Hyperbaric Oxygen Therapy

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Disclosure Statement

- Does not have any significant financial relationships to disclose.
- Has disclosed this activity will not include discussion of unapproved/investigational uses of products or devices.
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Objectives

- Define hyperbaric oxygen therapy.
- Explore the mechanisms of action of HBO.
- Discuss HBO indications.
- Review potential complications of HBO.

What is Hyperbaric Oxygen Therapy?

Definition of HBO

A treatment in which a patient breathes 100% oxygen while inside a treatment chamber at a pressure higher than sea level pressure.

(typically >1.4 ATA)

Oxygen under pressure is used as a drug:

- Route of delivery
- Mechanism of action
- Dosage
- Indications
- Contraindications
- Side effects


Multiplace HBO Chamber


Inside multiplace chamber


Monoplace HBO Chamber
SECHRIST

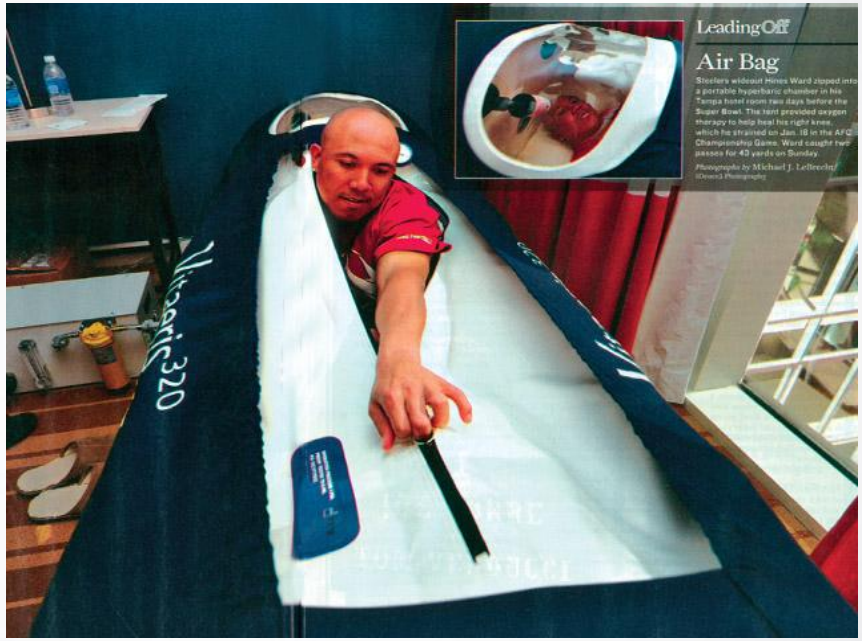
Hyperbaric Oxygen Misnomers

NOT Hyperbaric Oxygen

Topical Oxygen is not HBO

Low Pressure “HBO”

- Usually about 4 psi
- Equates to about 10 feet of seawater depth
- Not considered clinically significant HBO. Not indicated for any accepted treatable diagnoses.



Hines Ward

HBO: A History of Controversy

- Panacea
  - 1891 Corning used to treat “nervous disorders”
  - 1927 Dr. Cunningham built a pressurized hotel to treat Influenza, diabetes and cancer
  - 1980s Multiple sclerosis
  - AIDS, Lyme disease, etc…
- Previously poorly understood MOA

3 Atmosphere Hyperbaric Hotel Cleveland, Ohio


Main Lobby
Cunningham Sanitarium
Cleveland O.


Recreation Room in Main Tank
Cunningham Sanitarium
Cleveland O.


Bedroom
Cunningham Sanitarium
Cleveland O.


Laboratory
Cunningham Sanitarium
Cleveland O.

HBO was used for everything.

Did anything actually improve from treatment with HBO?

Picking the right patient will lead to good results.

Pick the right pt:

Hypoxic wounds who have not improved with standard care.

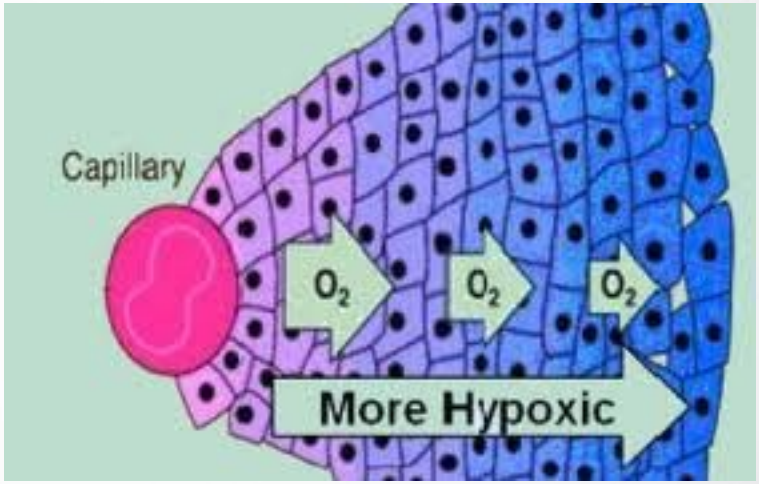
The Diabetic Foot Ulcer

- How do we treat?
  - Debridement
  - Antibiotics
  - Wound dressings
  - Large vessel arterial bypass

