MAKING CONNECTIONS
5TH ANNUAL PEDIATRIC BRAIN INJURY CONFERENCE AND RESOURCE FAIR

Austin, Texas
October 23, 2021!
8:00 am – 5:30 pm

- Woodlawn Baptist Church
- 4600 Menchaca Road

Hyperbaric Oxygen Therapy Facilitates Stem Cell Implantation: Yet Another Beneficial Effect of HBOT

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Harch Hyperbarics, Inc.
New Orleans, Louisiana

GOALS OF THIS TALK

1. CHARACTERIZE HBOT.
2. Discuss HBOT as a treatment for wounding conditions in any location in the body and of any duration
3. Ask/Answer the questions:
    a., "Why does it work for so many diseases?"
    B. "Does my child have a brain injury?"
    C. "What if my child doesn't have a brain injury?"
    D. "When is the best time to start HBOT?"
4. Discuss HBOT and Stem Cells:
    A. HBOT stimulates production, release of stem cells from bone marrow, and implantation.
    B. HBOT stimulates proliferation and specialization of stem cells at the site of injury.
    C. HBOT facilitates stem cell implantation after injection.
    D. HBOT stimulates proliferation of stem cells for harvest.

WHAT IS HYPERBARIC OXYGEN THERAPY?

WHAT IS HBOT?

ANSWER:

It HAS BEEN an Unanswered Question for 347 years (until 2008)

Physiologic Definition of HBOT

A treatment that uses increased pressure and increased oxygen to treat diseases

HBOT in Global Ischemia, Anoxia, and Coma. Chapter 18.
Textbook of Hyperbaric Med., K.K. Jain (Ed.), 1999

Functional Definition of HBOT

A treatment that exploits all living organisms' sensitivity to pressure and oxygen

Functional Definition HBOT

Everyone understands that all living organisms are sensitive to oxygen; without it they wouldn't exist

Barometric and Hydrostatic pressure

But, what about pressure?

What is pressure?

Something we live with, but never think about.

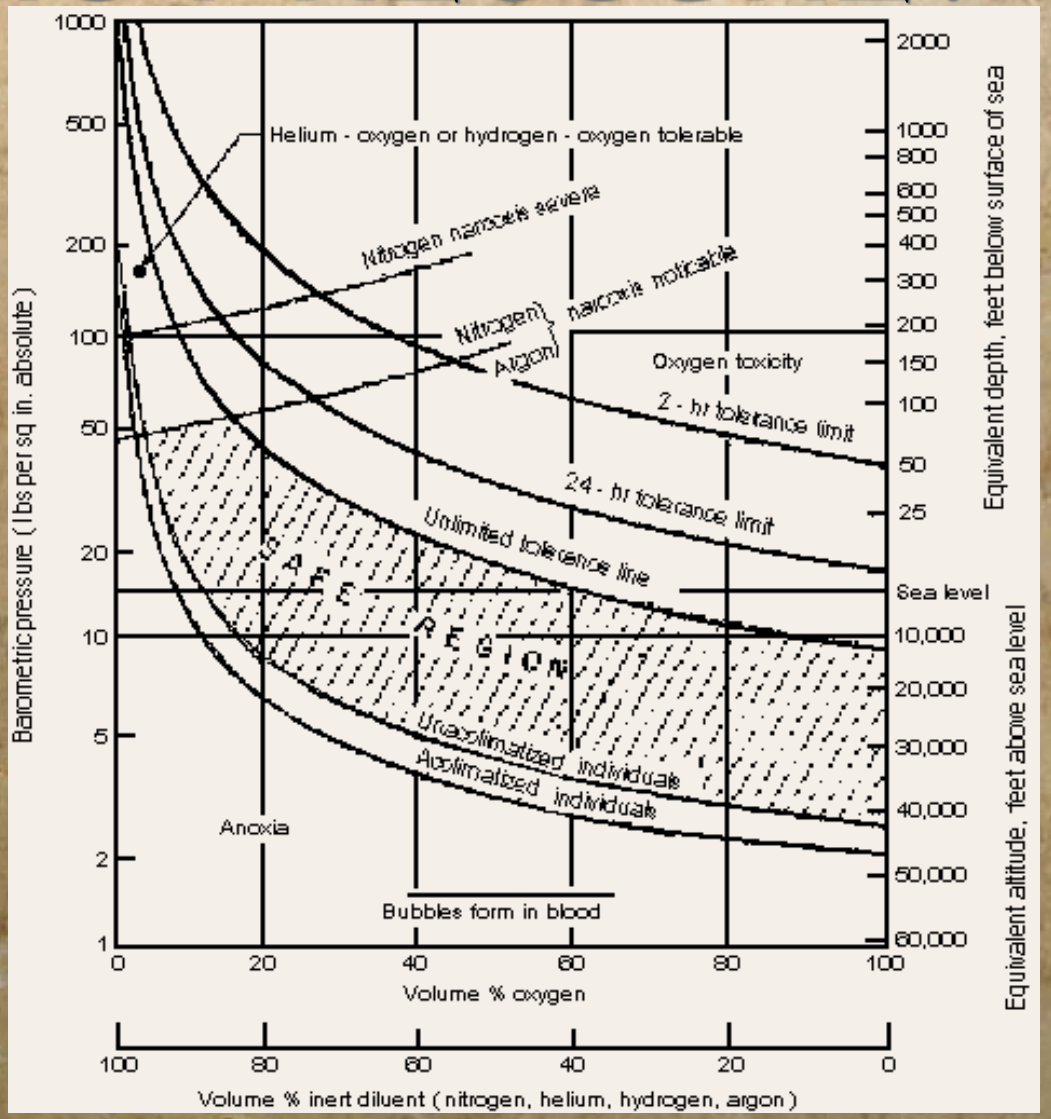
Atmospheric ressure is the weight of air from the elevation at which you are standing to the boundary of the earth's atmosphere/outer space, 62 miles about earth, and hydrostatic pressure is the weight of seawater at whatever depth you are at below the surface.

Atmospheric or Hydrostatic Pressure?

Human Pressure and O_2 Range:

HBOT Rx Range: {

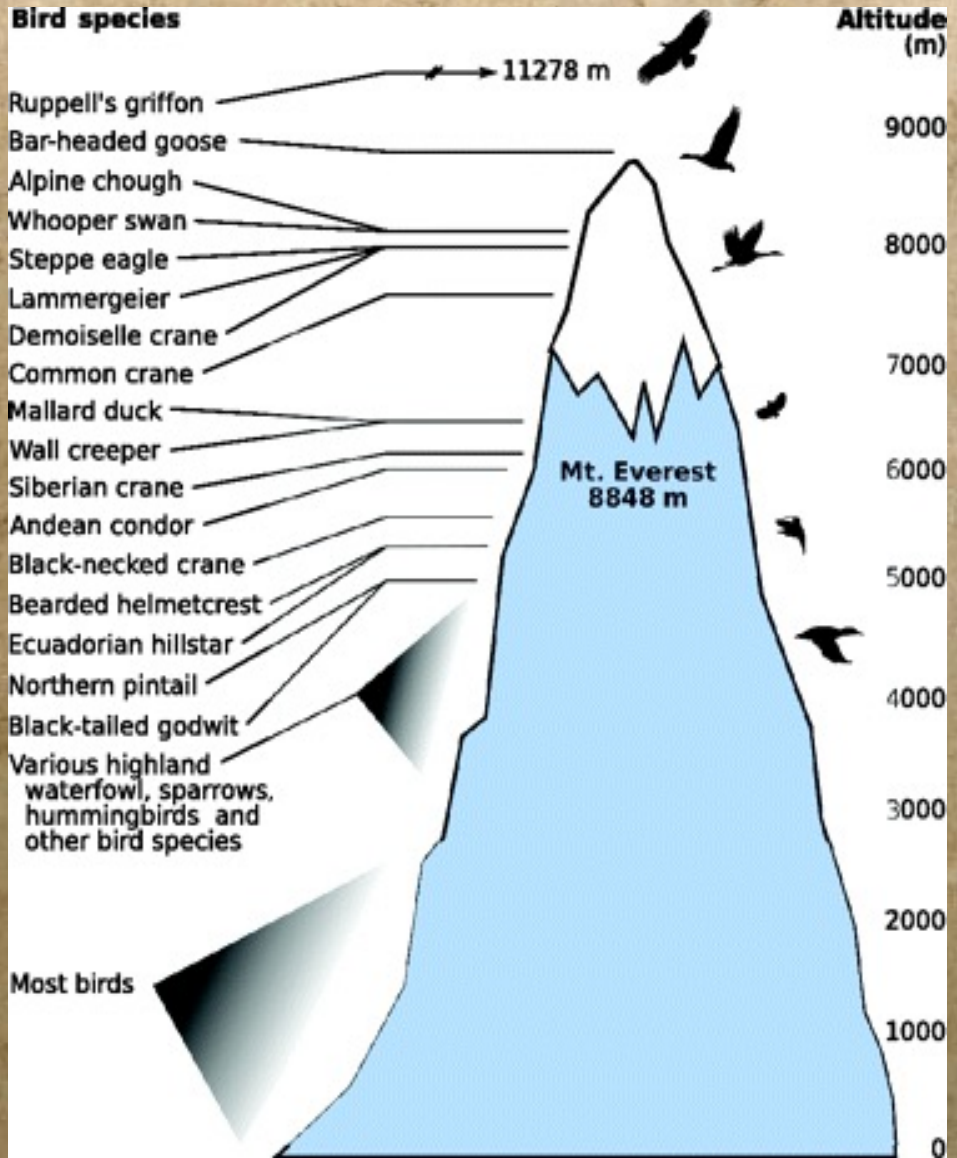
60,000 Ft.Altitude



https://www.reddit.com/r/askscience/comments/5l7nj4/ifwe_could_drain_the_ocean_could_we_breath_or/ –

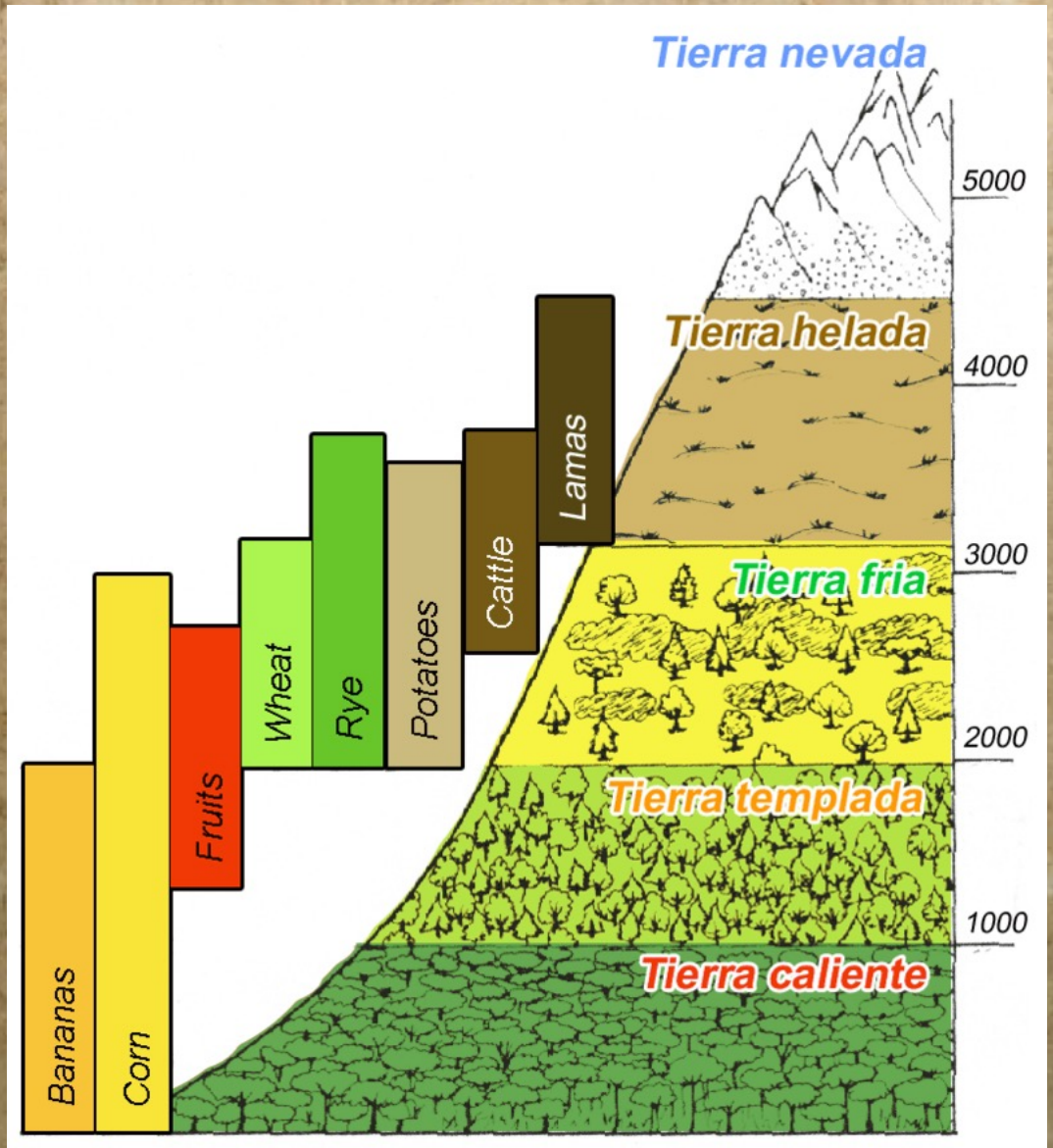
Bird Species at Great Altitude

http://people.eku.edu/ritchisong/birdcirculatory.html



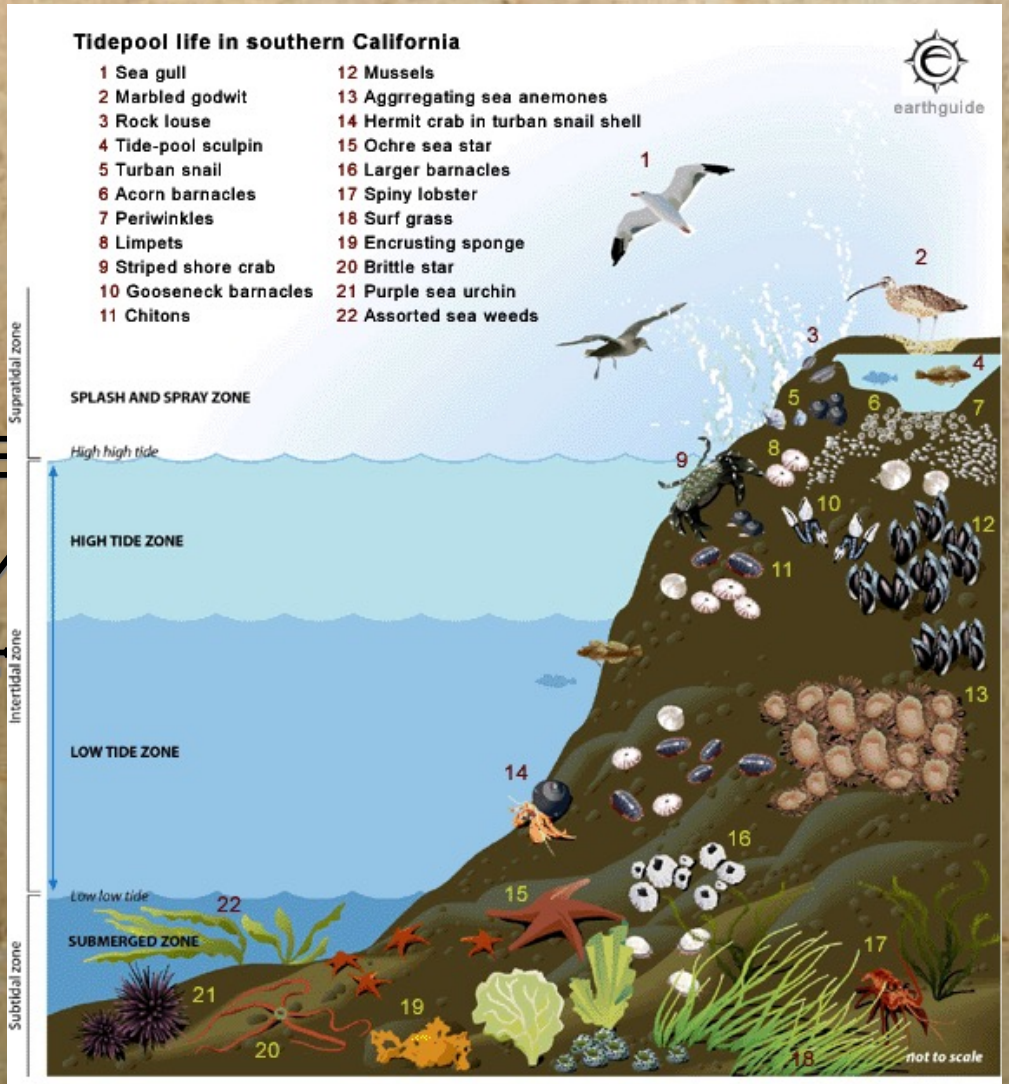
Agriculture and Livestock at Low Altitude (Andes)

https://en.wikipedia.org/wiki/Altitudinal_zonation



Living Organisms at increased atmospheric pressure

http://earthguide.ucsd.edu/earthguide/imagelibrary/images/Tidepool_zones_2.gif



SIO Explorations & Earthguide [http://earthguide.ucsd.edu]

