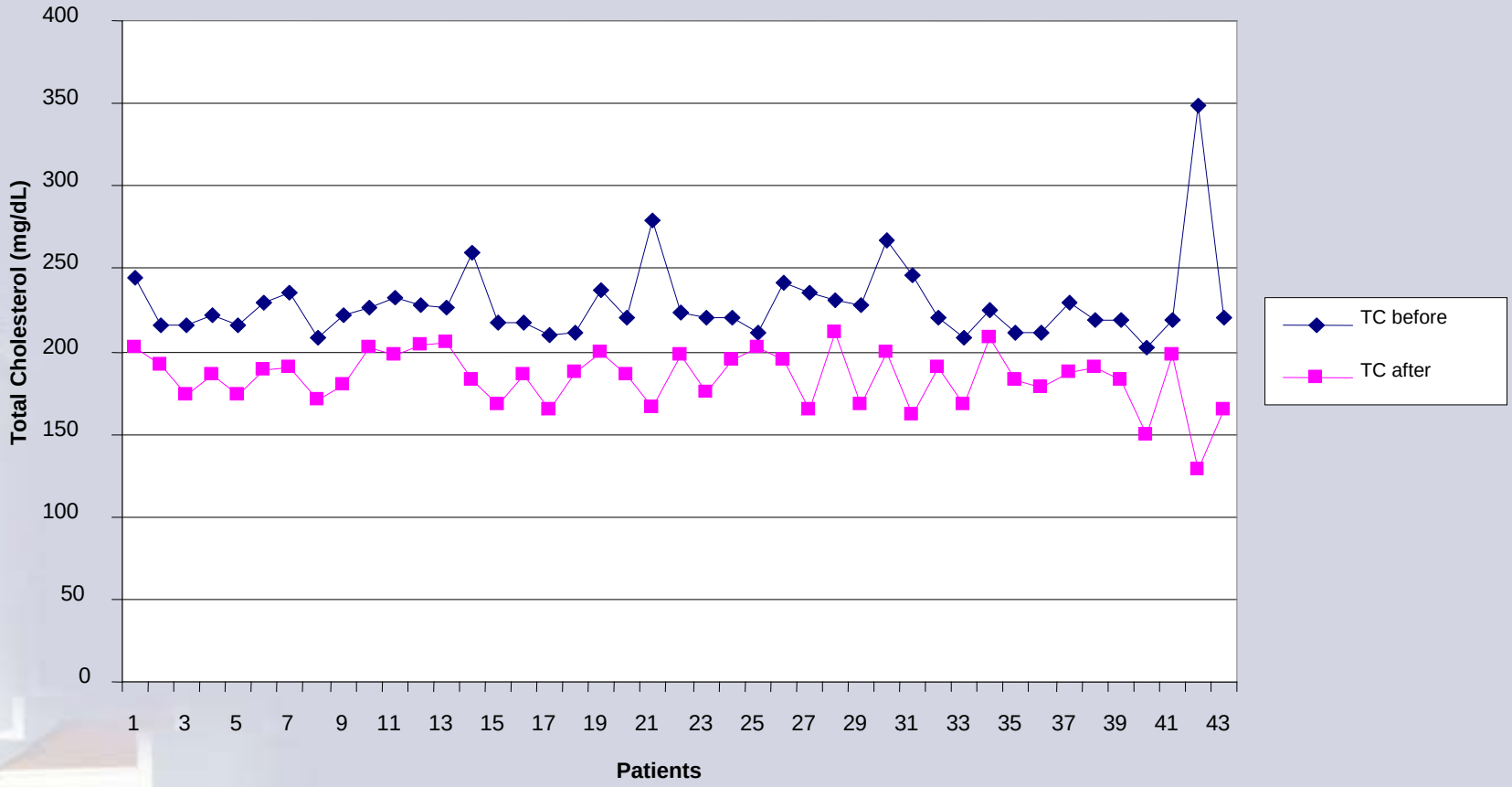
Correction of Steroidopenia[54]