- It's still not healing. Have we adequately addressed the hypoxia?
- What other drug can we give to help the hypoxic wound? Hyperbaric Oxygen

First, what is causing the hypoxia?

- Poor blood supply/perfusion
  - Macrovascular
  - Microvascular
- Edema
- Infection
- Inflammation
- Vasoconstriction



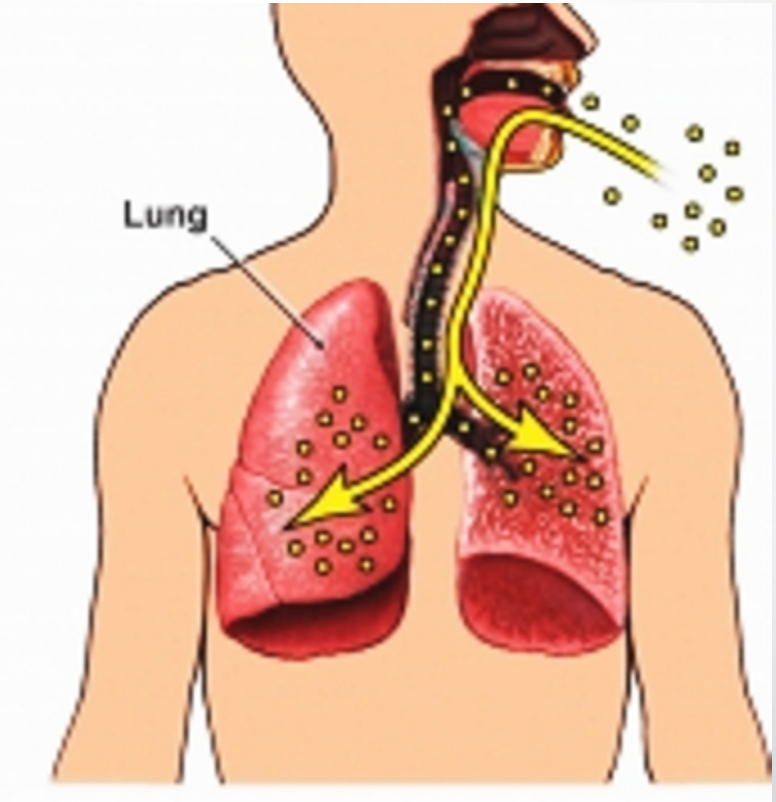
How does HBO help hypoxic wounds? Mechanisms of Action

MOA of HBO

- Reverse ischemia and hyperoxygenate tissues
- Enhanced leukocyte killing of bacteria
- Fibroblast proliferation
- Collagen production
- Angiogenesis
- Cellular signaling
- Reduce ischemia-reperfusion injury

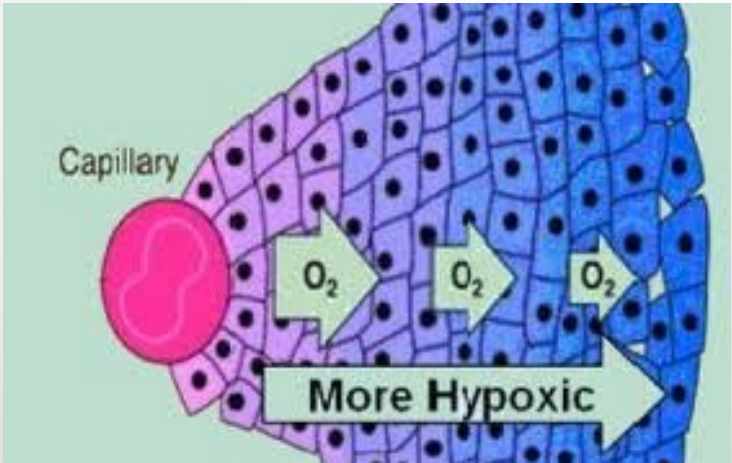
Route of delivery

- Not Topically Absorbed.
- Oxygen needs to be Inhaled under pressure to have significant effect.