Living Creatures at Great Pressures

http://slideplayer.com/slide/8678805/

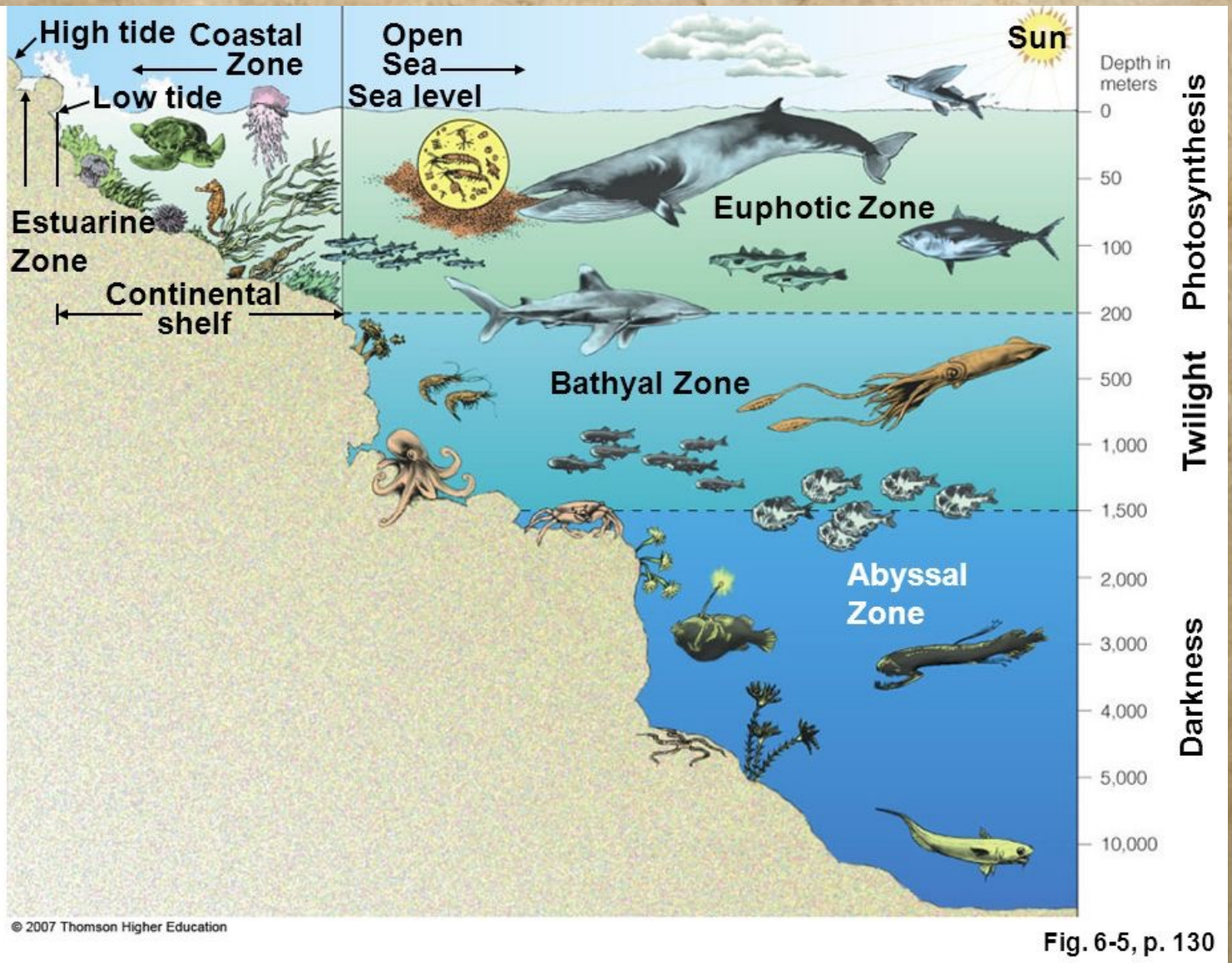
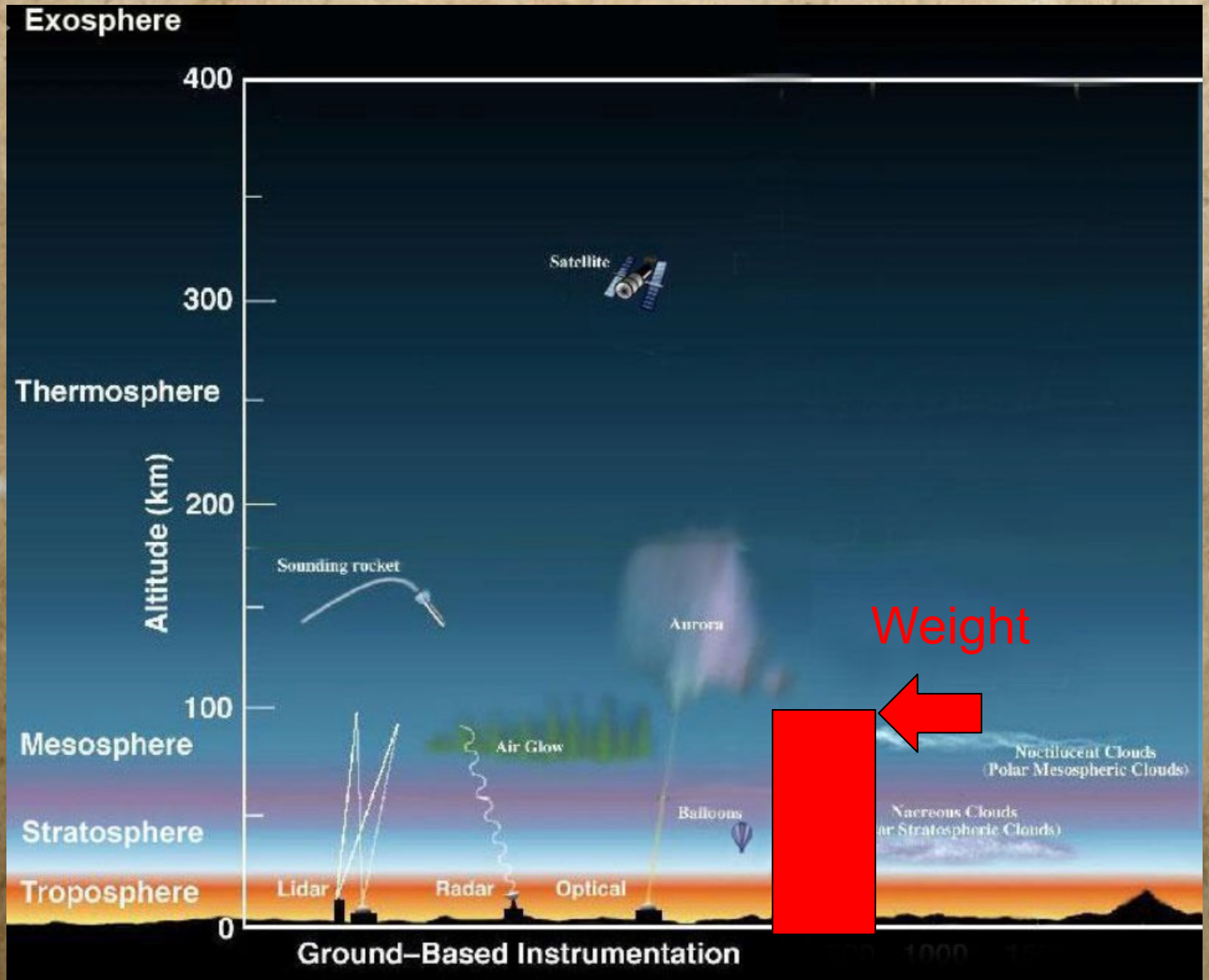
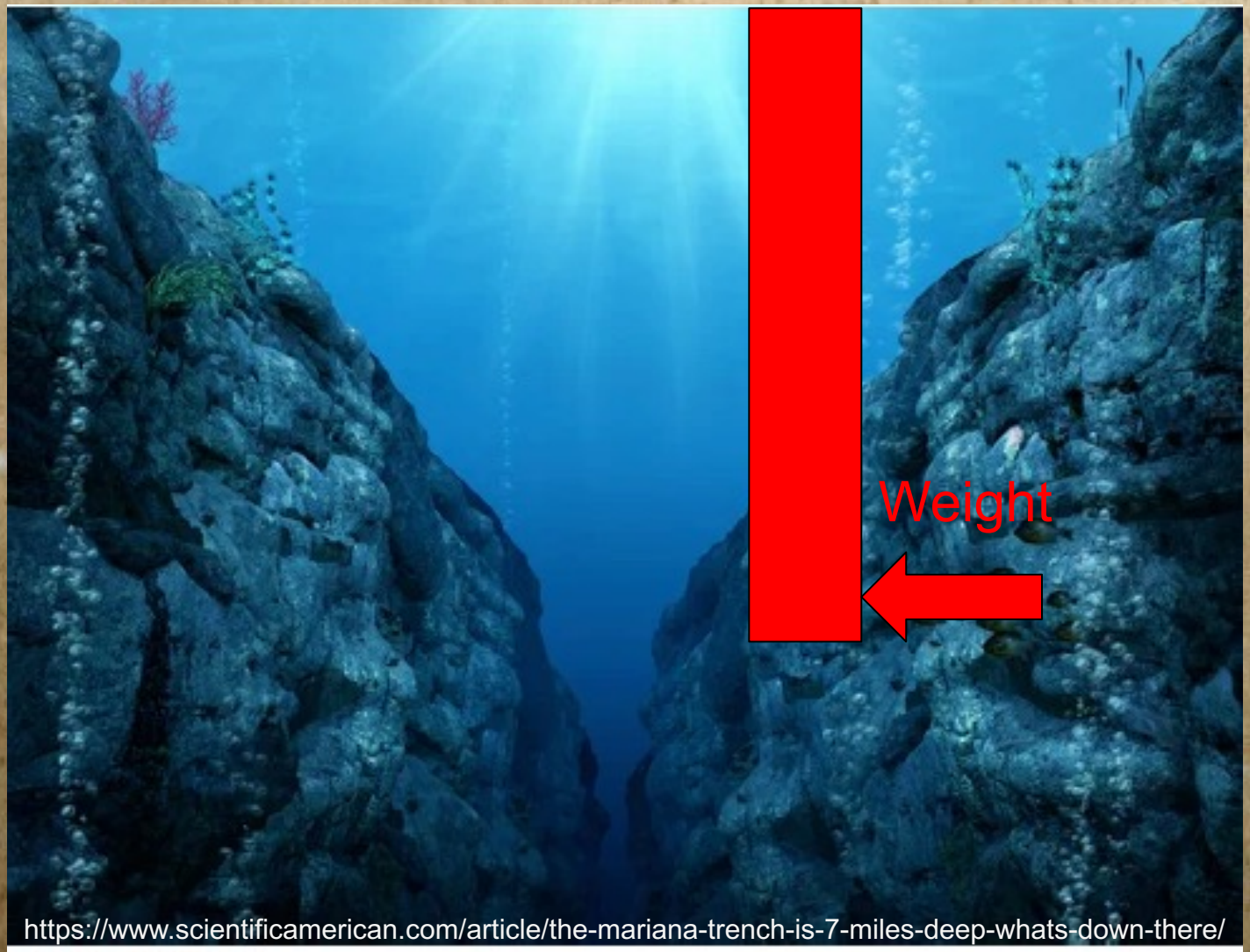


Fig. 6-5, p. 130

Atmospheric Pressure



Hydrostatic Pressure



Pressure

1. Affects every chemical reaction in every living organism.
2. It is characterized as a thermodynamic intensity parameter comparable to temperature and contributes to the free energy of a reaction by the equation:

$$\Delta G = (\Delta E + P \times \Delta V) - T \times \Delta S,$$

where:

ΔG=free energy of the reaction,
ΔE is the change in internal energy,
P is pressure, ΔV is molar volume change,
T is temperature, and ΔS is the change in entropy

Pressure

When we deliver a hyperbaric treatment:

We potentially affecting every chemical reaction in our bodies and
The effect starts the second the chamber door is closed and pressurization begins.

What else are we affecting?

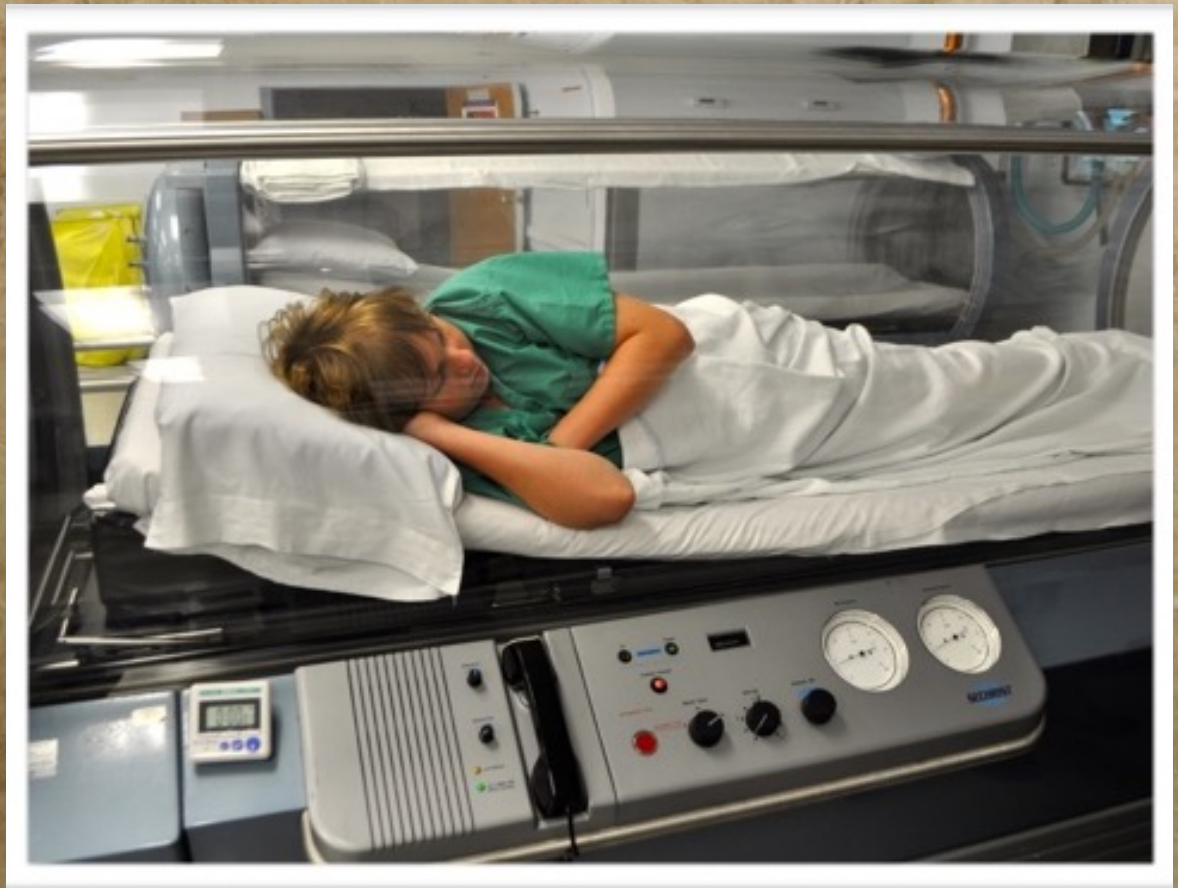
Over 8,101 of our 19,000 genes
In our 46 chromosomes.

An effect that is unique in all of medicine.

Pressure

To achieve the pressure effects of HBOT you have to expose the entire body to increased pressure.

The only way to do that is in a hyperbaric chamber:



Physiologic Definition of HBOT

A treatment that uses increased pressure and increased oxygen to treat diseases

What kind of diseases?

Wounding conditions.

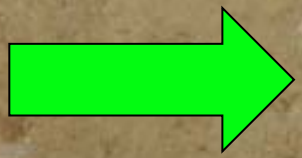
HBOT is a treatment for wounds in any location and of any duration

HOW DO WE HEAL ACUTE AND CHRONIC WOUNDS WITH HBOT?

WE GROW NEW TISSUE

INPUT:

Daily intermittent exposure to hyper-oxia and increased pressure



OUTPUT:

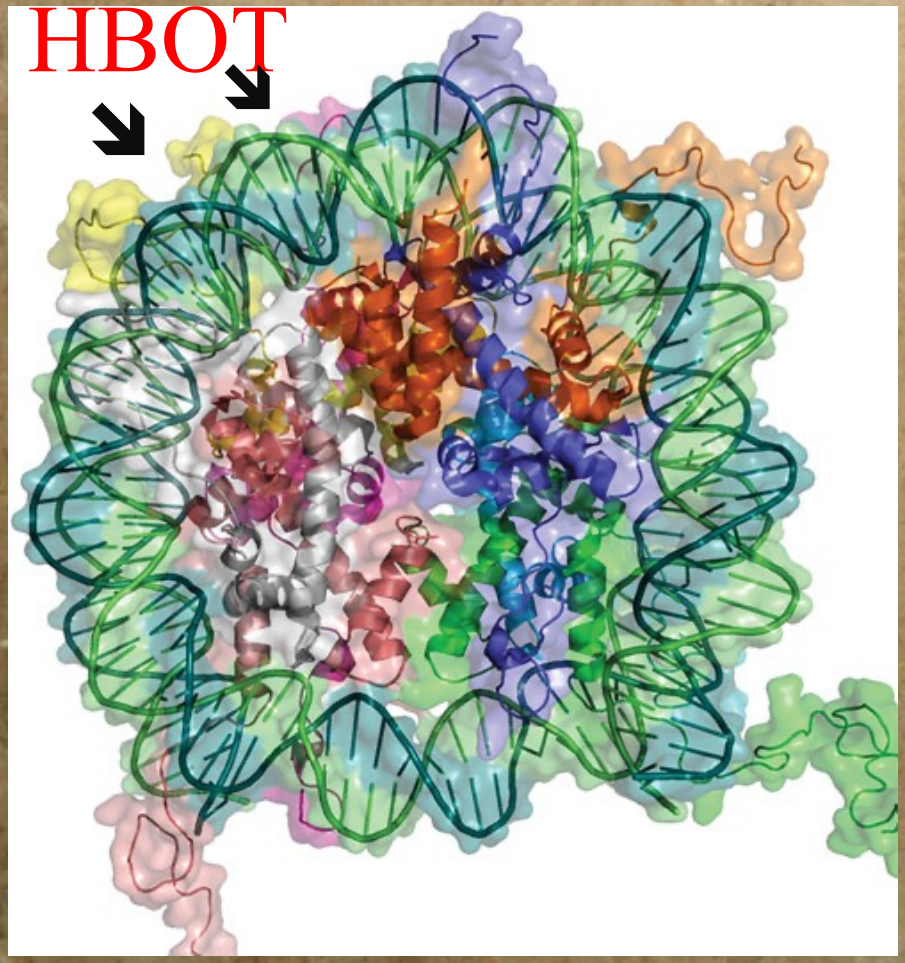
Reversal of pathophysiology and growth of new tissue

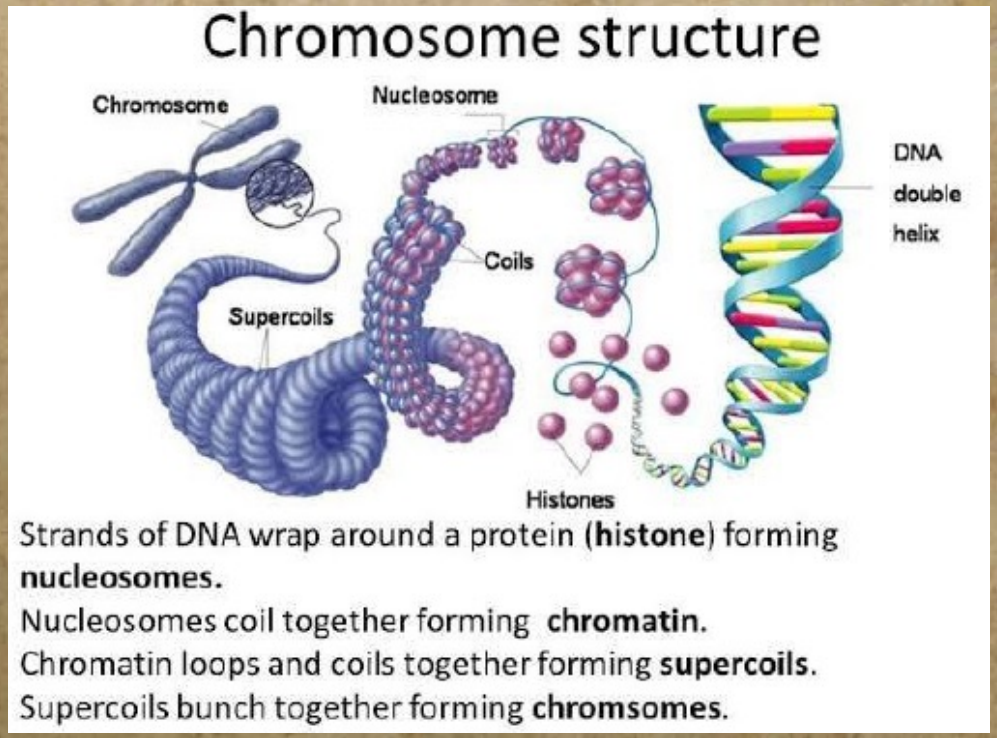
What is the Mechanism of Action for growth of new tissue?

Gene Signaling

HBOT and Epigenetic Effects

DNA coil with histone protein interior.





https://www.facebook.com/108014754067239/photos/a.110468583821856/111089703759744/

http://www.genengnews.com/gen-articles/awaken-dormant-dna-epigenetically/5818

HBOT and Gene Effects

Godman CA. Cell Stress and Chaperones, DOI 10.1007/s12192-009-0159-0 (Courtesy Dr. Philip James)

Human microvascular endothelial cells, in vitro

1st HBOT: 2.4 ATA/60 mins.

Continuous mass gene analysis for 48h

2nd HBOT at 24h

Results:

1. At 24h 8,101 of >19,000 protein-coding genes up or down regulated compared to control
2. Genes upregulated: anti-inflammatory and growth/repair hormones
3. Genes downregulated: pro-inflammatory and cell death.