- 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



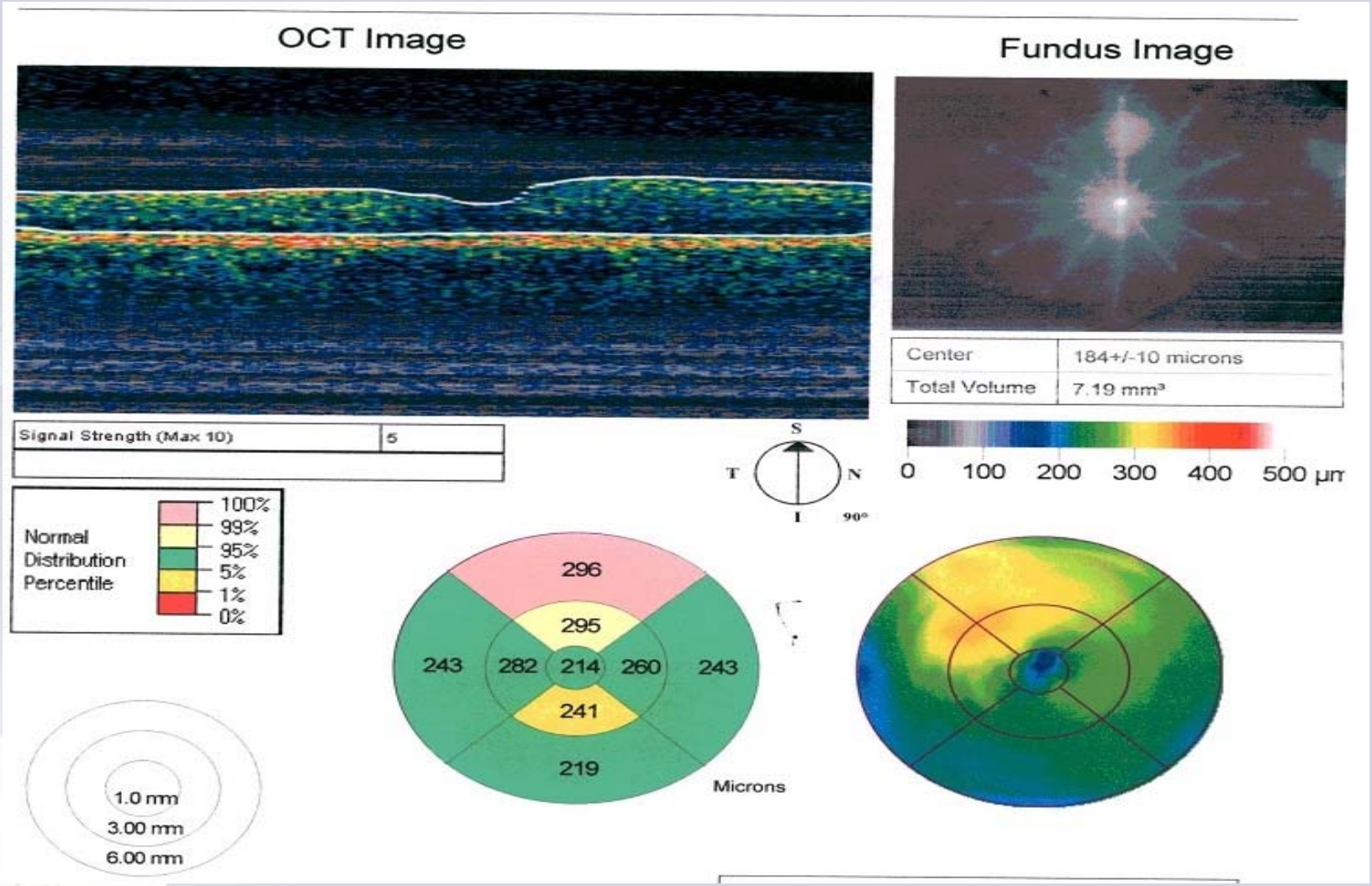
Diabetic retinopathy

Diabetic retinopathy – Stem cell therapy[61-71]