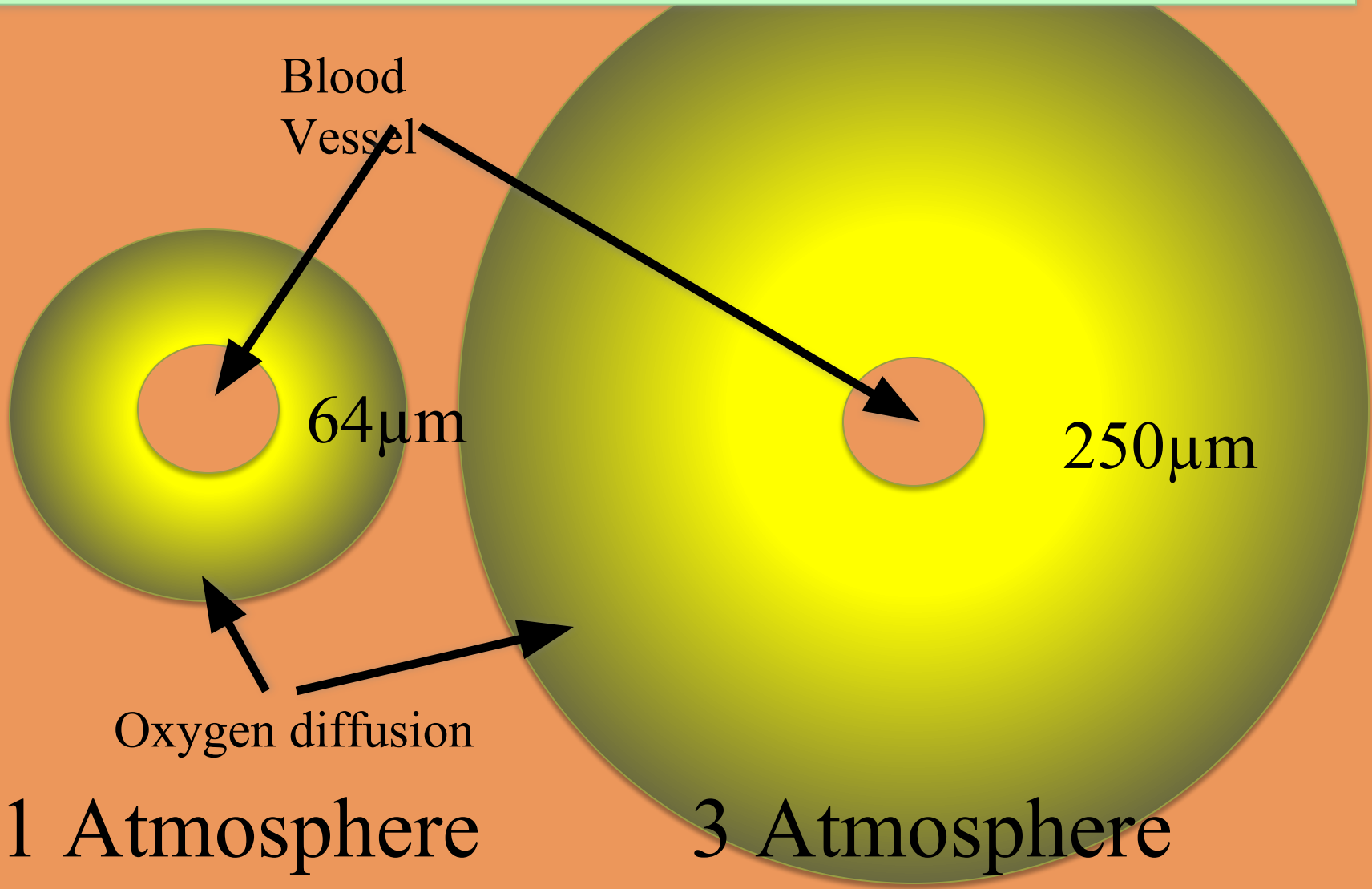


Getting oxygen into hypoxic tissue

- Breathing oxygen at increased pressure
  - does not increase binding of oxygen to hemoglobin
  - Does increase concentration of dissolved oxygen in liquid portion of blood (PaO2)
- Increased concentration of oxygen leads to increase in diffusion gradient



Comparison of oxygen tissue diffusion



How long does the tissue stay saturated with oxygen after an HBO two hour long treatment?