At 48h:

1. Cells formed microtubules (blood vessels) in a petri dish

HBOT in the U.S.

1. Air or Gas Embolism — Acute Wd
2. CO Poisoning/Smoke Inhalation — Acute Wd
3. Crush Injury, Compartment Syndrome, and other acute Traumatic Ischemias — Acute Wd
4. Decompression Sickness — Acute Wd
5. Selected Problem Wounds (diabetic, arterial insufficiency, venous stasis, etc.) — Chronic Wd
6. Exceptional Blood Loss (Anemia) — Acute Wd
7. Radiation Tissue Damage (Osteoradionecrosis and Soft Tissue) — Chronic Wd

UHMS HBOT Committee Report, 2014

HBOT in the U.S.

8. Skin Grafts and Flaps (Compromised)	Acute Wd
9. Thermal Burns	Acute Wd
10. Central Retinal Artery Occlusion	Acute Wd
11. ISSHL (Sudden hearing loss)	Acute/Subacute Wd
12. Clostridial Myonecrosis (gas gangrene)	Acute Wd
13. Necrotizing Soft Tissue Infections (Flesh-eating Bacteria)	Acute Wd
14. Osteomyelitis (Refractory) or (Acute) in Compromised Hosts (Bone Infections)	Chronic, Acute Wd
15. Intracranial Abscess (Brain)	Acute Wd

UHMS HBOT Committee Report, 20014

HBOT internationally

Russia: 70 diseases[1]

China: 49 diseases[1]

Japan: 33 diseases[1]

U.S: 15 diseases[1]

Gabb/Robin article: 132 diseases[2]

- Vast majority are wounding and
- inflammatory conditions

- My experience: 90-100 different conditions, 80% of which are neurological. (Gabb/Robin lookout!)

1. Textbook of Hyperbaric Medicine, 5th and 6th Editions, K.K. Jain, editor. Springer, Switzerland, 2009, 2017.

2. Gabb G. Chest. 1987;92(6):1074-82.

Why does it work for so many wounds?

- Because it treats the underlying disease processes that cause the wounds/diseases.
- These processes are common to many diseases.

1.Textbook of Hyperbaric Medicine, 5th and 6th Editions, K.K. Jain, editor. Springer, Switzerland, 2009, 2017.

2. Gabb G. Chest. 1987;92(6):1074-82.

Biggest Question

- Does my child have a wound, specifically, a wound in his/her brain?
- Very often the answer to this question is not apparent or deliberately concealed.
- I'll give you some examples.

Occult wounds in the brain-One of the most common causes

- Birth Injury
  - B.R: 5.5 year old boy with "CP." Story told in The Oxygen Revolution. Mom, 3 wks. overdue, nearly 11 lb. baby, distorted head, one-sided motor findings, delayed milestones, autistic behavior. Evaluated by 3 neurologists.
  - Hypoglycemic child, ~2001. 2 y.o. girl with severe developmental delays of unknown cause. "new" records of lab tests at time of birth suddenly appear in medical record at 2 years of age. Surprise finding and diagnosis.

Occult wounds in the brain-One of the most common causes

- Most recent example
- 4.5 year old boy with "Mild autism" and motor/coordination deficits.
  - 2.5 wks. premature
  - hospital records-normal birth
  - mom states no birth injury, but in her one page medical summary:

    "XX was born at 37 weeks, weighed 2.6 kg. Meconium was present at birth. No family history of autism."

Occult wounds in the brain-One of the most common causes

- Cerescan project:
- Cowan study 2001
- Conclusion:
  - The trip down the birth canal is one of the most perilious in life (Ox Rev)
- So why is it concealed?
  - Liability.

What if my child doesn't have a birth injury?

- Is it an acquired injury?
  - ADD, ADHD
- Is it a "genetic" or "congenital" disorder?
- Example:
  - Ceroid lipofuscinosis of the brain
  - Recent child with "Ring 18 chromosomal defect"
  - Over 30 genetic disorders

When is the best time to start HBOT?

- Immediately, in the ER or ICU.
- Timeline of wound evolution:
  - Six months: Chronic. Tissue loss.
- Goal is to halt the wounding process and accelerate healing/recovery.
- Jain, Chapter 20.

When is the best time to start HBOT?

- E.G., Drowning
- Review of Drowning experience
- 40 patient pre-Eden
- 60+ patients post-Eden
- Best outcome to date: Christopher Dixon, New Orleans. 90 minutes from pool to HBOT.

Results of HBOT for Drowning in New Orleans?

- Over 100 children treated.
- In two cohorts: before Eden Carlson and after Eden Carlson.
- The subject of a retrospective study Will Boytim and Dr. Harch have undertaken based on a request from a pediatric intensivist at Texas Childrens' Hospital.

Results of HBOT for Drowning in New Orleans?

- General findings:
  - Global Ischemia/ANOXIA: One of most difficult neurological diagnoses to treat.
  - Prior to HBOT and other current Rx's, dismal results, NO TREATMENT.
  - HBOT: 85% response
    - 15% very subtle or no effect.
    - Of the 85%:
      - 2 Functions with near 100% response: CVI and autonomic dysfunction

Results of HBOT for Drowning in New Orleans?

- General findings:
  - Of the 85%:
    - Improvement in 5/8 neurological functions:
      - Alertness/awareness
      - Gross motor function
      - Fime motor function
      - Tone
      - Balance: sitting or standing
      - Oral motor: lip, tongue, pharynx function, secretion handling, swallowing.
      - Speech and cognition: advance of one speech level. Cog: engagement, responsiveness, reactivity
      - Temperment

When is the best time to start HBOT?

- Realistically, at time of discharge from the hospital
- What can be done in the acute care Hospital?
  - Normobaric oxygen (over 90% of children respond in first 24-48h.
  - Using oxygen for Signaling, like HBOT, but without pressure.
  - E.G., Eden Carlson

Barriers to NBO and HBOT in the hospital and beyond?

- Mentality in Neurology:
  - Therapeutic nihilism
- Medical Paternalism: E.G.'s
  - "Your child will have no quality of life."
  - "We are saving you a life-time of heartache only to Prolong the inevitable Result."
  - "Your child is going to be A plant."

https://www.freepik.com/premium-photo/serious-doctor-with-arms-crossed-medical-office_2452865.htm

Barriers to NBO and HBOT in the hospital and beyond?

- Rush to organ harvest:
  - Big $ involved for the harvest
  - Young parents most at risk

https://www.healtheuropa.eu/im-going-to-china-theyre-shooting-my-donor/97063/

Barriers to NBO and HBOT in the hospital and beyond?

- Dr. Ego
  - IF is worked we would know about it and we would be doing it.
  - NBO and HBOT are immediately confrontational because they are not doing it.
- Dr. Ignorance
  - Survey of American medical school curriculum wrt hyperbaric medicine by Dr. Sarah Parks. 75% teach nothing about HBOT.
  - Very little published in English on HBOT in drowning or acute pediatric brain injury (except China-31 studies, recent x in CP).

Reality of Decision-making in acute severe pediatric neurological injury?

- Extremely personal decision
  - Religious implications
  - Involves our basic human instinct to preserve life, especially the life of our children.
  - Complicated by the uncertainty and inability to predict outcomes
    - Often done based on MRI findings-a fallacy.
  - Complicated by inability to discern how much neurological/cognitive activity is present: parents insist child responsive, doctors say it is only reflex
  - Now achieving outcomes never seen before.
  - Have no idea the limits with HBOT and other therapies: we are finding out!

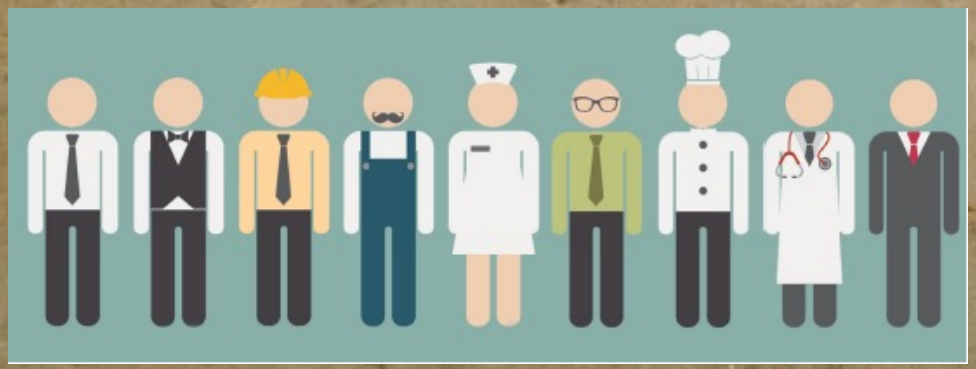
How are we achieving these results?

- By using HBOT to treat the underlying disease processes in pediatric brain injury/wounding.
- One component of wound healing involves stem cells.
- HBOT has been shown to have a number of effects on stem cells.

Stem Cells-

What are they?

- Stem cells are undifferentiated cells that are present in the embryonic, fetal, and adult stages of life and give rise to differentiated cells that are building blocks of tis-sue and organs.
- Analogy: A child is a stem cell that differentiates into a mother, caregiver, engineer, lawyer (maybe a de-differentiation), banker, dentist, etc.



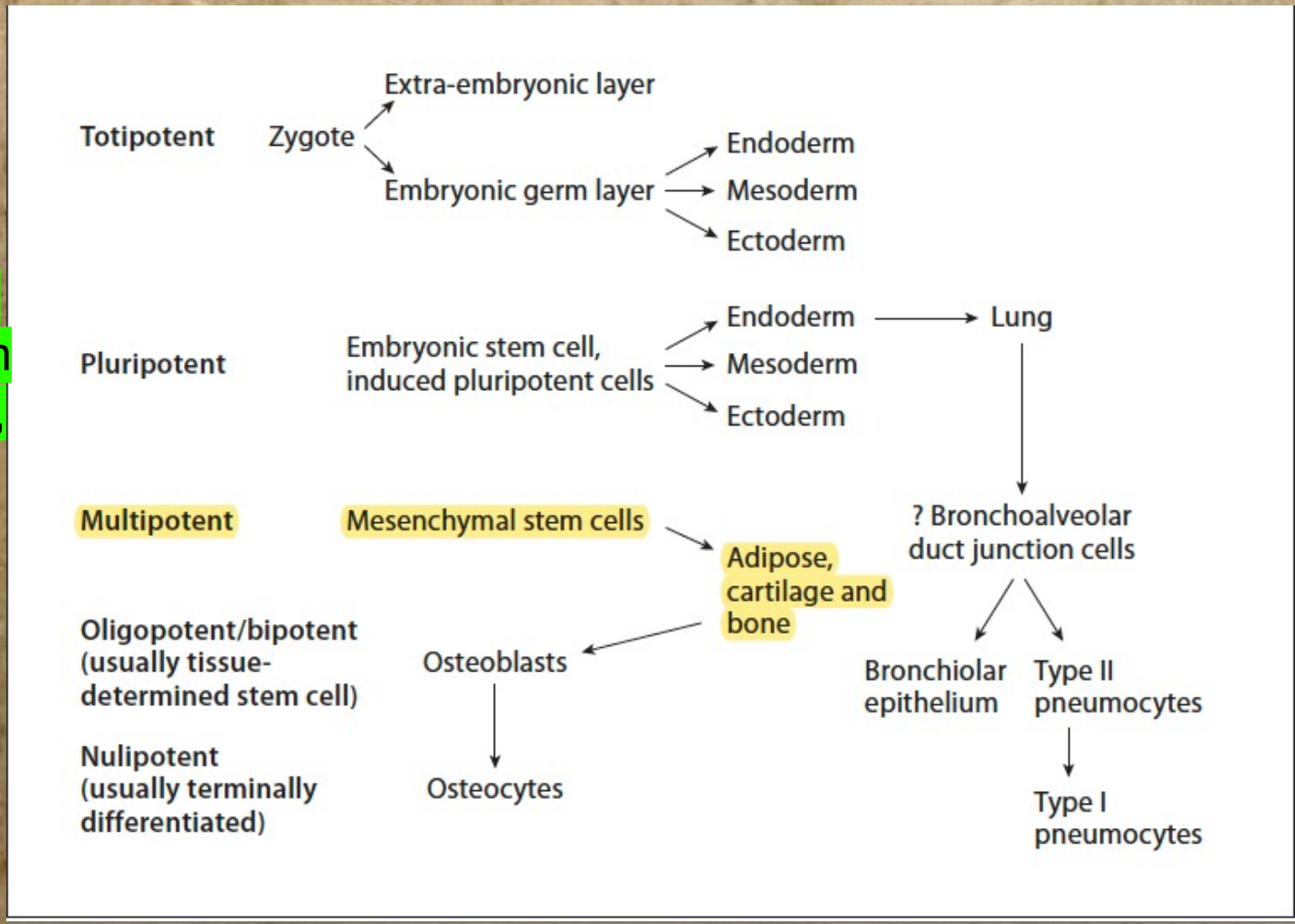
https://www.wallpapertip.com/wdown/oJTxi_cute-baby-images-hd/

https://bornrealist.com/career-choices/

Stem Cells-

What kinds are there?

Mesenchymal SC's:
Can be derived from
Bone, bone marrow,
Adipose tissue,
Wharton's
Jelly, umbilical and
Peripheral blood



Kolios G. Respiration. 2013:85:3-10

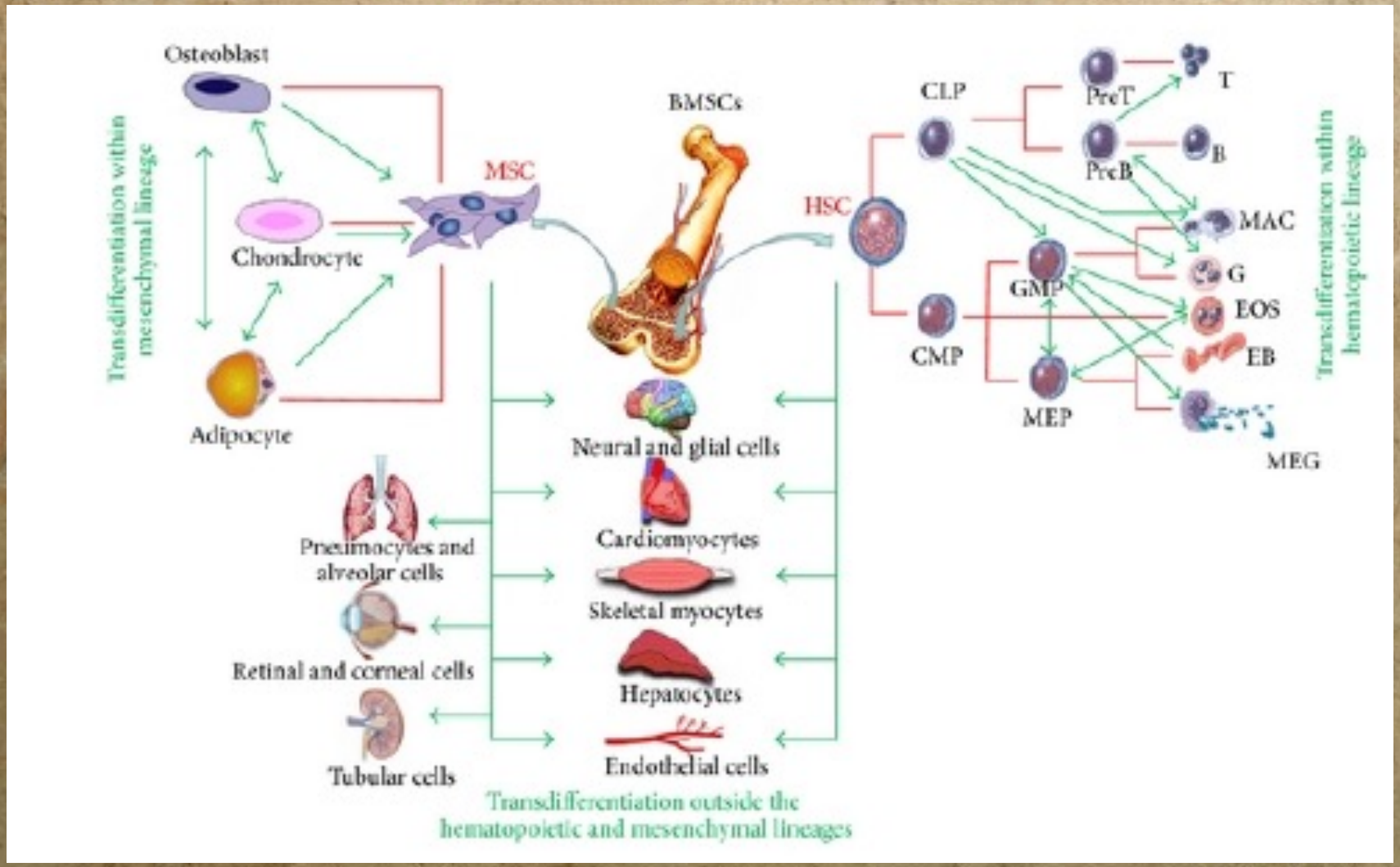
What does HBOT have to do with stem cells?

Kolios G. Respiration. 2013:85:3-10

Where are stem cells found in the human body?

- In every tissue and organ. For the purposes of this discussion, our most important sites are:
  - Bone Marrow
  - Adipose Tissue (Dr. Proefrock will discuss)
  - The brain.

OUR BONE MARROW-STEM CELL DEPOT



https://www.hindawi.com/journals/sci/2013/589139/fig1/

Can Harvest or Stimulate the Release of Bone Marrow Stem Cells

Bone marrow aspiration vs. stimulation of release by Granulocyte Colony Stimulating Factor: the cells are identical.