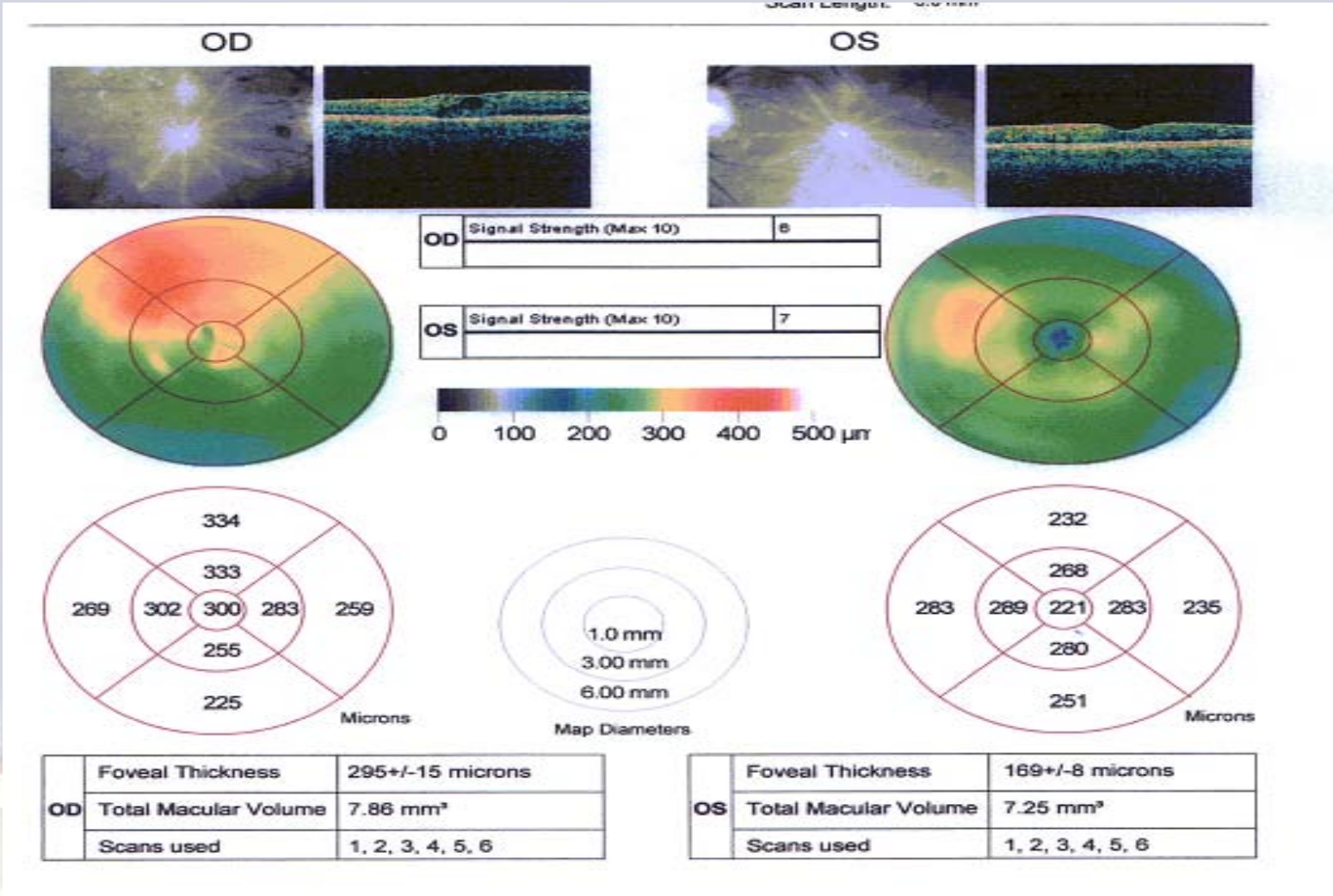
- stem cell therapy is a potentially effective new therapeutic alternative approach in the treatment of diabetic retinopathy

- stem cell technologies hold the promise of autologous grafts to stabilize vision loss through cellular replacement or paracrine rescue effects