Oxygen Tension with HBO

Tissue Oxygen Response To Hyperbaric Oxygen Therapy

Ischemic Wound Model

2.0 ATA compression

PO_2 of 250 to 350mmHg attained

PO_2 returned to baseline in 4 hours

Siddiqui et al. Plas Recon Surg; 99:148-55, 1997

So the hypoxic tissues get properly oxygenated for 4 to 6 hours per 24 hour period.

Does that even matter?

MOA of HBO

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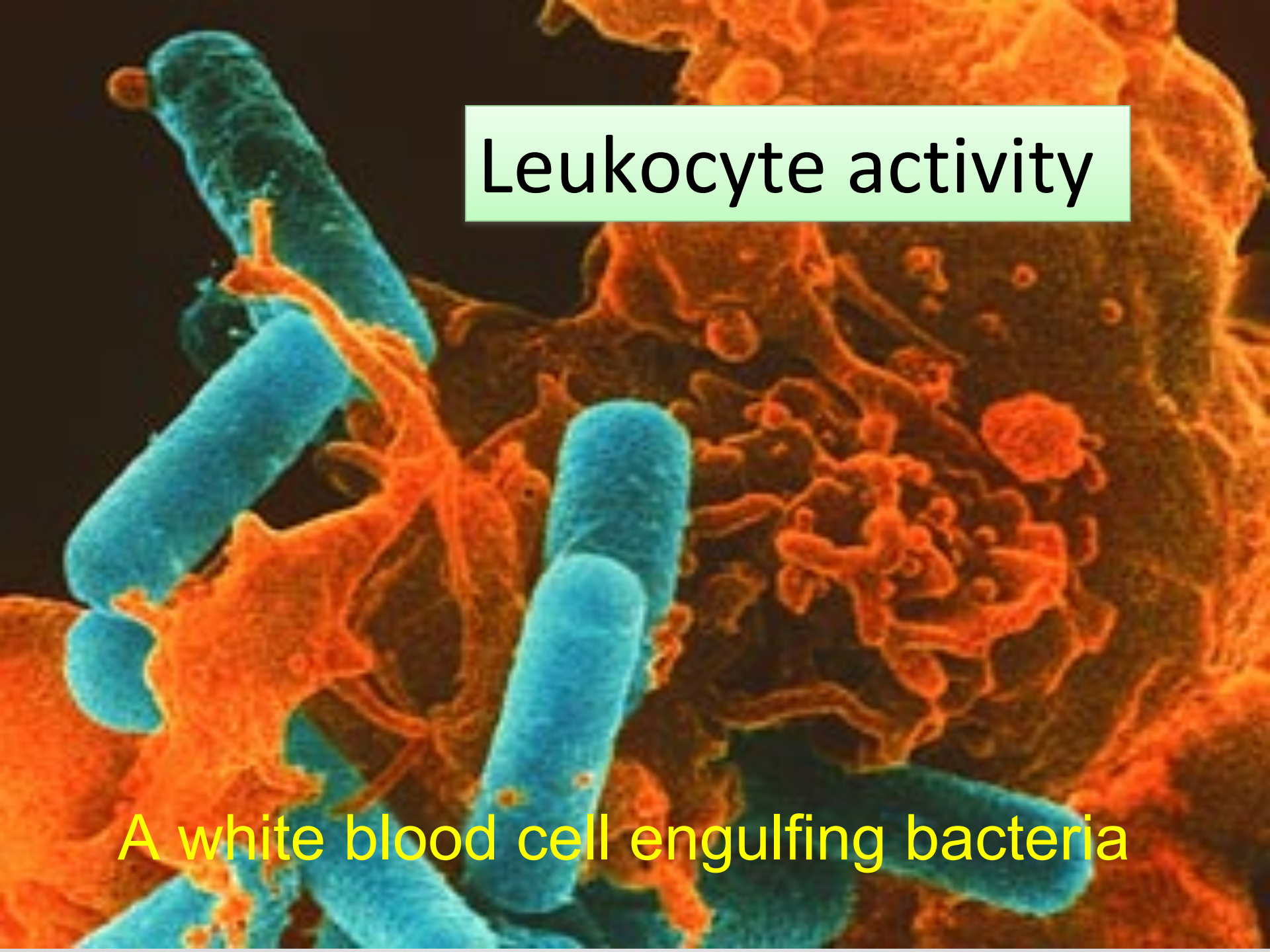
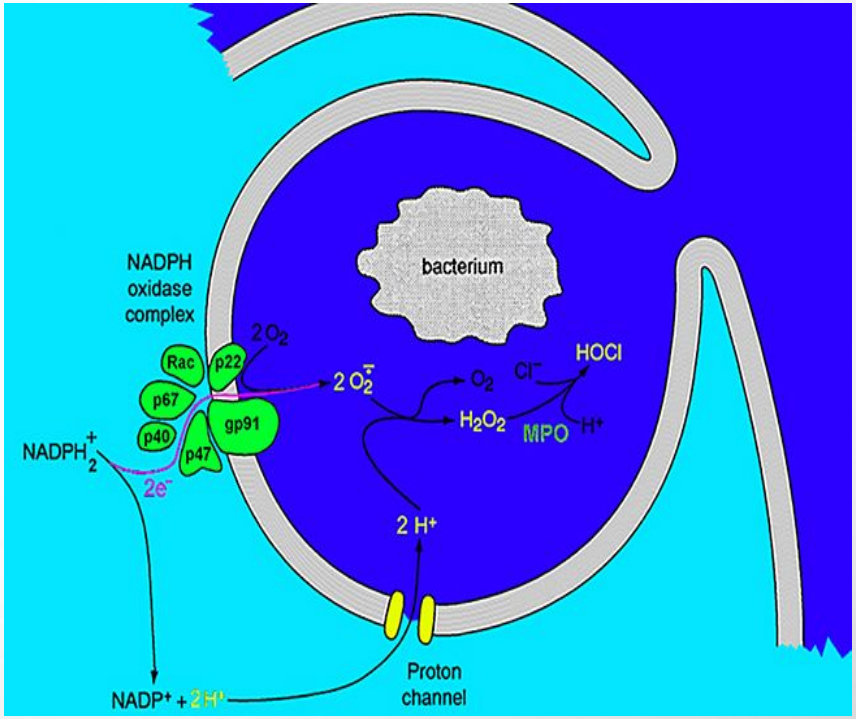
Leukocyte activity