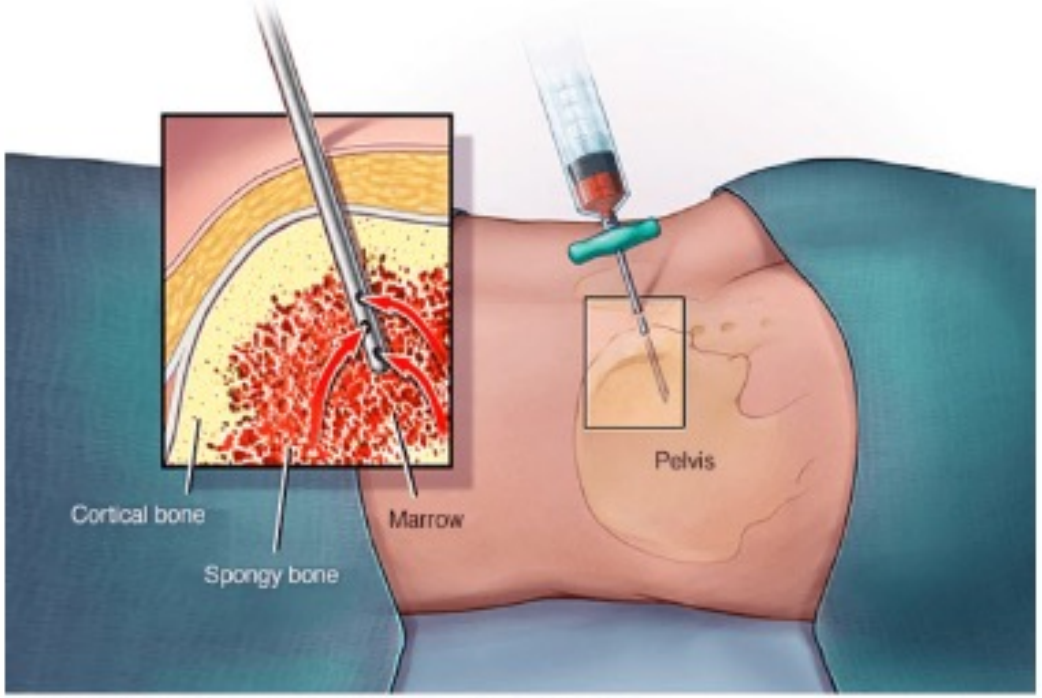
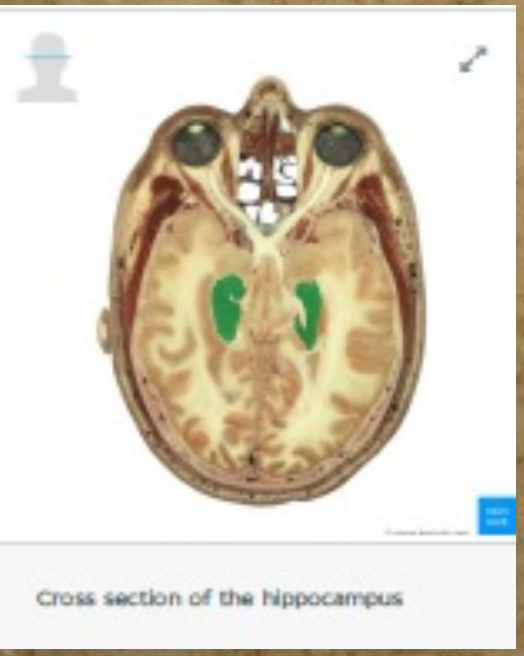


Image Source: https://www.mayoclinic.org/tests-procedures/bone-marrow-biopsy/about/pac-20393117

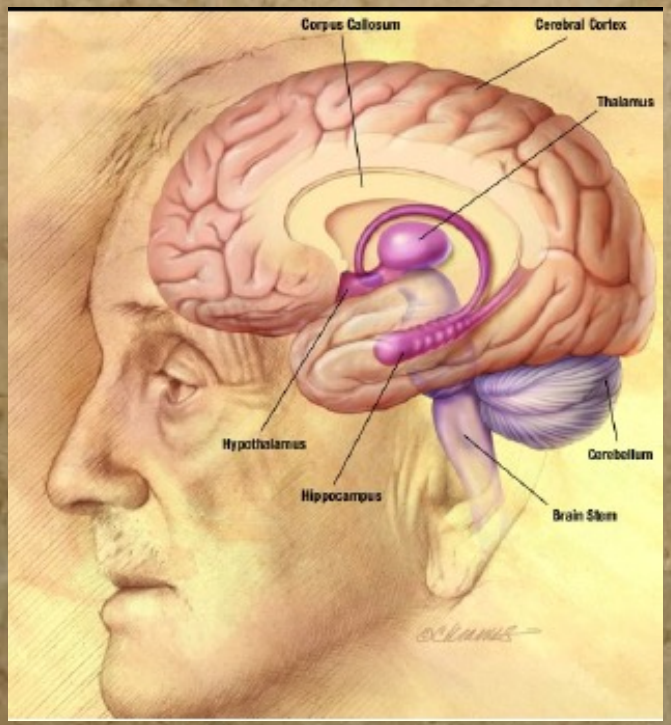
https://cellero.com/blog/advantages-of-mobilized-stem-cells-vs-bone-marrow-stem-cells/

Production of stem cells in the normal brain

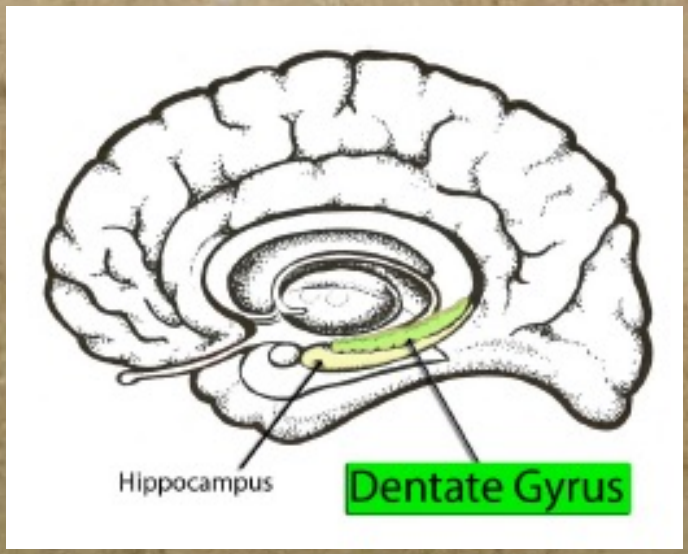
Stem cells are produced in two primary areas in the brain: 1. The hippocampus (short-term memory area of the brain) dentate gyrus



https://www.kenhub.com/en/library/anatomy/dentate-gyrus



https://en.wikipedia.org/wiki/Neuroanatomy_of_memory#/media/File:NIA_human_brain_drawing.jpg



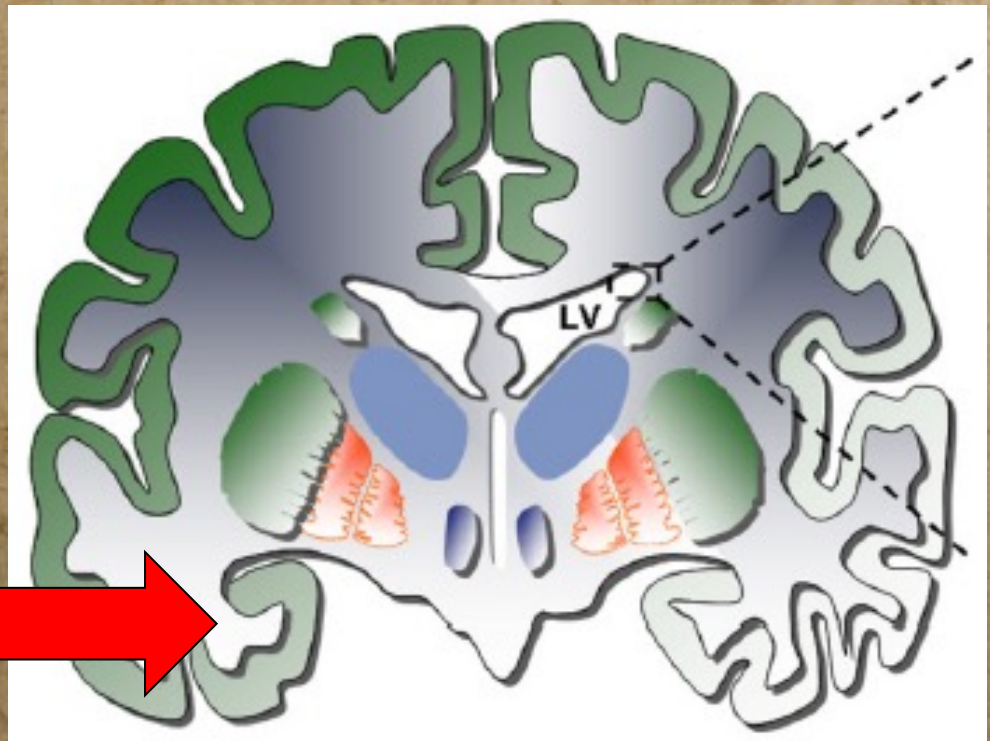
https://www.child-encyclopedia.com/sites/default/files/docs/glossaire/Glossary_Brain_DG.pdf

Production of stem cells in the normal brain

Stem cells are produced in two primary areas in the brain: 2. the subventricular zones (lateral walls of the lateral ventricles)

https://qbi.uq.edu.au/brain-Basics/brain-physiology/adult-neurogenesis

Hippocampus/
Dentate gyrus



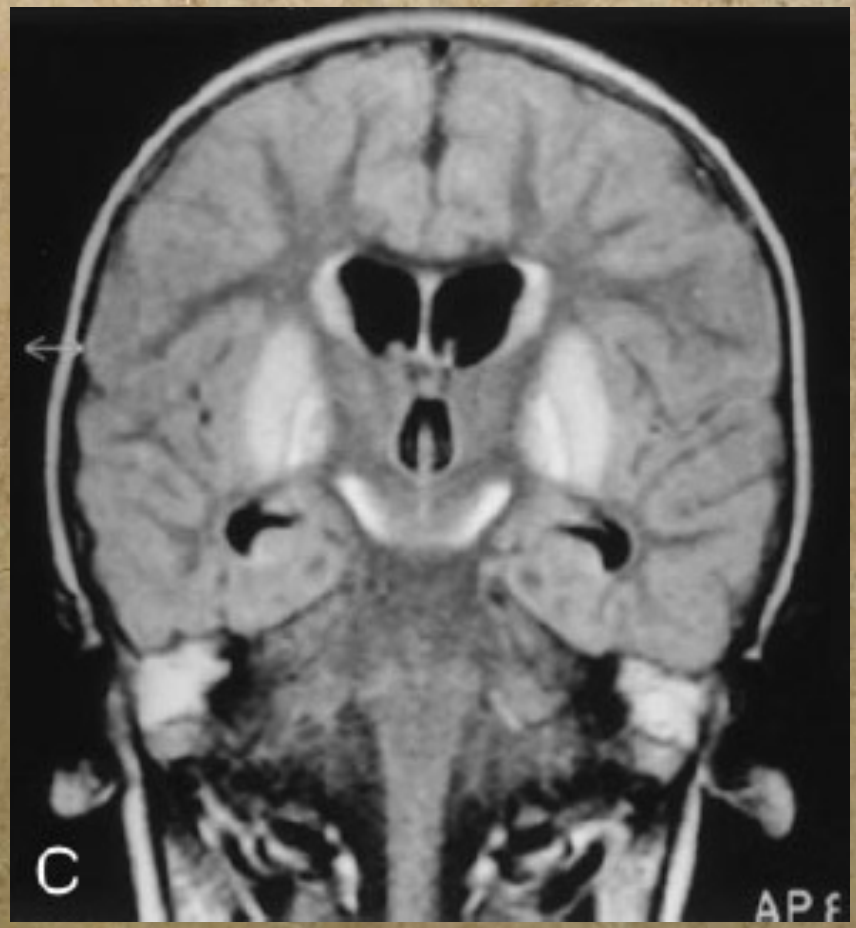
A coronal view of the adult human brain shows the lateral ventricles (LV) and the subventricular zone (arrows), where adult neurogenesis occurs. (Image: Oscar Arias-Carrión / CC BY 2.0 via Commons)

Stem cell migration in the brain and homing to brain injury from the bone marrow

1. Stem cells migrate from their birthing places in the brain to sites of injury in the brain.
2. Stem cells home from the bone marrow to sites of injury in the brain.

For our purposes, The most important homing is to and within the brain. However:

1. Natural homing from the dentate gyrus and SVZ are slow.
   a. what if the DG and SVZ are injured?



Chrisrophe C. AJNR. 2002;23:716-723

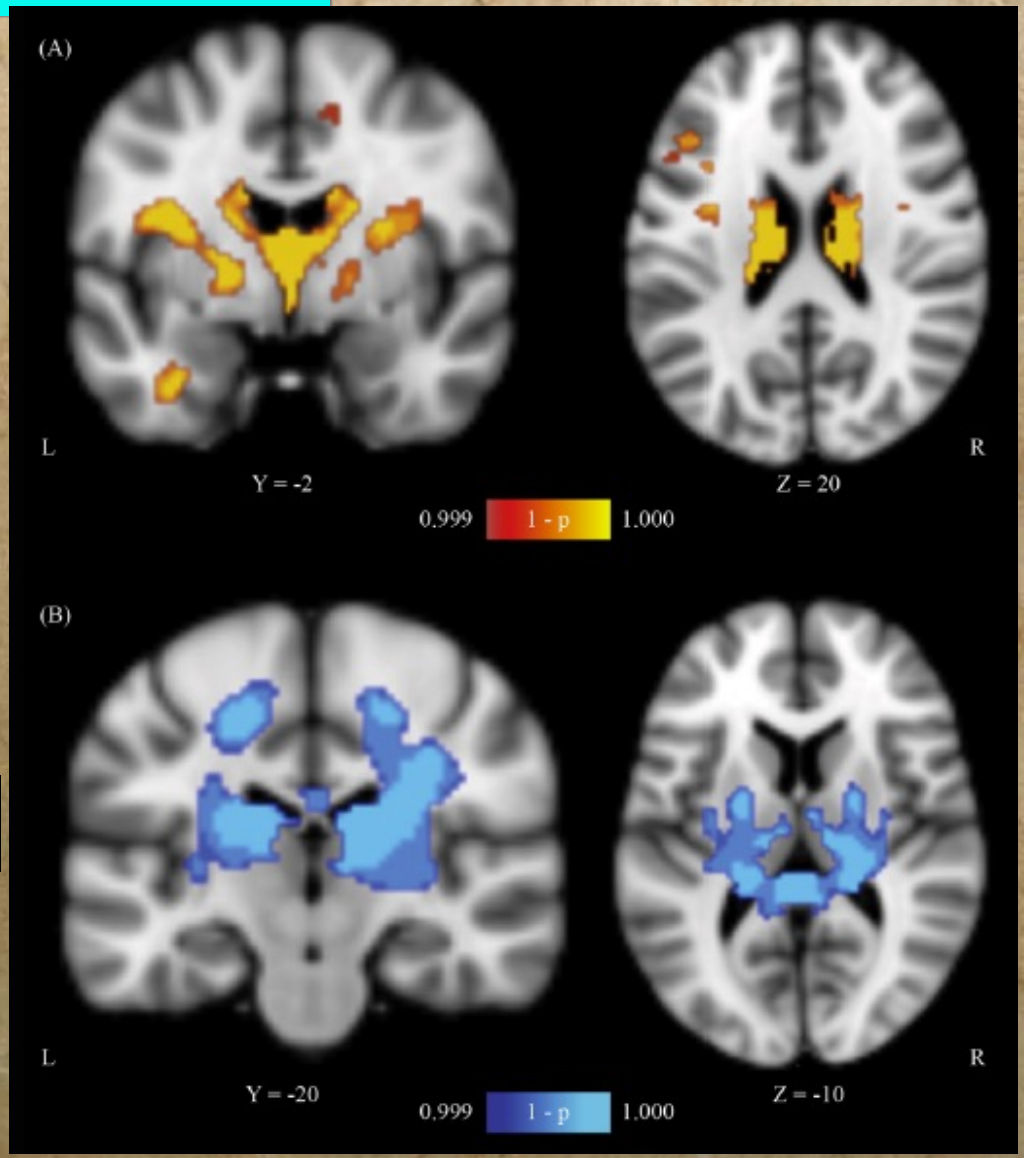
What if the DG and SVZ are injured?

MRIs of drowned Children In chronic phase compared To controls:

Areas of atrophy

Gray Matter

White matter



Ishaque M. NeuroImage: Clinical. 2016;11:167-172

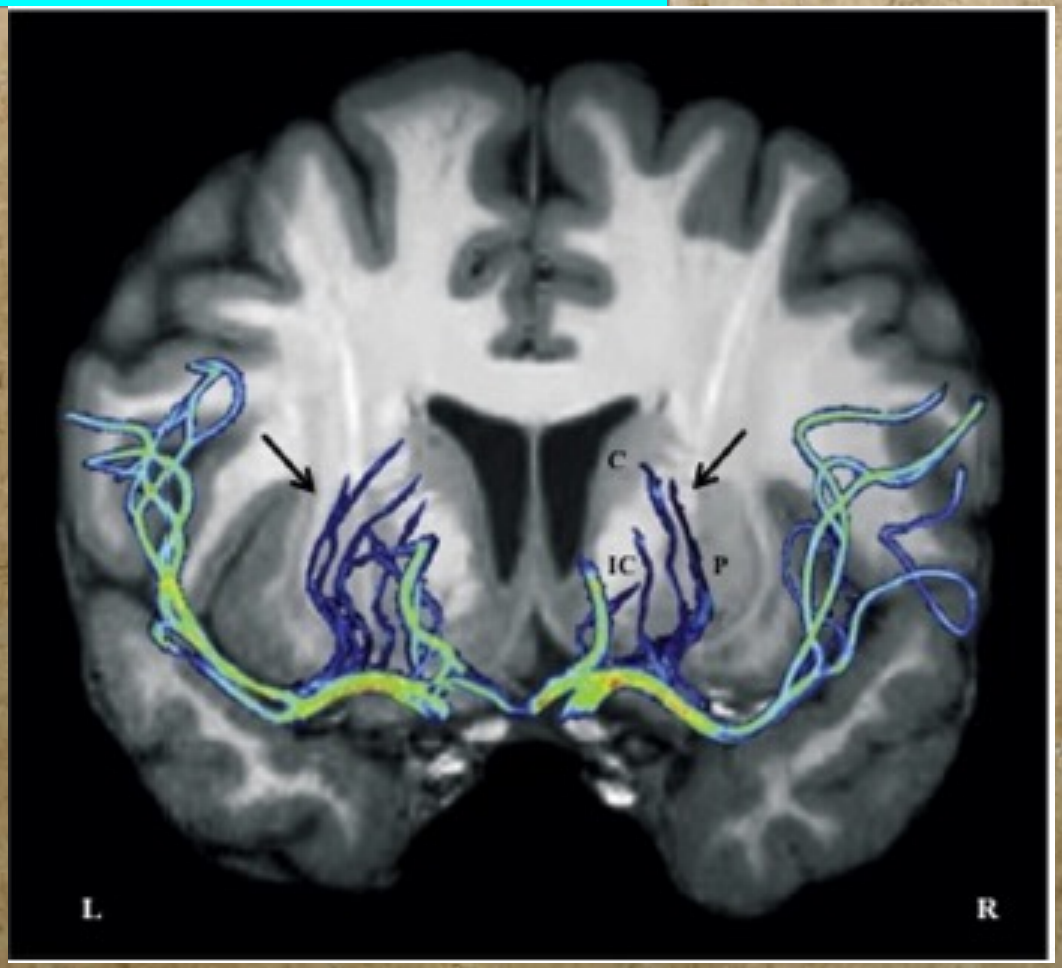
Why are these areas preferentially injured?

It is due to the peculiar blood supply:

the candelabra ArteriesWhich Supply the deep motor Area and White Matter Tracts For motor.

Result:

"Locked In."



Ishaque M. NeuroImage: Clinical. 2016;11:167-172

For our purposes, The most important homing is to and within the brain. However:

2. Natural homing from the bone marrow is slow and minor.

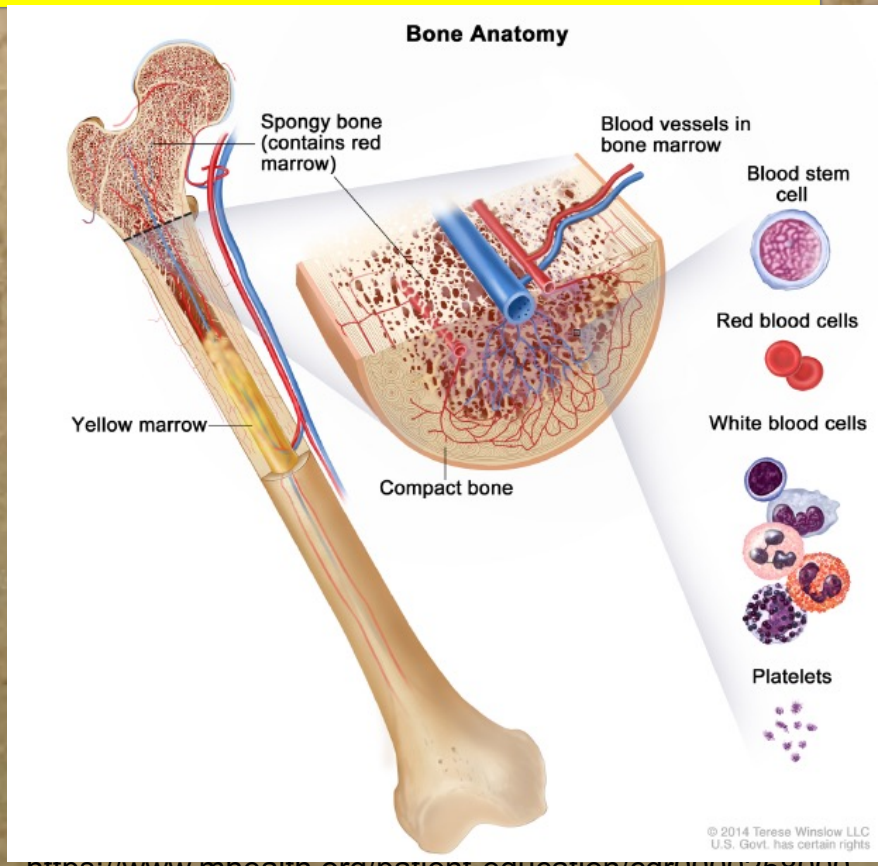
For all of these reasons, neurological recovery is painfully slow and needs assistance.