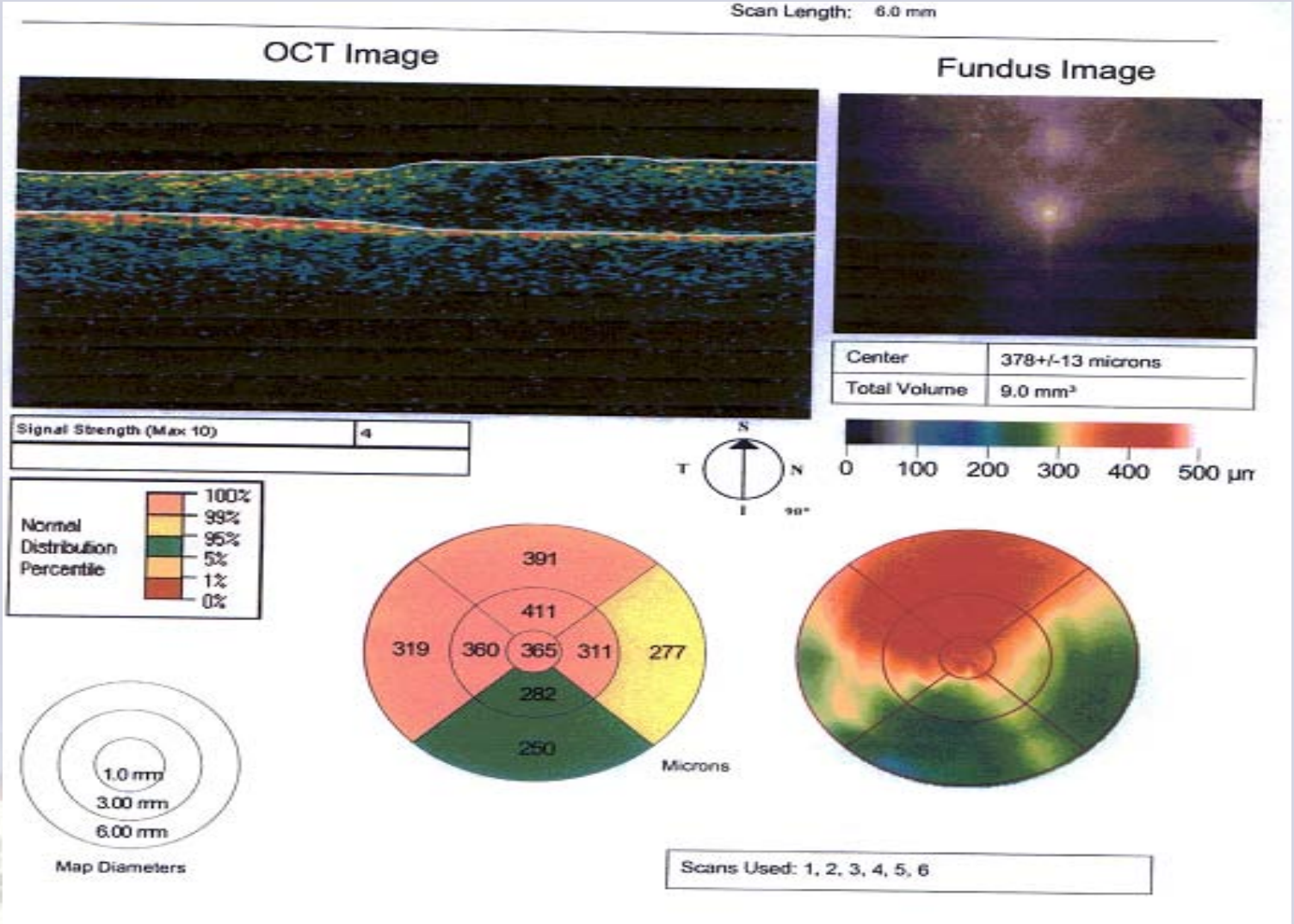
July 2009: patient received 130 laser pulses to the right eye.



May 2010: She received 54 pulses of laser by a highly skilled retinologist. OCT Pre Laser Below.