A white blood cell engulfing bacteria

Leukocyte Activity

- Bacterial killing requires oxygen to form Reactive Oxygen Species (ROS).
- Superoxide production (ROS) depends on oxygen tension.
- Leukocyte mediated bacterial killing begins to fail when the P_TO2 falls below about 30 to 40 mmHg.



Hunt TK: The Physiology of Wound Healing. Ann of Emerg Med 1988;17:1265-1273

MOA of HBO

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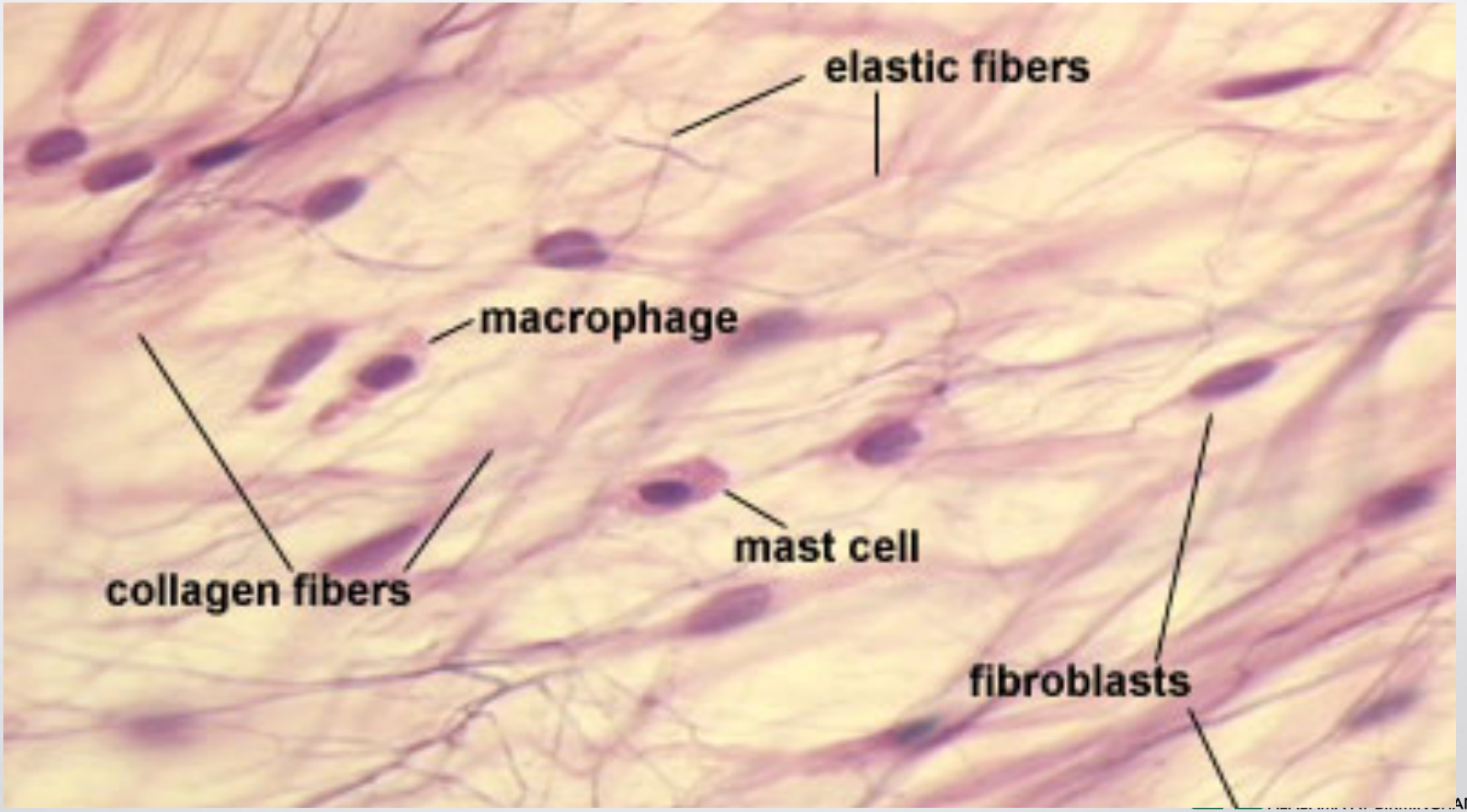
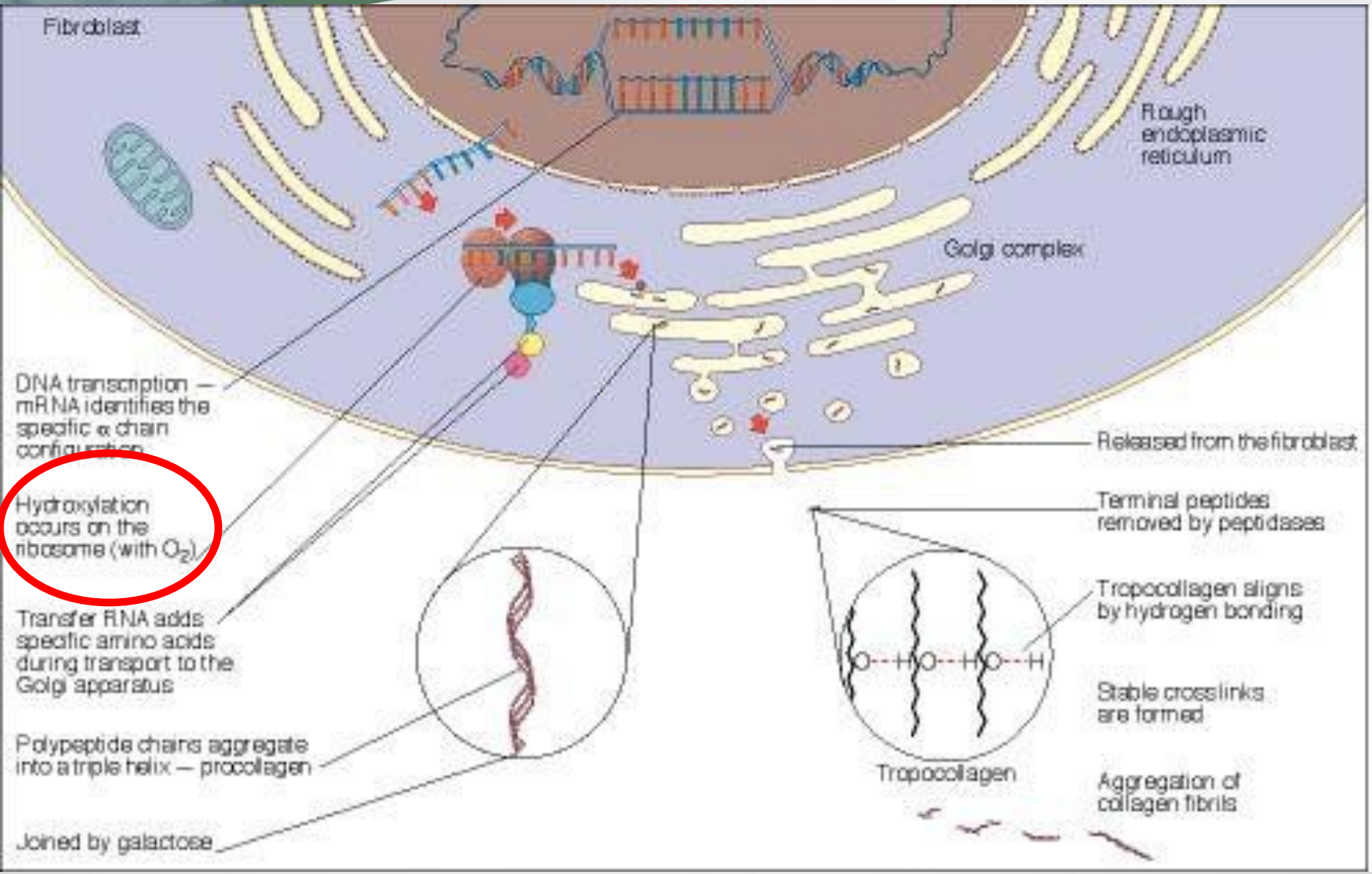
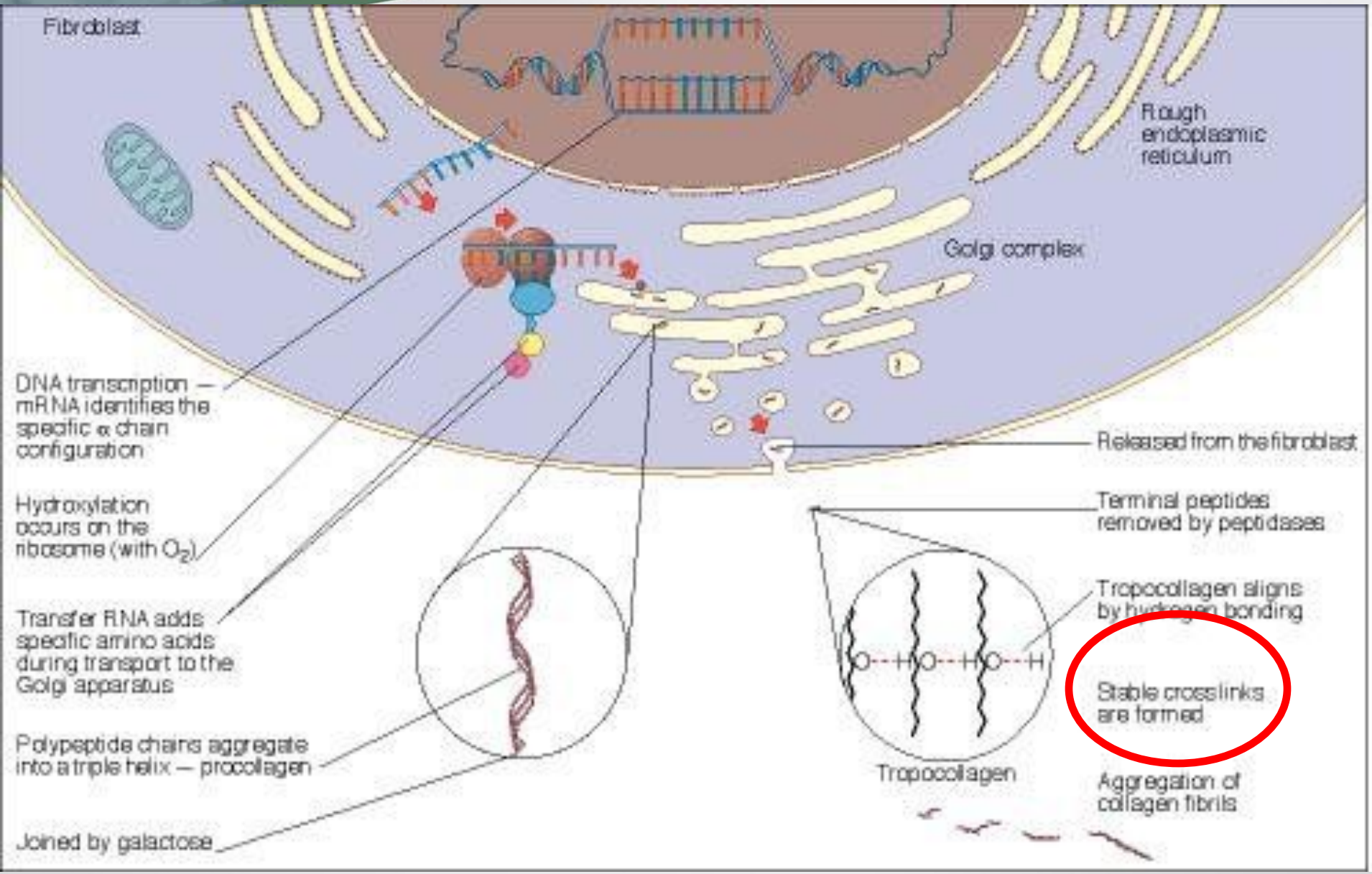
Fibroblasts are the major producers of collagen in the repair response of an ulcer.