What effects does HBOT have on stem cells? Multiple

- Stimulates production and release of stem cells from the bone marrow to our circulation.
- Stimulates differentiation of the stem cells that are released from the bone marrow.
- Stimulates proliferation and differentiation of SC's at sites of injury.
- Facilitates implantation of stem cells.
- Increases production of stem cells in tissue for harvest.

HBOT Stimulates release of stem cells from the bone marrow to our circulation

- We know that HBOT grows new tissue to heal wounds and we know that stem cells are released from bone marrow to heal wounds. So, it only makes sense that HBOT might affect BM SCs.
- Thom SR, 2006
  - 26 patients with previous cancer and radiation
  - Getting HBOT: 2.0/2h
  - Measure stem cells in blood before/after the 1st, 10th, and 20th HBOT.

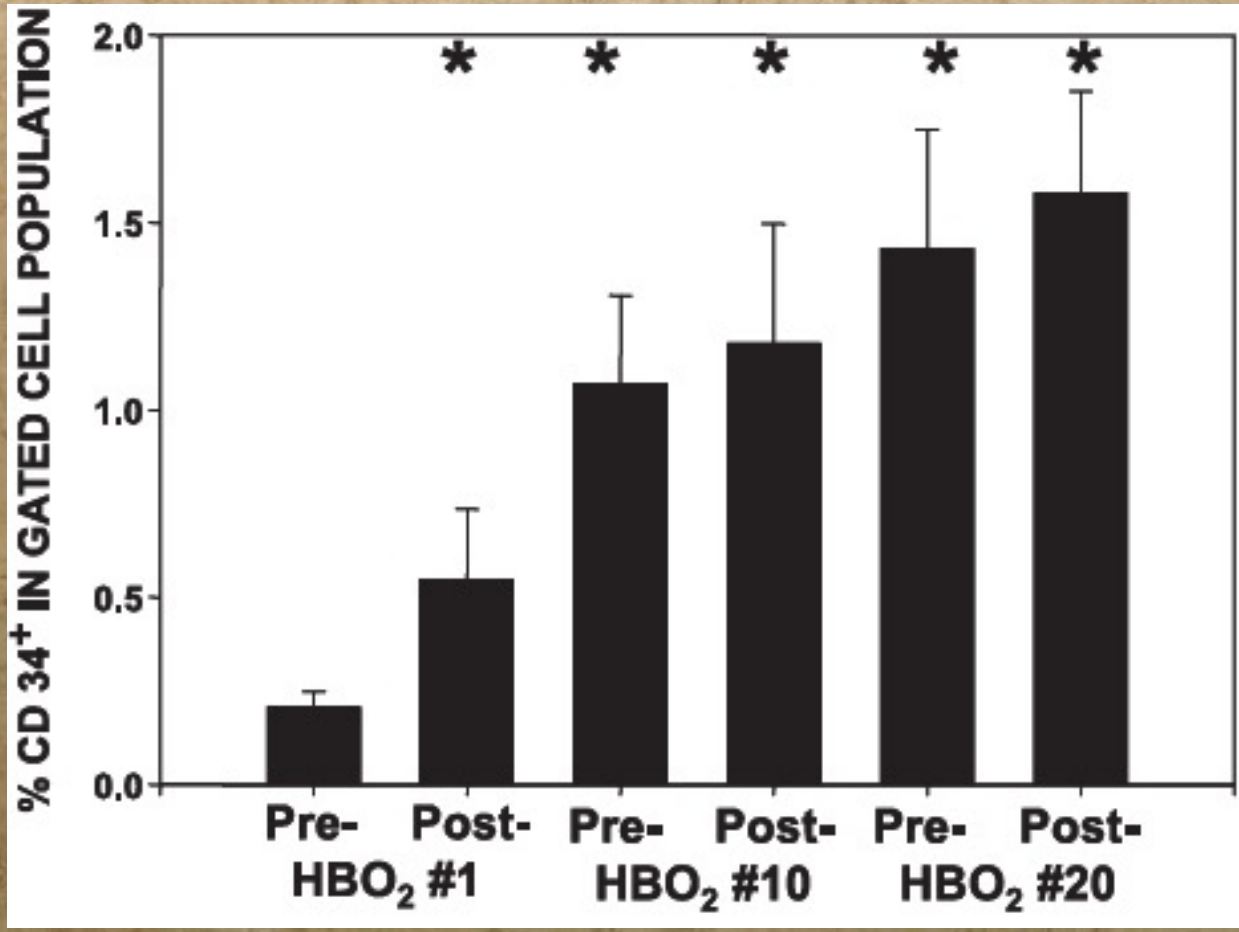


https://www.mnhealth.org/patient-education/cdr0000258000

Source: National Cancer Institute Research, www.cancer.gov

HBOT causes release and differentiation of stem cells

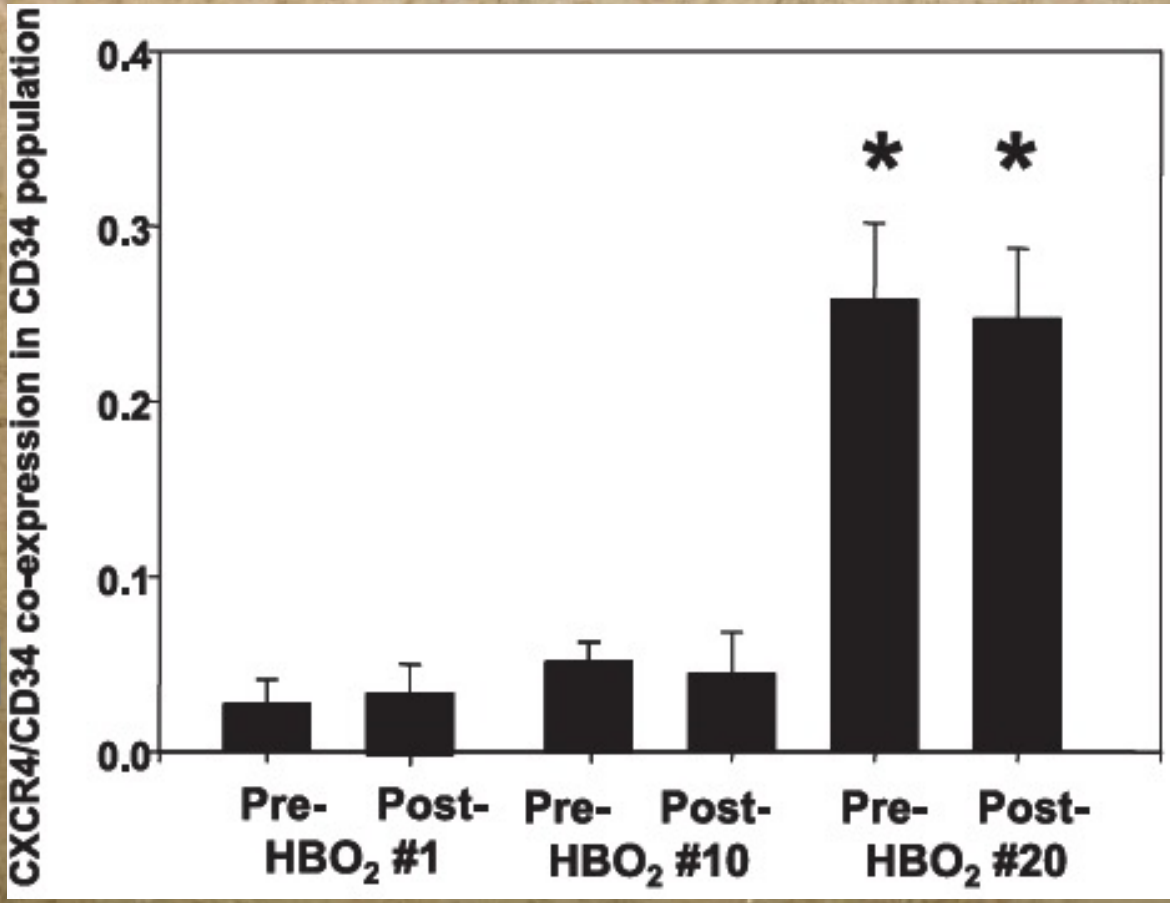
- Findings:
  - Significant increase in bone marrow stem cells in blood after 1st HBOT.
  - Further increase after 10th and 20th HBOTs.



Thom SR, Bhopale VM, Velazquez OC, Goldstein LJ, Thom LH, Buerk DG. Stem cell mobilization by hyperbaric oxygen. Am J Physiol Heart Circ Physiol. 2006;290:H1378-1386.

HBOT causes release and differentiation of stem cells

- With increasing numbers of HBOTs, stem cells evolve to express new proteins (CXCR4) on their surface that are necessary for homing to sites of injury.



1. Thom SR, Bhopale VM, Velazquez OC, Goldstein LJ, Thom LH, Buerk DG. Stem cell mobilization by hyperbaric oxygen. Am J Physiol Heart Circ Physiol. 2006;290:H1378-1386. 2. Milovanova TN, et al. Hyperbaric oxygen stims. Vascloenic stem cell growth and different. In vivo. 2009.J Appl Physiol;106:711-728.

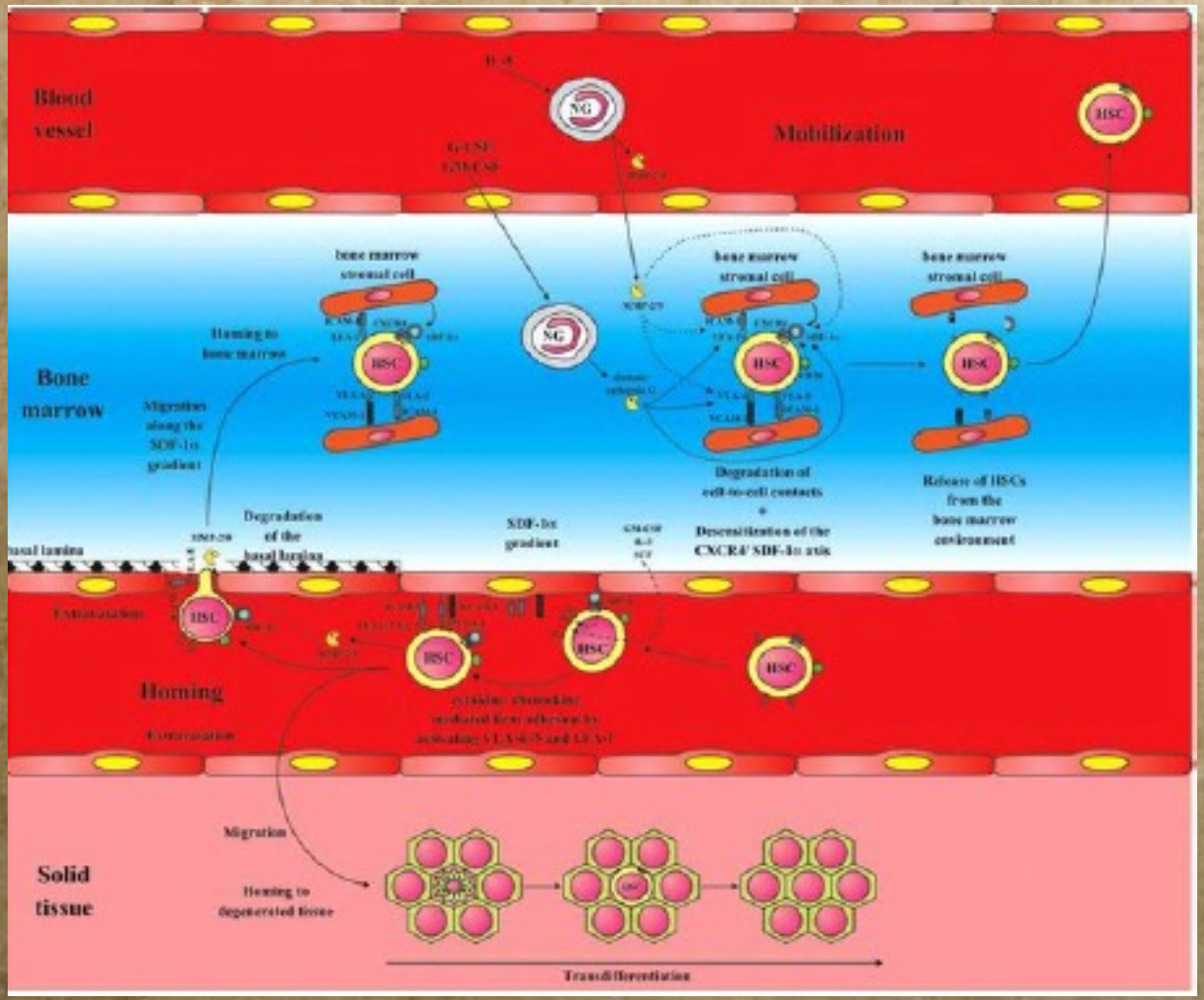
HBOT also causes Proliferation of stem cells in the bone marrow

- Mice, 2 HBOTs at 2.8 ATA/90 mins., ~2 and 14 hours after Matrigel implantation
- Other mice with once/day HBOT for 5 or 10 days.
- Measure stem cells in blood and bone marrow

Time	Blood		Bone marrow	
	Air	HBO_2	Air	HBO_2
18 h				
Cells, $\times 10^6$/ml	5.0±0.2	6.2±0.7	4.2±0.1	6.4±0.3
Leukocytes expressing CD34, %	0.30±0.02	0.63±0.01	13.4±0.2	28.1±3.3
5 days				
Cells, $\times 10^6$/ml	5.2±0.3	7.4±0.1	4.8±0.1	18.9±0.8
Leukocytes expressing CD34, %	0.27±0.01	1.73±0.08	14.3±0.8	59.7±3.2
10 days				
Cells, $\times 10^6$/ml	5.1±0.3	7.8±0.2	4.5±0.3	13.6±1.0
Leukocytes expressing CD34, %	0.29±0.02	0.97±0.05	14.9±0.4	65.6±3.7

Milovanova TN, et al. Hyperbaric oxygen stims. Vascloenic stem cell growth and different. In vivo. 2009.J Appl Physiol;106:711-728.

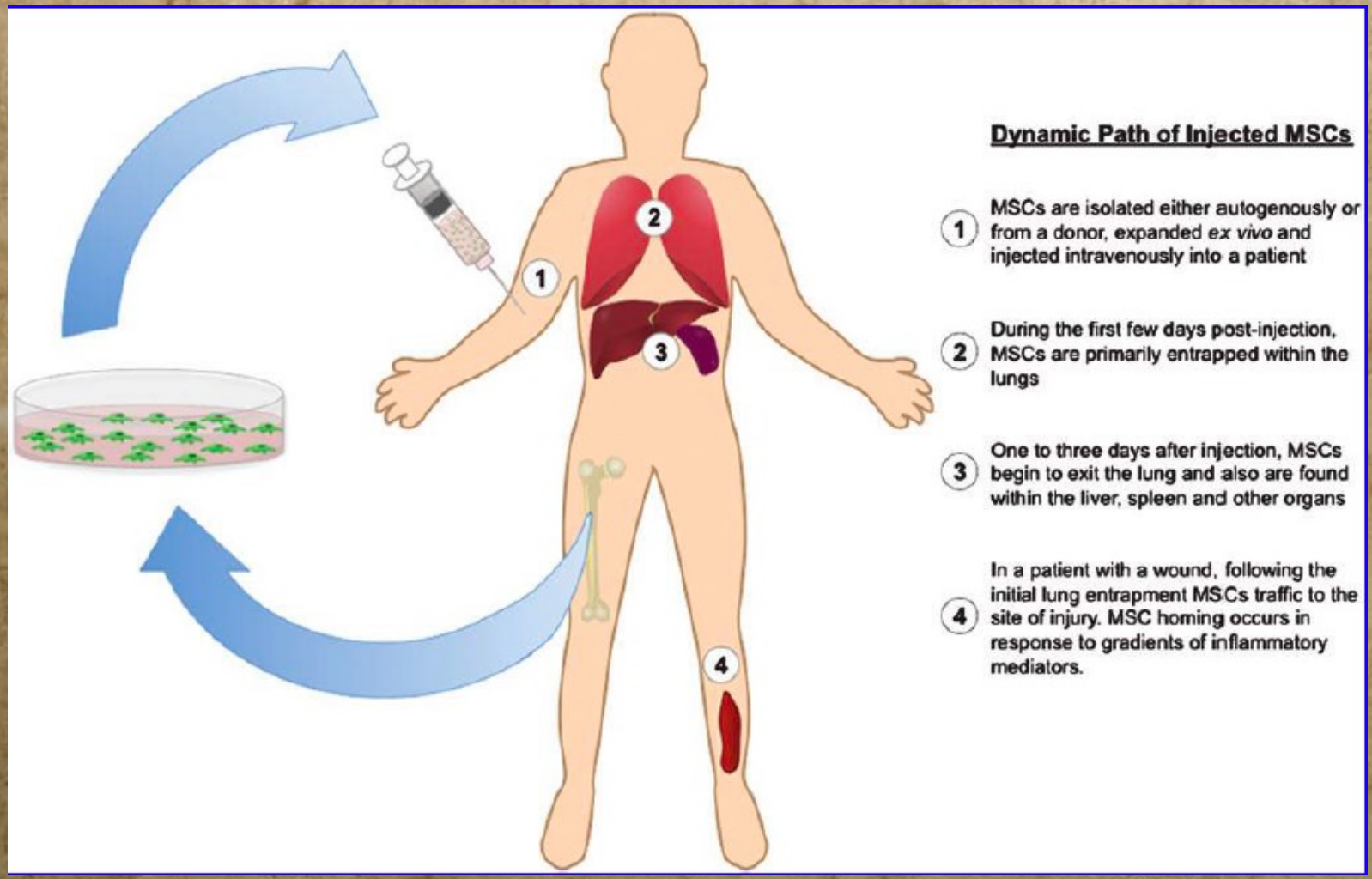
Once out of the bone marrow stem cells have to home to sites of injury or inflammation



https://www.researchgate.net/publication/5630702_Stem_Cell_Migration_A_Quintessential_Stepping_Stone_to_Successful_Therapy/figures?lo=1