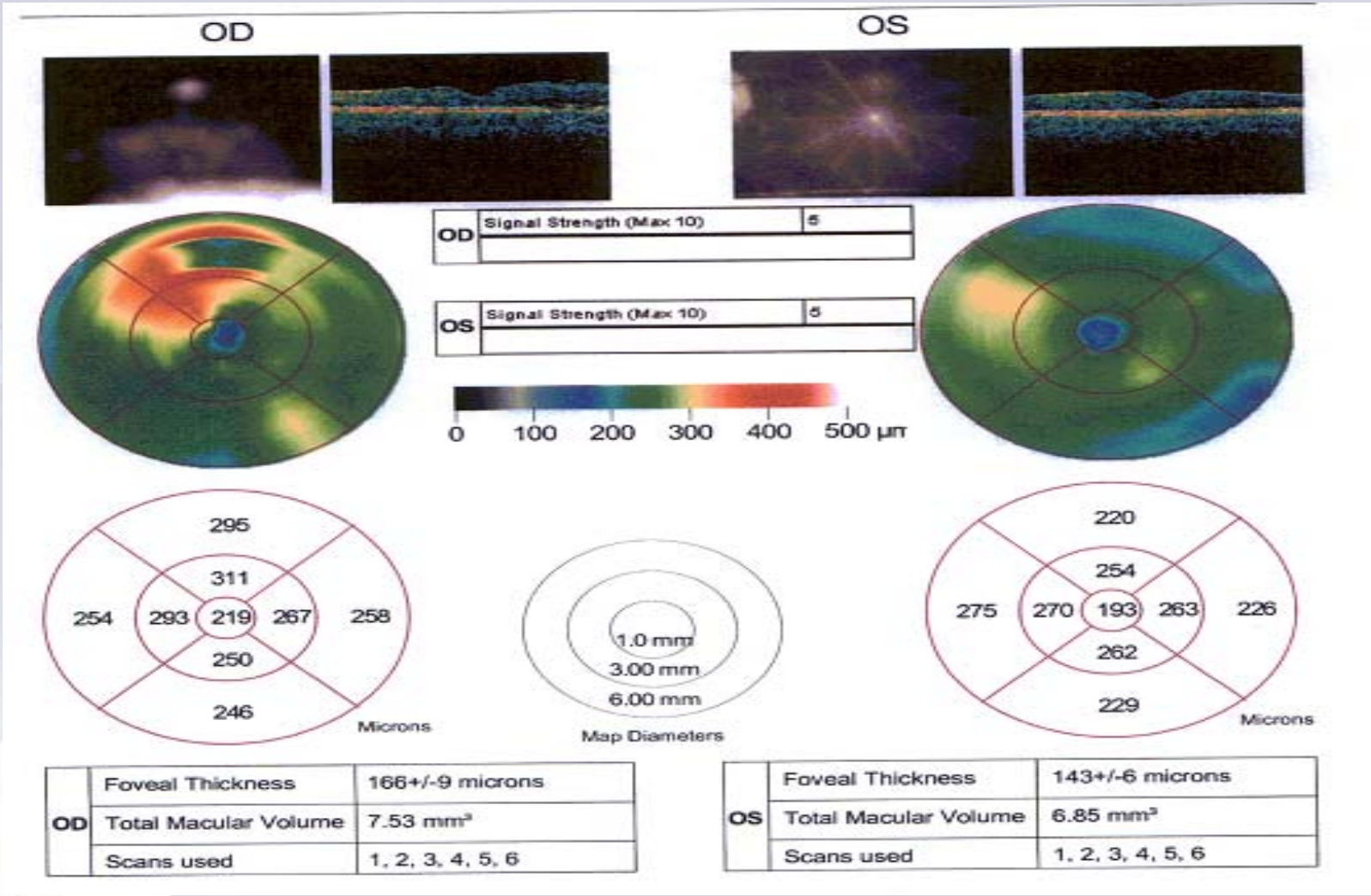
August 2010: Patient told she may need Avastin or Focal Laser. Obviously no improvement from May laser.