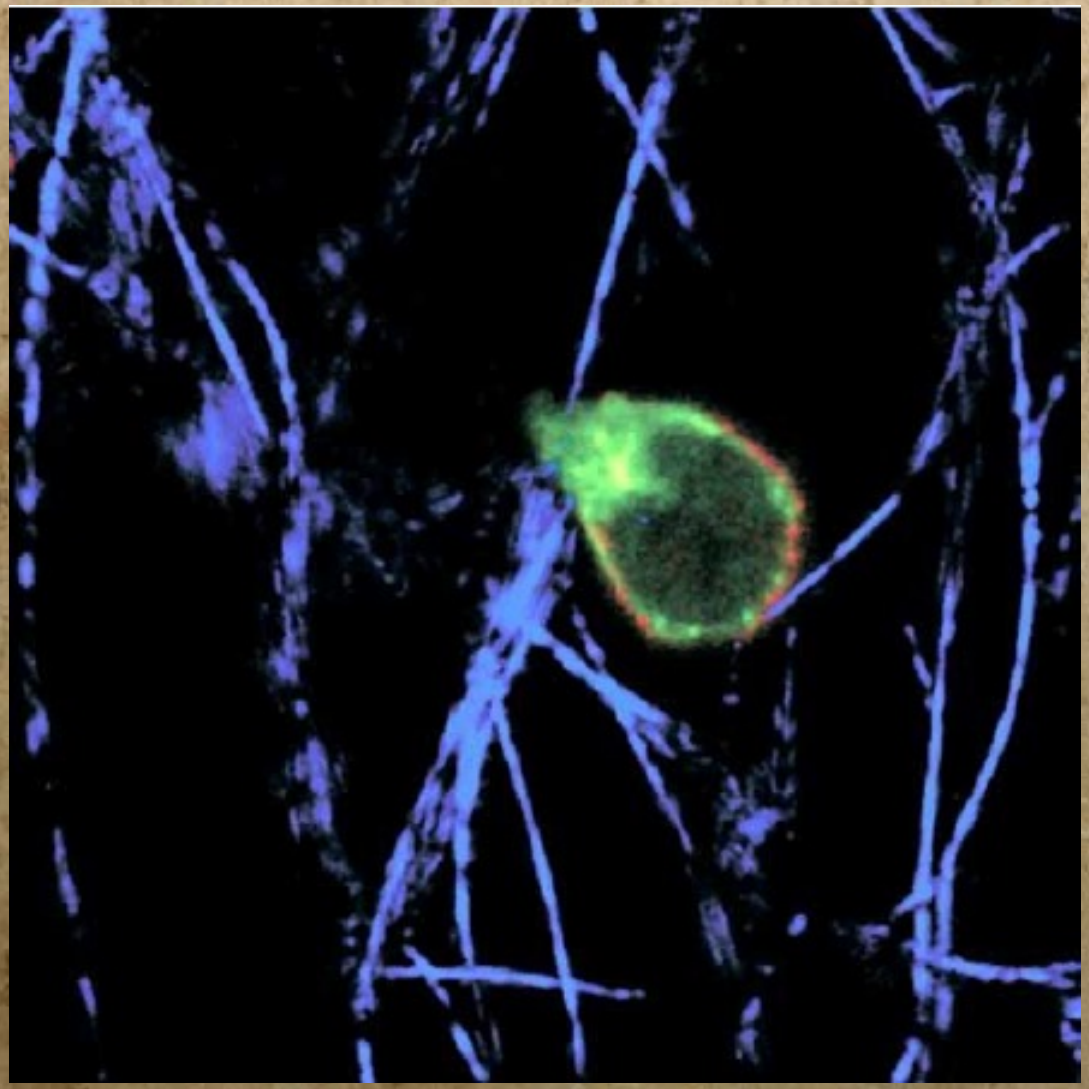
Homing of stem cells

True for Injrected Or Stimulated Stem cells



https://www.liebertpub.com/doi/pdfplus/10.1089/wound.2011.0314

Once in Tissue they multiply and become new tissue cells



https://www.researchgate.net/publication/5630702_Stem_Cell_Migration_A_Quintessential_Stepping_Stone_to_Successful_Therapy/figures?lo=1

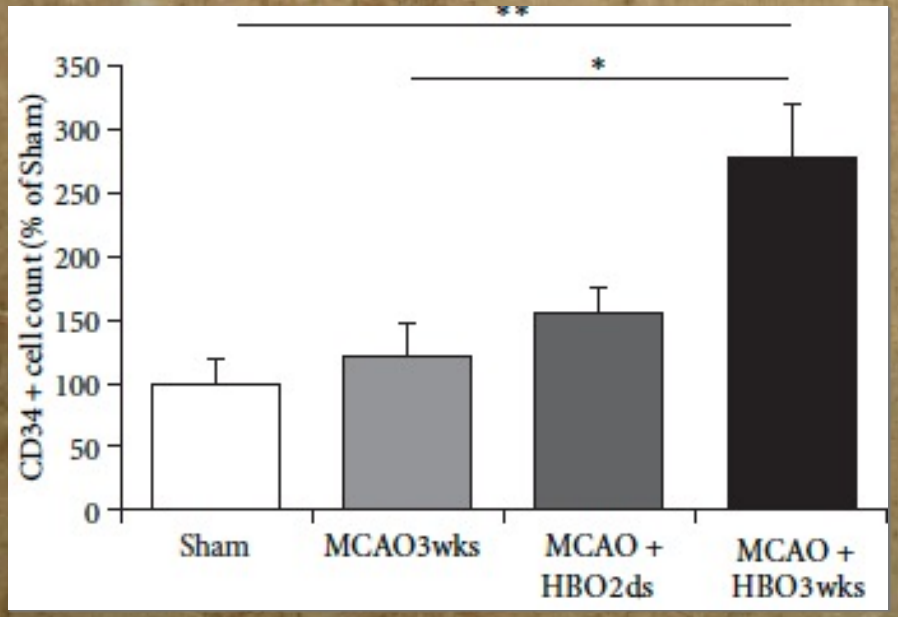
HBOT promotes homing and differentiation of Bone marrow stem cells in acute stroke

- Rats, acute stroke, transient occlusion of artery for one hour
- HBOT immediately after: 2.5 ATA/90 at depth, once/day x 2d or once/day, 5d/week, x 3 wks. (2 or 15 HBOTs).
- Results:
  - HBOT Decreased size of stroke after just 2 HBOTs. No data for 15 HBOTs.
  - HBOT increased the number of stem cells at the margin of the stroke, moreso with 15 HBOTs.
  - HBOT increased new neurons at the margin of stroke, moreso with 15 HBOTs.
  - HBOT reduced inflammation, moreso with 15 HBOTs.
  - HBOT improved neurological function, moreso with 15 HBOTs.

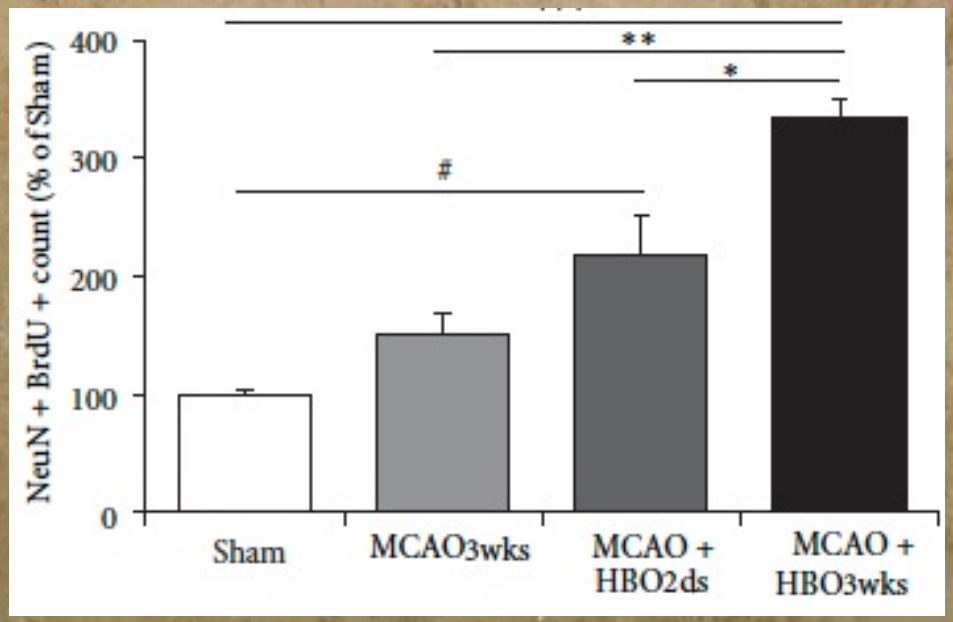
Lee Y-S. Long course hyperbaric oxygen stimulates neurogenesis and attenuates inflammation after ischemic stroke. Mediators of Inflammation, 2013, Article ID 512978. http://dx/doi.org/10.1155/2013/512978

HBOT promotes homing and differentiation of Bone marrow stem cells in acute stroke

Bone marrow SCs



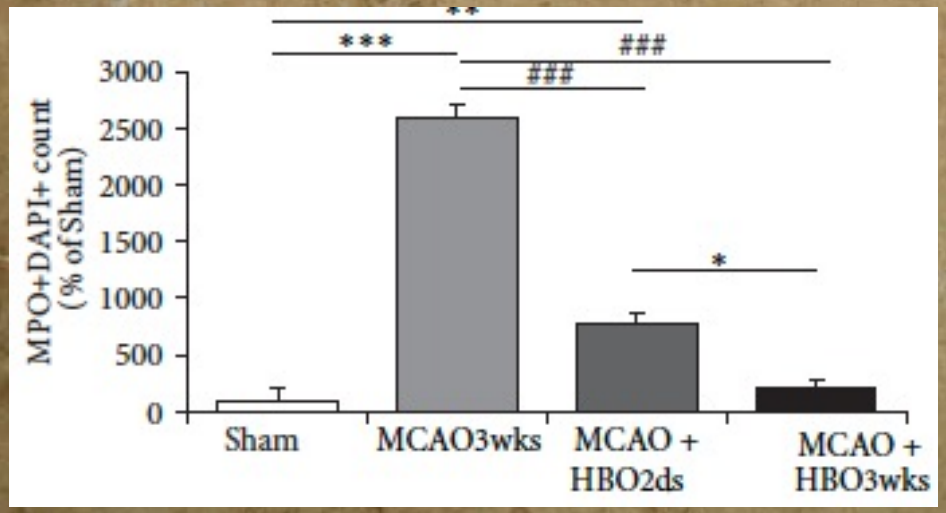
New Neurons



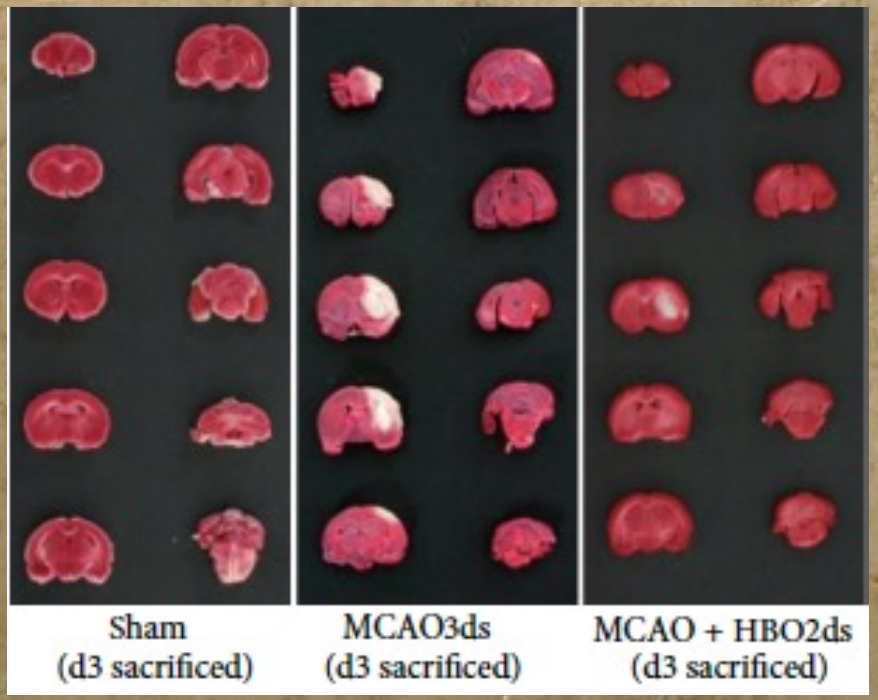
Lee Y-S. Long course hyperbaric oxygen stimulates neurogenesis and attenuates inflammation after ischemic stroke. Mediators of Inflammation, 2013, Article ID 512978. http://dx/doi.org/10.1155/2013/512978

HBOT promotes homing and differentiation of Bone marrow stem cells in acute stroke

Inflammation



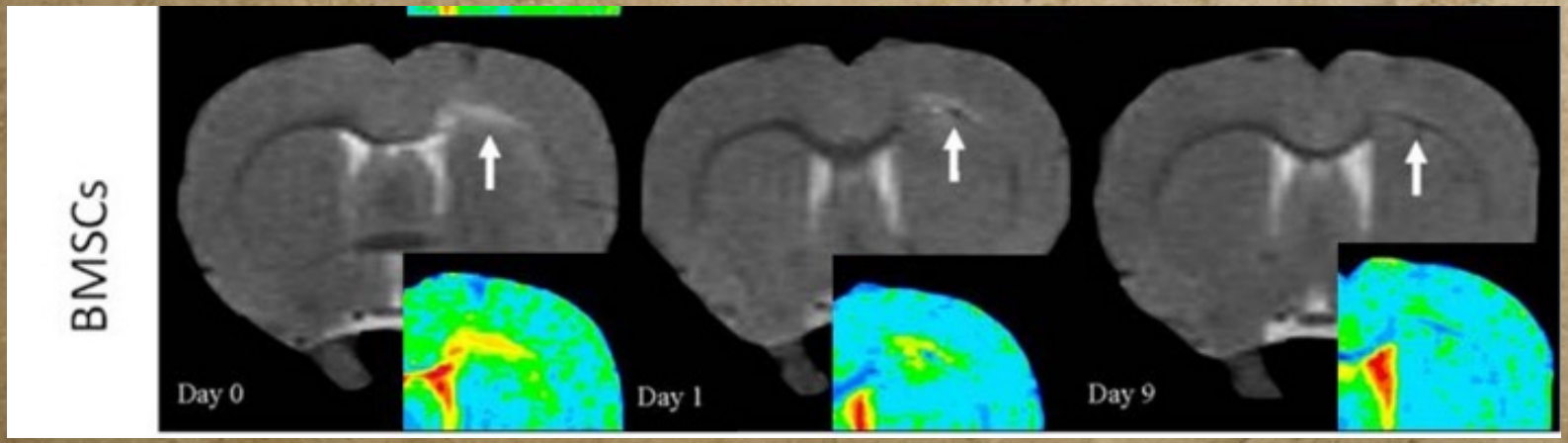
Stroke size

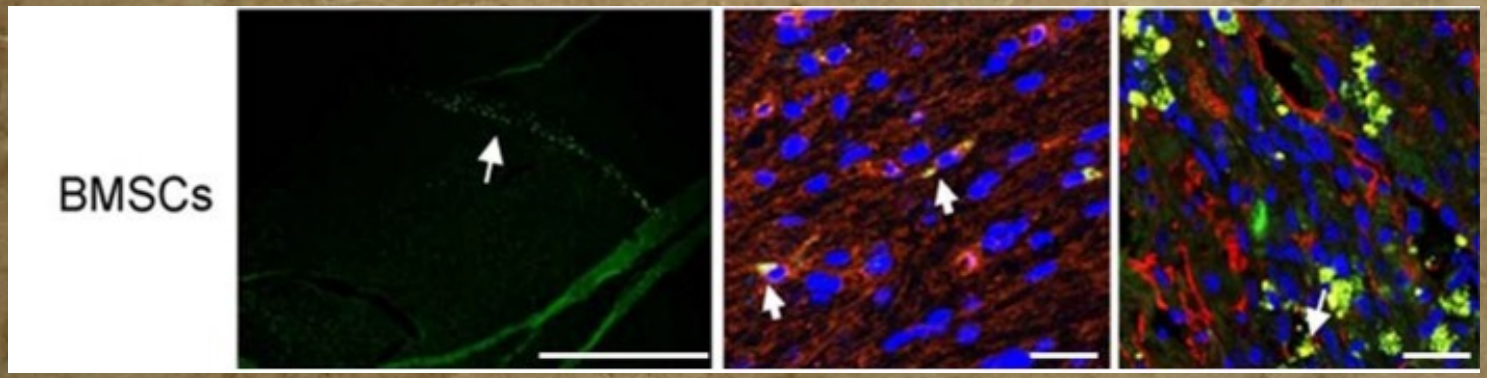


Lee Y-S. Long course hyperbaric oxygen stimulates neurogenesis and attenuates inflammation after ischemic stroke. Mediators of Inflammation, 2013, Article ID 512978. http://dx/doi.org/10.1155/2013/512978

Can also inject SCs IV and they will home and differentiate in brain

- Inflammatory lesion in brain, Inject bone marrow stem cells IV
- SC's enter brain and migrate to lesion.



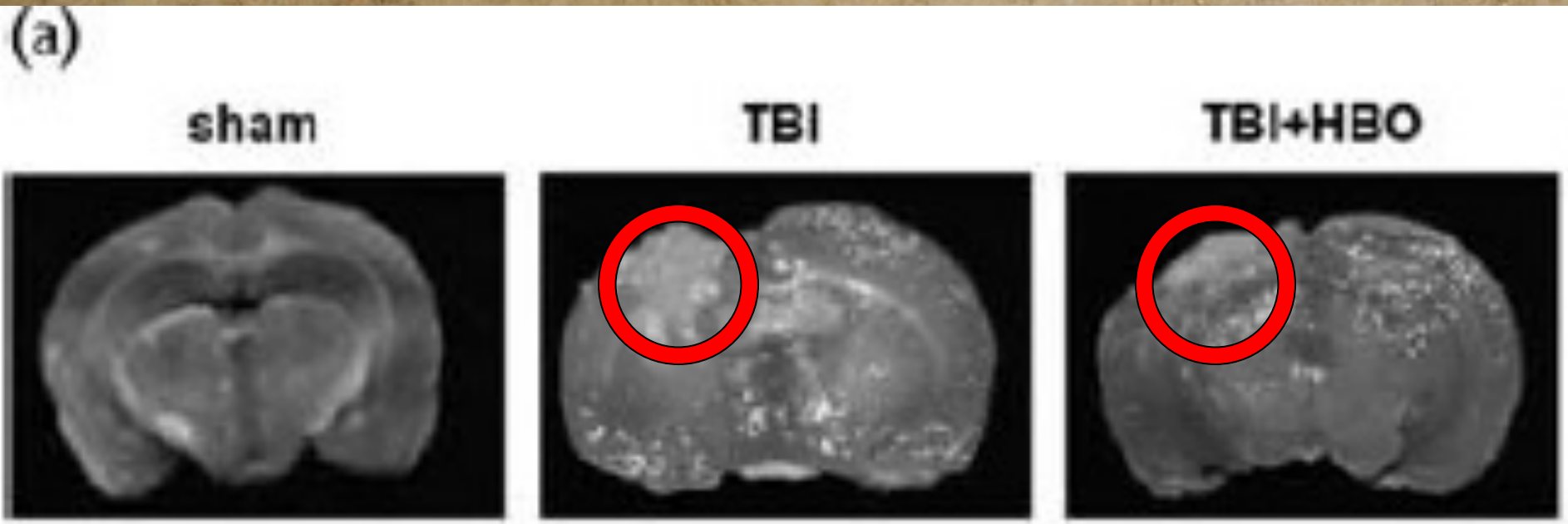


Red are stem cells and green are new glia cells

Jackson *et al. Stem Cell Research & Therapy* 2010, **1**:17
http://stemcellres.com/content/1/2/17

HBOT Stimulates proliferation and differentiation of SC's at sites of injury.

- Rats, TBI weight drop onto brain.
- Three hours later HBOT: 2.0 ATA/60 mins. at depth, once/day for 7d then analyze rat brains.
- Results: Smaller injury area and increased neurol. function



Yang Y. NeuroReport. 2017:28:1232-38

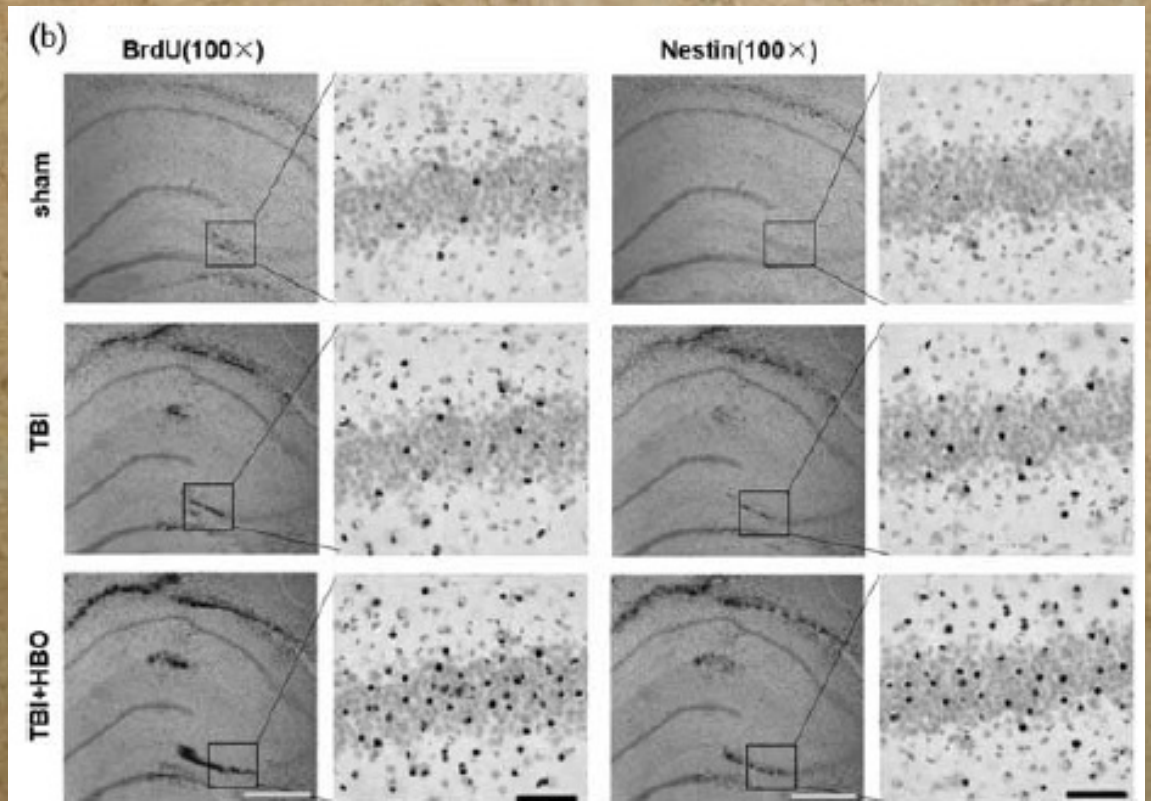
HBOT Stimulates proliferation and differentiation of SC's at sites of injury.

- Results: Increased number of stem cells in DG of hippocampus and increased number of neurons.

Increased number of neurons at site of lesion in cortex.

New stem cells

New neurons



New neurons

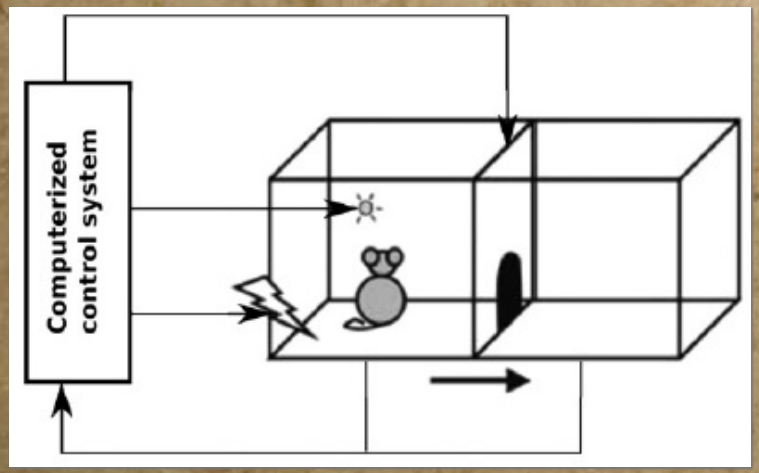
All of the above are acute situations. How about HBOT and SCs in chronic conditions?

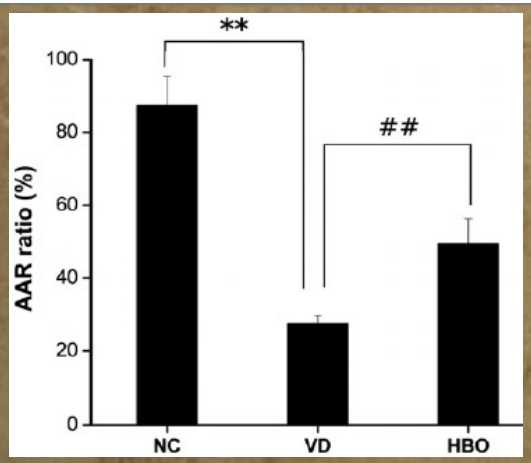
- Demented Rat study: (can't find a water bottle?)
- Rats with bilateral common carotid artery ligations:
- 30 days later, Active Avoidance Response Test (shock to foot), then HBOT (2ATA/90 at depth), 1x/day x 10 vs. controls and shams
- Repeat AAR, CT Perfusion imaging, stain brains for stem cells and new neurons in the piriform cortex, an area associated with cognition (similar to our parietal cortex).
- Results:
  - HBOT improved learning and memory, brain blood flow,
  - HBOT improved neural stem cells (Nestin) and new neurons (Double Cortin cells-DCX) in the piriform cortex and hippocampus.
- Conclusions: In a chronic vascular brain injury animal model HBOT reverses memory /learning loss, improves blood flow, neural stem cells, and new neurons in cortex and hippo.

Zhang T. Brain Injury, 2010;24(11):1350-1357

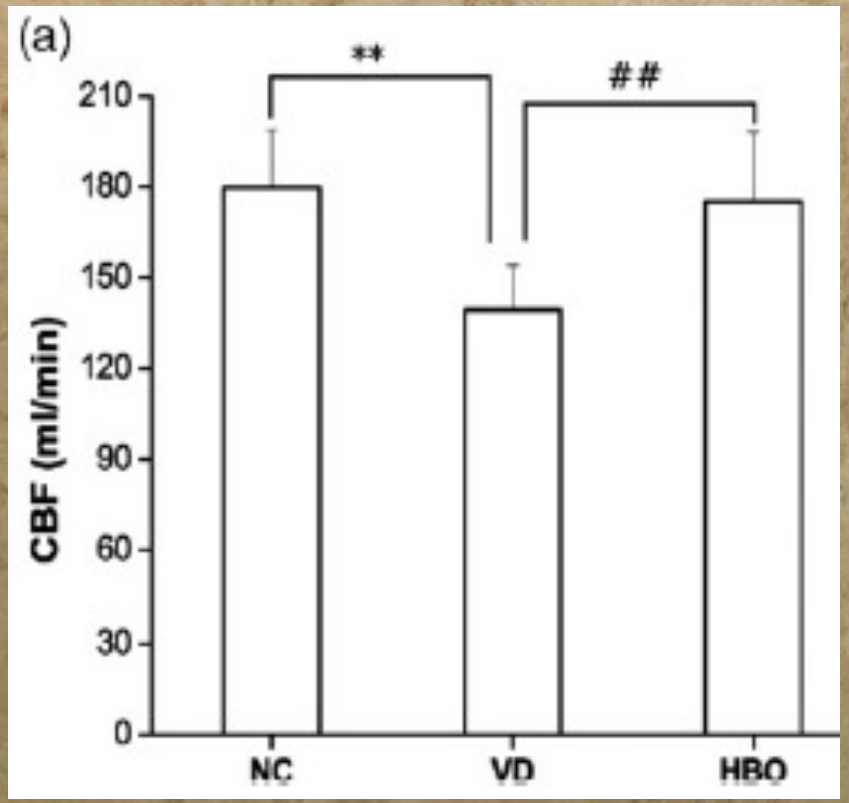
All of the above are acute situations. How about HBOT and SCs in chronic conditions?

AAR





Brain blood flow



Zhang T. Brain Injury, 2010;24(11):1350-1357

All of the above are acute situations. How about HBOT and SCs in chronic conditions?

New Neurons and Neural Stem Cells in the Piriform Cortex

	NC group	VD group	HBO group (10 days)	HBO group (30 days)
DCX(+) cells (total number/Pir zone)	36.56 ± 2.83	9.94 ± 2.10**	20.74 ± 2.86**##	31.26 ± 2.17**##
Nestin(+) cells (total number/10*40 visual field)	39.77 ± 4.06	50.98 ± 3.59**	70.31 ± 5.67**##	65.55 ± 6.12**##

**$p < 0.01$, compared with NC group; ##$p < 0.01$, compared with VD group.

New Neurons and Neural SCs in the Hippocampus after 30d

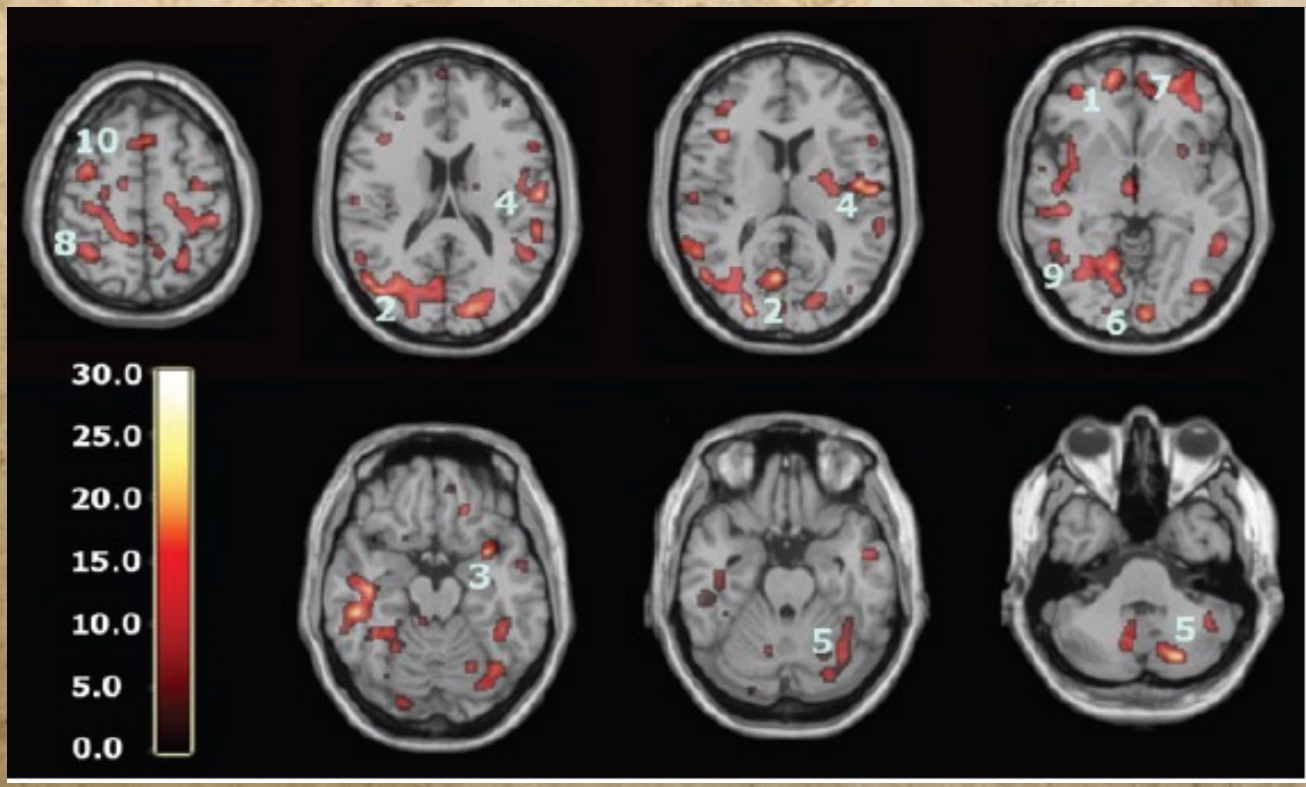
	NC group	VD group	HBO group
DCX positive	123.74 ± 16.90	66.27 ± 9.22**	155.13 ± 18.28** ##
Nestin positive	131.98 ± 13.24	160.46 ± 17.38**	187.82 ± 15.49** ##

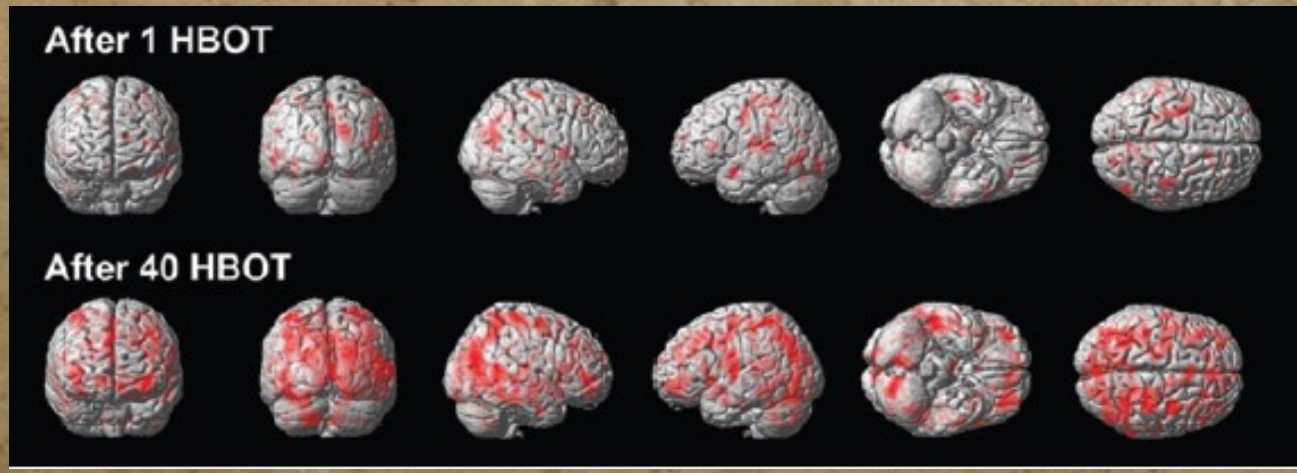
**$p < 0.01$, compared with NC group; ##$p < 0.01$, compared with VD group.

Zhang T. Brain Injury, 2010;24(11):1350-1357

Where have we seen this before?

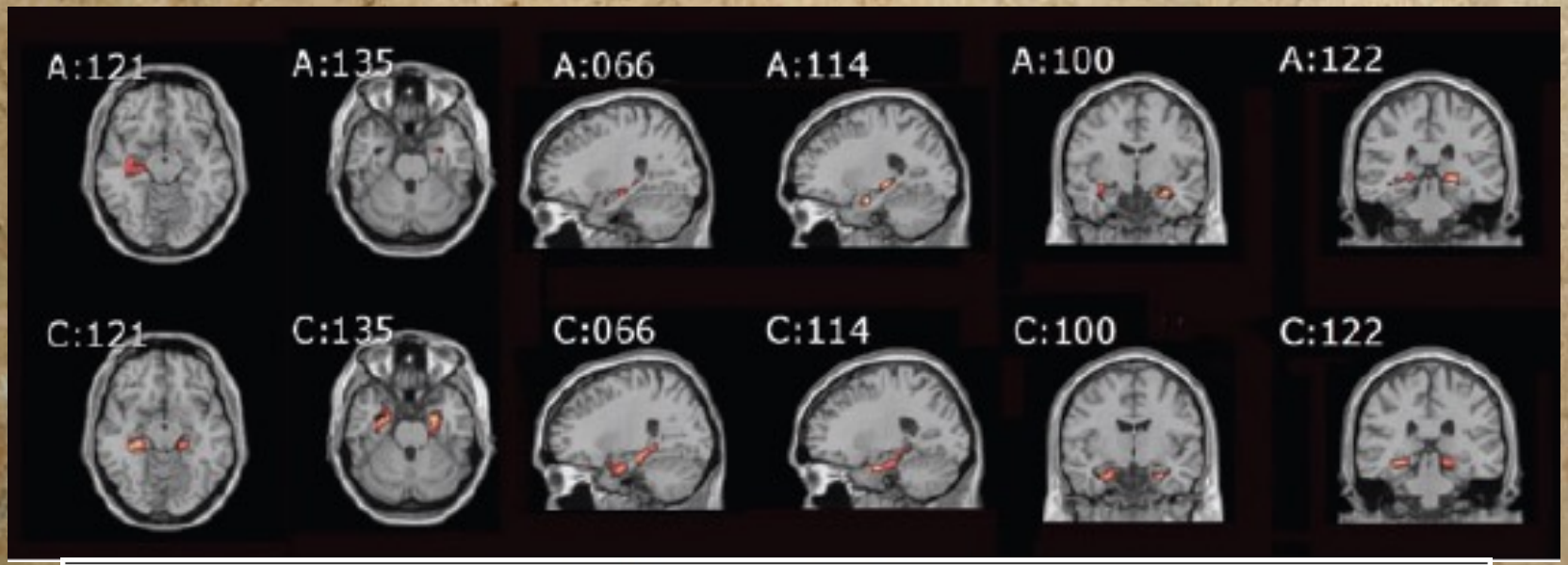
Improved memory and cognition and improved blood flow in the brain?





Harch PG. J Neurotrauma. 2012;29(1):168-185.

Where have we seen this before? Improved memory, cognition, blood hippocampus?



Outcome variables[a]	*Pre-HBOT mean ± SD (15) median (range)*	*Post-HBOT mean ± SD (15) median (range)*	*Pre:post diff ± SD 95% CI*[b]	*Significance of pre to post*[c]
Full scale IQ[d]	95.8 ± 8.4 98 (80–106)	110.6 ± 10.3 110 (97–129)	14.8 ± 7.4 CI: 10.7 to 18.9	$p < 0.001$
Delayed memory (WMS-IV)	97.7 ± 13.3 94 (76–125)	106.9 ± 15.4 107 (80–142)	9.2 ± 14.3 CI: 1.3 to 17.1	$p = 0.026$
Rivermead Paragraph	9.5 ± 2.4 (15) 10 (6–14)	7.5 ± 3.6 (15) 8 (2–13)	−2.1 ± 3.7 CI: −4.1 to −0.0	$p = 0.049$
Working memory (WMS-IV)	97.0 ± 13.6 91 (85–131)	106.9 ± 13.1 105 (88–127)	9.9 ± 10.3 CI: 4.1 to 15.6	$p = 0.003$[e]
Stroop color/word interference	84.3 ± 12.2 80 (65–108)	95.3 ± 12.8 94 (67–118)	11.0 ± 9.2 CI: 6.0 to 16.2	$p < 0.001$

Harch PG. J Neurotrauma. 2012;29(1):168-185.