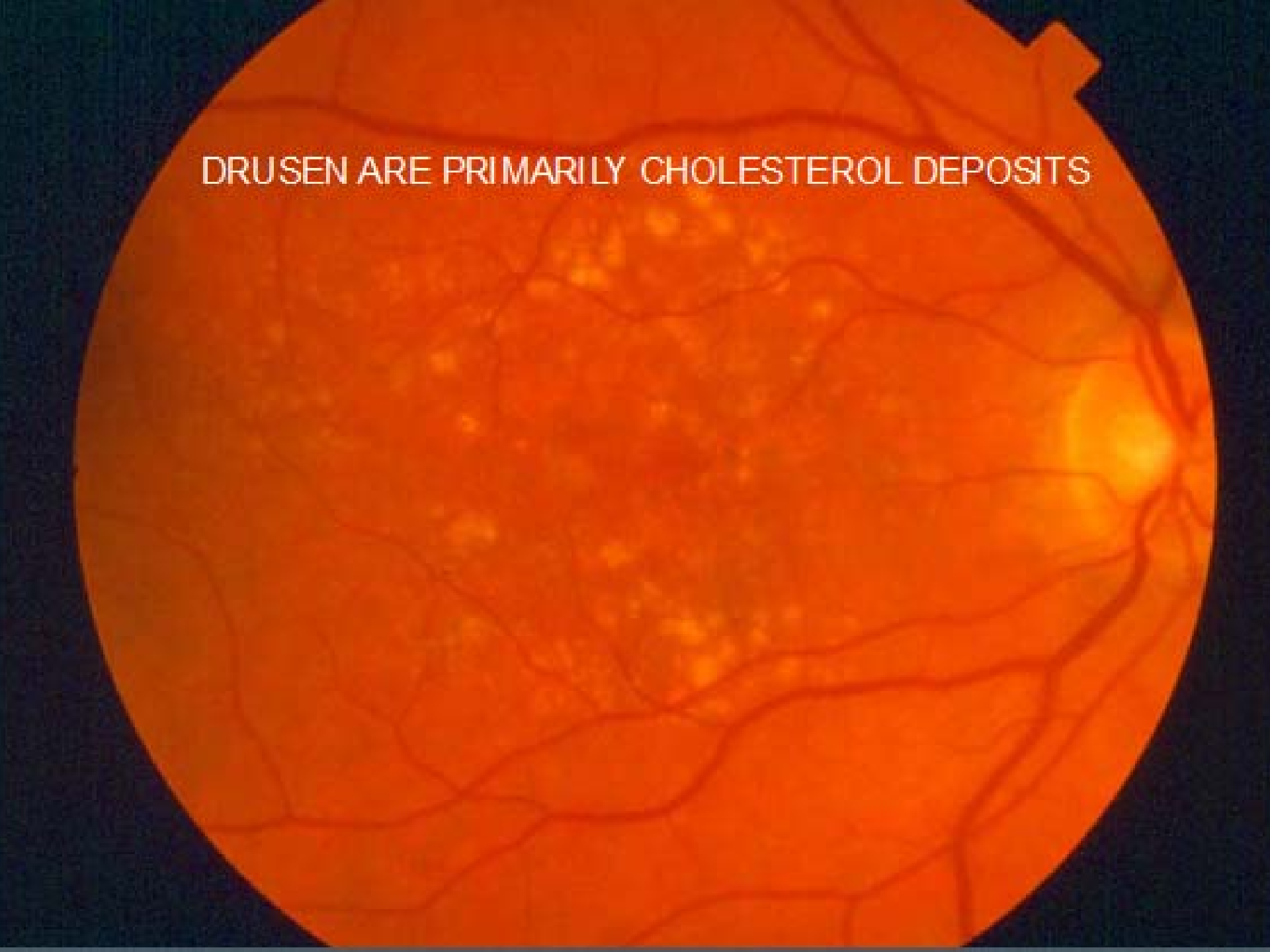
September 2010:

Physiology optimized with Restorative Medicine.

January 2011: Dramatic change in thicknesses. Patient told: Good News. No need for anything. See you in 6 months.



Age-related macular degeneration (dry form)


DRUSEN ARE PRIMARILY CHOLESTEROL DEPOSITS

Why do drusen contain cholesterol?