Net result of HBOT effects on stem cells: The happiest little guy on earth

Jerzy Micholajczak

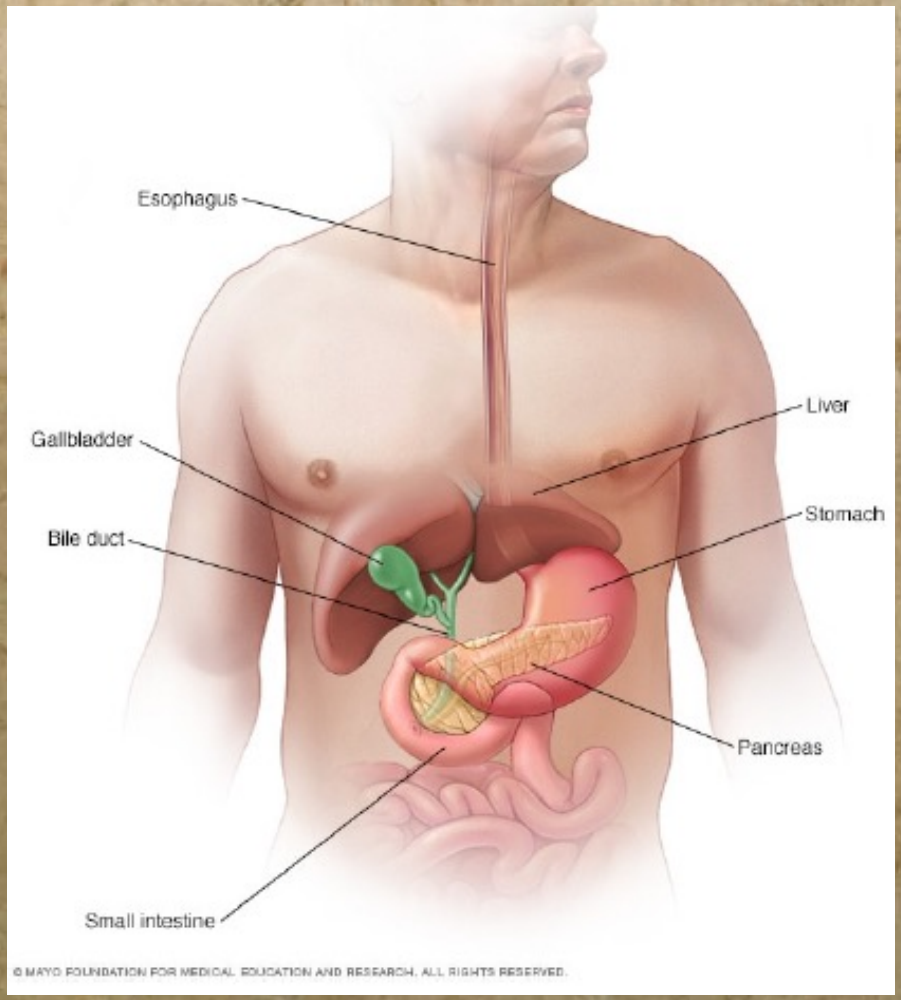
Premie, quad CP, HIE, global Developmental Delays.

HBOT Facilitates implantation of administered stem cells-Humans

- 25 Type II Diabetic Patients:
- HBOT: 10 @ 2.3-5 ATA/60 mins. at depth, once/day: 5 before stem cell and 5 after.

  Bone marrow stem cell harvest and immediate injection into the main pancreatic artery.

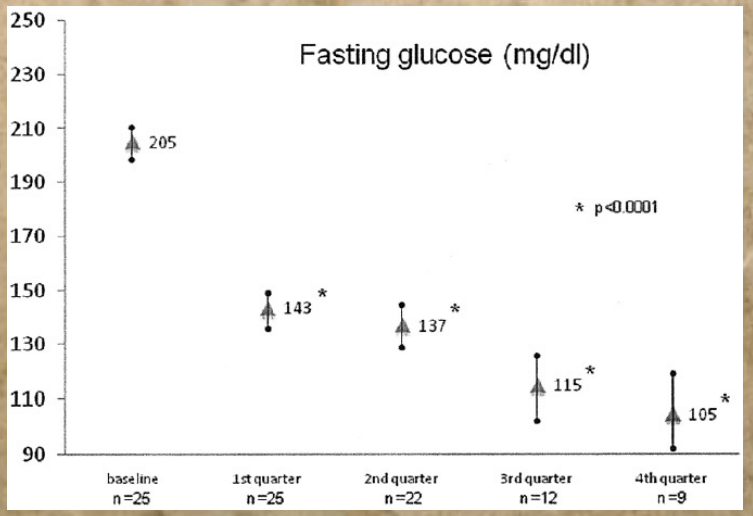
Measure outcomes one year later

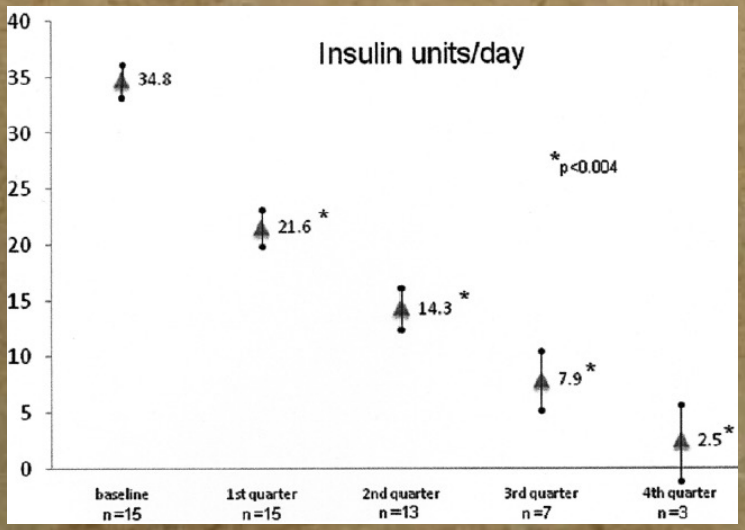


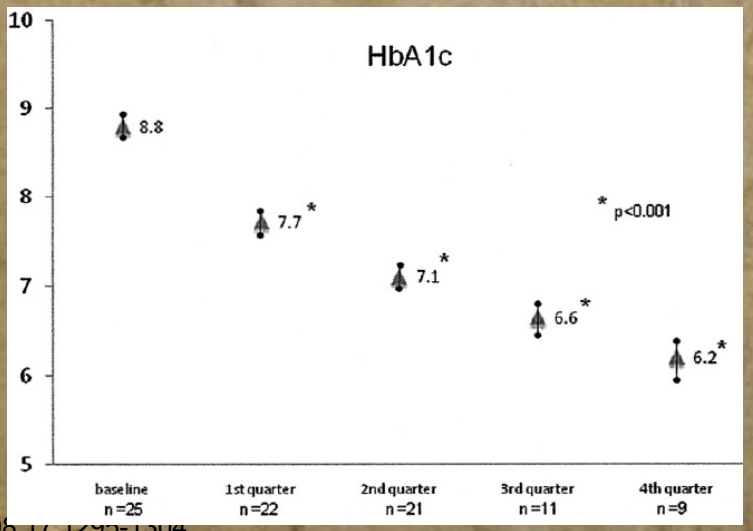
Estrada E. Cell Transplantation. 2008:17:1295-1304

HBOT Facilitates implantation of administered stem cells-Humans

- Results:
  - Fasting glucose de-creased by 50%
  - HGB A1C decreased from 8.8 to 6.2
  - Insulin decreased from 34.8U to 2.5U/d



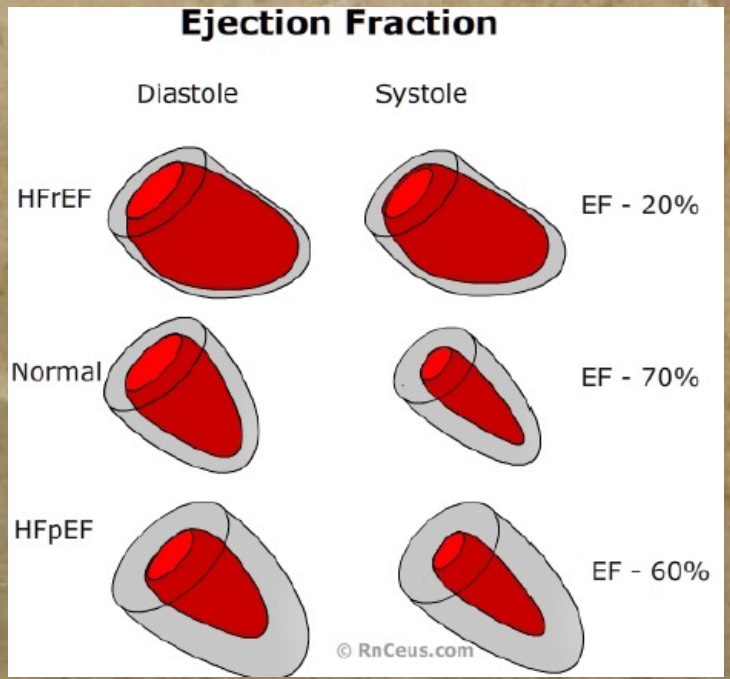




Estrada E. Cell Transplantation. 2006.17:1295-1304

HBOT Facilitates implantation of administered stem cells

- 16 year old boy, Congenital Carnitine Transporter Deficiency Type-2. (carnitine is an ammonium compound that transports fatty acids into mitochondria to burn for energy. Very important for heart function).
- Progressive heart failure. 3 siblings died of same during teen years.
- 20 HBOTs at 1.5 ATA/90 mins. TDT
- Wharton's jelly stem cells injected Into heart.
- 20 more HBOTs.
- Measure heart function:
  - ejection fraction 2/2015: 30% pre
  - 35% by discharge from hospital
- Repeat HBOT and SCs one year later



Arun M. Dev Disabil: 1(1): DIDD.000504. 2017 http://www.rnceus.com/CHF_16/ESC_HF.html

HBOT Facilitates implantation of administered stem cells

- Results: 5% increase in EF by
  - Hospital discharge
- 20 % increase 5 months later
- 54% two years later

Seven years old

2006/12/29	AK Univ. Hosp. Karachi	59
2007/02/26	AK Univ. Hosp. Karachi	60

Sixteen years old

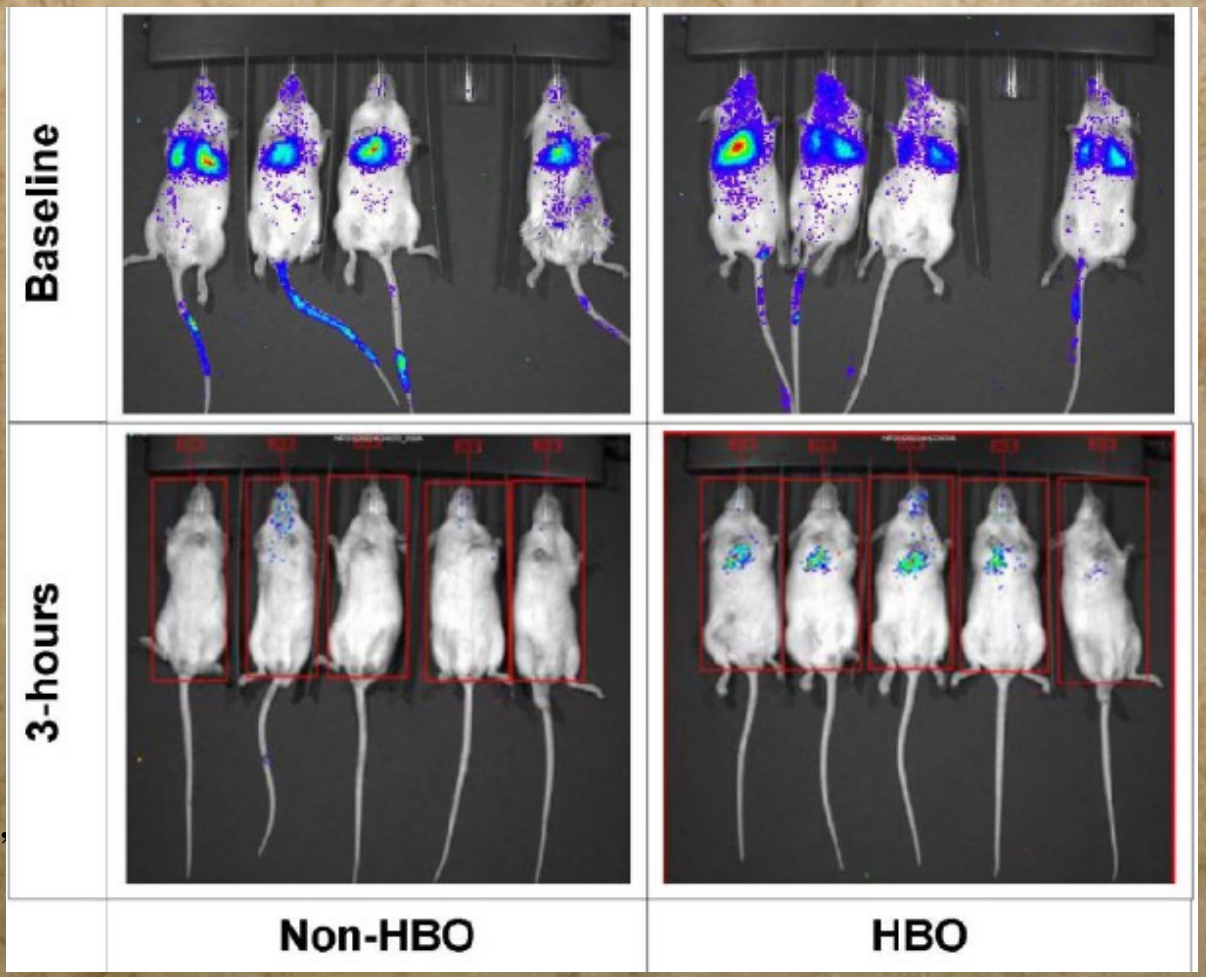
2015/02/31	National Heart Institute, Delhi: Post Procedure/HBOT	35
2015 July	AK Univ. Hosp. Karachi	55
2016 January	National Heart Institute, Delhi: Post Procedure/HBOT	55
2017 January	AK Univ. Hosp. Karachi	84, stable

HBOT Facilitates implantation of administered stem cells

- Irradiated immune-deficient mice, 24h later one HBOT (2ATA/2h), 4h later umbilical cord stem cell infusion. Image 3h later:

Result: Increased uptake in bone.

At 4.5 months: significant BM, blood, and spleen retention and engraftment.



Aljitawi OS. Blood Cells Mol Dis. 2014;52(1):59-67

HBOT Facilitates implantation of administered stem cells

- Cancer patients (Multiple myeloma, non-Hodgkins lymphoma, and Hodgkins Disease), chemical ablation of bone marrow, single HBOT 2.5 ATA/90 mins. at depth with 2 ABs, 6h later infusion of patients' own peripheral blood stem cells.
  - Results:
    - Significant reduction in
    - time to PMN and platelet recovery
    - mucositis: 26.3% in HBOT, 64.2% in historical controls
    - use of growth factors (granulocyte colony stimulating factor).
- Conclusions: HBOT appears to facilitate SC engraftment.

Abdelhakim H. Biol Blood Marrow Transplant. 2019;25:1713-1719

HBOT Facilitates implantation of administered stem cells

- My most famous patient: 2017
  - Middle-aged man with heavy metal poisoning and cognitive decline.
  - Extensive array of treatments, failed, except chelation which reduced mercury levels.
  - HBOT at 8 facilities nationally and internationally.
  - SPECT, dive, SPECT. Dosing with HBOT.
  - By 26 HBOTs, remarkable improvement in Sx.
  - Umbilical cord SCs IV.
  - 9 more HBOTs in 11 days
  - "Best I've ever felt. These SCs are incredible."
  - SC facility: "This is not due to our stem cells."

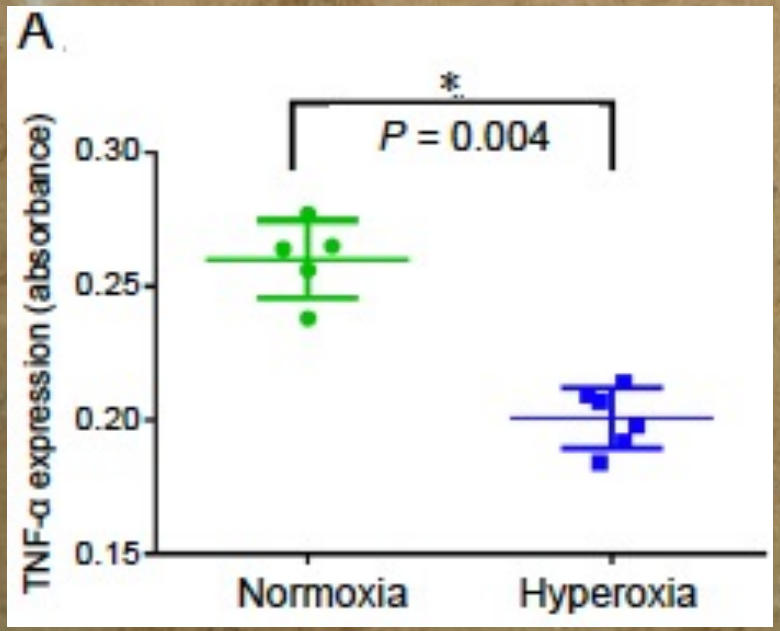
HBOT has multiple effects on stem cells?

- Stimulates production and release of stem cells from the bone marrow to our circulation.
- Stimulates differentiation of the stem cells that are released from the bone marrow.
- Stimulates proliferation and differentiation of SC's at sites of injury.
- Facilitates implantation of stem cells.
- Increases production of stem cells in tissue for harvest.

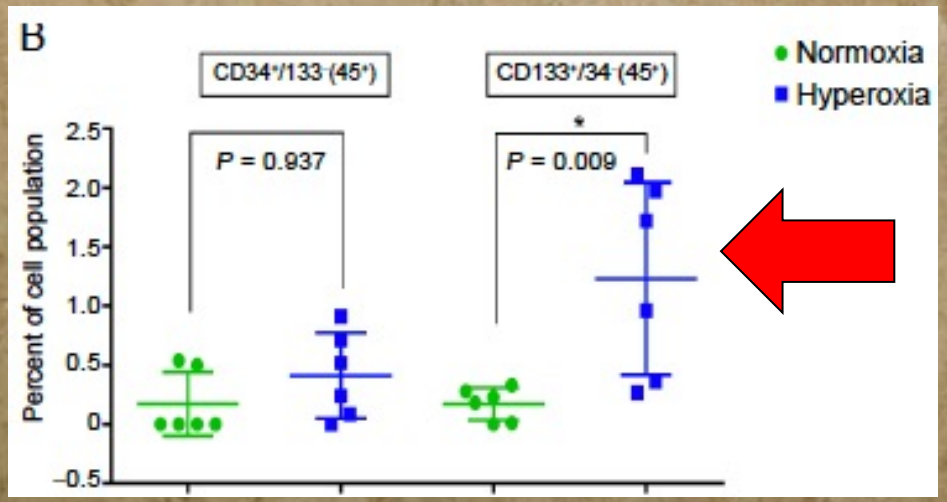
How about NBO and stem cells?

1. Rats, Room air vs. 42% O2 breathing 2h/d x 10d.
2. Measure Stem cells in blood and cytokines
3. Results: increased stem cells and reduction in inflammatory TNF-alpha.

TNF-alpha



Stem cells



McLaughlin KJ. Med Gas Res. 2019;9(3):139-144..

Have now administered NBO to over 50 children in ICUs all over the U.S.

The net Result of the wide-ranging genetic and stem cell effects of HBOT and NBO:

- Taking a child from this to this:
- Eden at discharge from hospital

Lastly, HBOT Increases production of stem cells in tissue for harvest.

- Surprise finding with patients who used the above studies and clinical experience to enhance stem cell implantation
- > 12 consecutive patients: adipose stem cell harvest: approximately four-fold increase in stem cells from ~80-100 million to > 340 million
- Improvement in vitality of stem cells by microscopic examination.

Take Aways

- HBOT uses increased pressure and oxygen to treat wounds In any location and of any duration.
- HBOT treats human disease by treating the underlying disease processes.
- HBOT treats disease processes thru extensive activity on gene expression/suppression.
- HBOT grows new tissue to heal wounds.
- HBOT helps grow new tissue through its gene activity and its wide-ranging effects on stem cells.
- HBOT stimulates production, release, implantation, and maturation of stem cells to grow new brain tissue.
- HBOT may also increase production of stem cells in fatty tissue for harvest and implantation.
- HBOT is likely additive or synergistic with administered stem cells.

Thank You