Our Hypotheses[72]

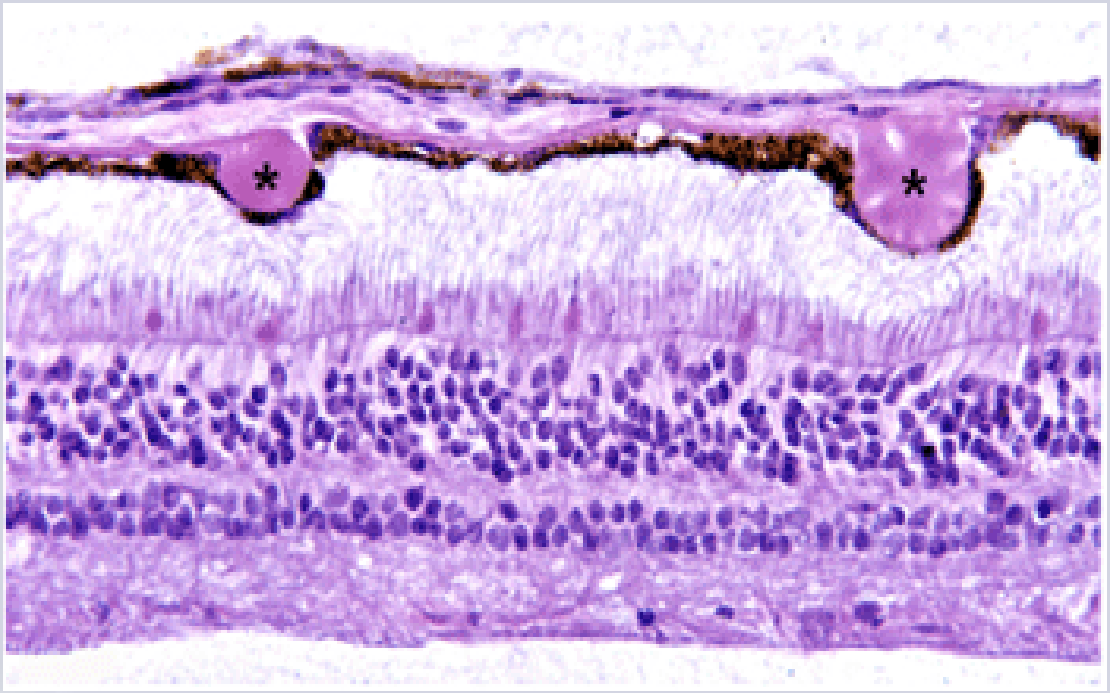
- macula tries to increase the production of steroid hormones by increasing absorption of cholesterol, but it cannot, due to aging enzymatic failure

- it leads to drusen formation and macula degeneration

- low hormones down regulate stem cell function leading to inability of stem cells to maintain optimal macular function and structure

Our Hypotheses

- also, drusen may be the body's attempt to repair micro-breaks in RPE or Bruch's membrane



Histological section shows drusen (asterisks) forming between the retinal pigment epithelium (RPE) and Bruch’s membrane

The eye is external part of the brain

The retina requires steroidal hormones to function!

Steroids in the Retina[73]

- 17α hydroxypregnenolone
- 17α-hydroxyprogesterone
- Dehydroepiandrosterone (DHEA)
- DHEA – S
- Progesterone
- 5α-dihydroprogesterone
- 3α-hydroxy-5α-dihydroprogesterone
- 5α-androstenedione
- Androsterone
- Testosterone
- 5α-dihydrotestosterone
- Deoxycorticosterone
- Androstenediol
- Estrone
- Estradiol
- Pregnenolone

Stem cells and Retinal pigment epithelium

- retinal stem cells exist throughout life within the retina
- the bone marrow can produce stem cells that will differentiate into retinal pigment epithelium cells
- there is a possibility to restore the retinal pigment epithelium with the stem cell therapy

Material and Method[74]

- **we analyzed 53 patient with dry form of macular degeneration**

- **male – 26**
- **female – 27**

Preliminary results

- **our study found that several basic hormones were significantly declined most notably in:**

- **DHEA and pregnenolone in male and female**
- **total estrogen and progesterone in females**

Preliminary results (cont.)

- improvement in dark adaptation
- stability of the macula
- improvement in quality of life

Impression

- physiology optimization with the correction of steroidopenia may help stop the progression of age-related macular degeneration

Conclusion

- **the use of a multimodal method of physiology optimization and stem cell therapy can be a very powerful approach in the treatment of many deteriorative diseases**

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