Collagen Synthesis

- In hypoxic tissue, oxygenation becomes the rate-limiting factor for collagen deposition and cross linking.

- Functional collagen cannot be produced by fibroblasts in hypoxic tissue.

Gordillo et al. Amer J Surg 2003;186; 259-263

MOA of HBO

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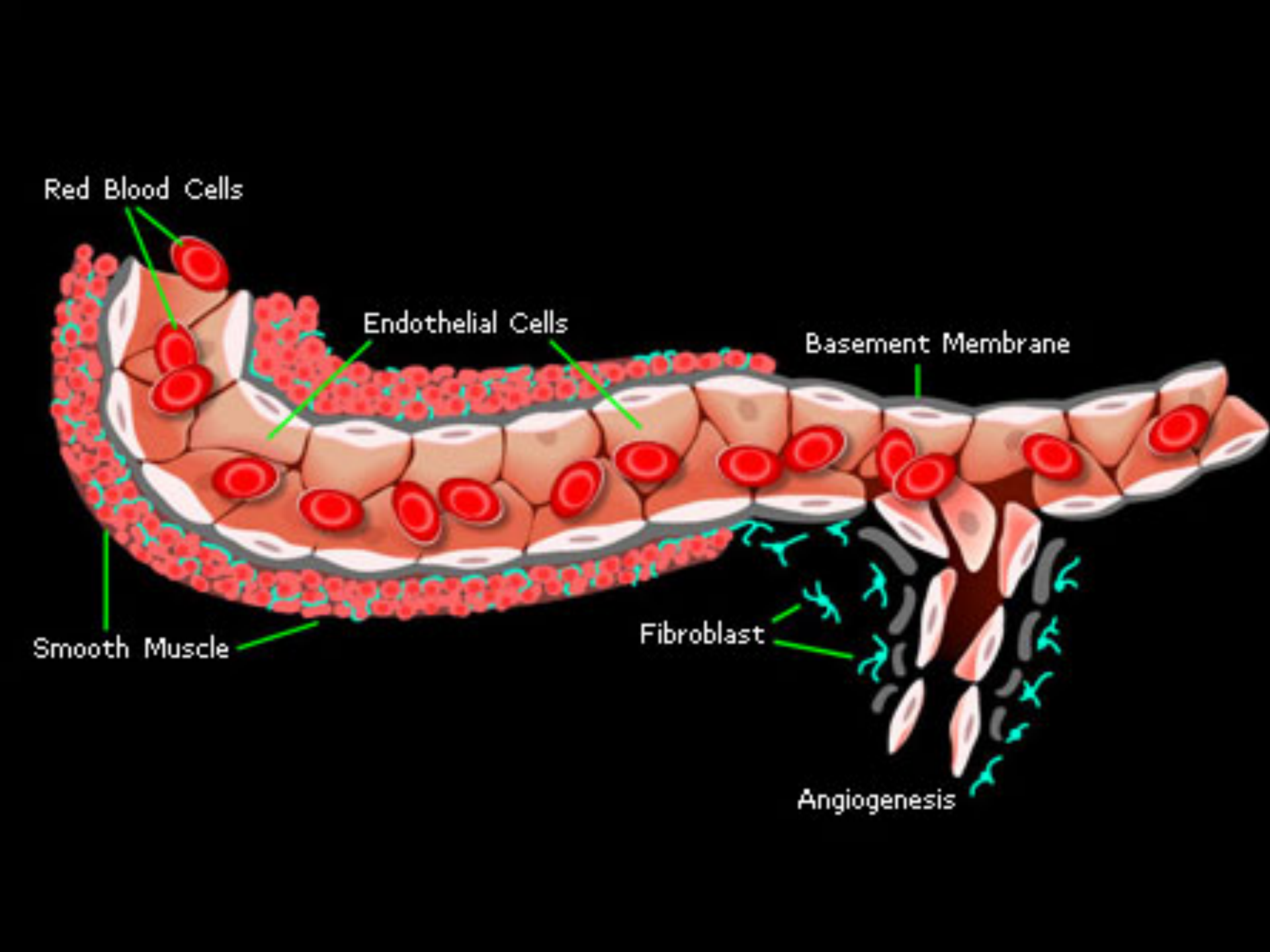
Red Blood Cells
Endothelial Cells
Basement Membrane
Smooth Muscle
Fibroblast
Angiogenesis

MOA of HBO

- Reverse ischemia and hyperoxygenate tissues
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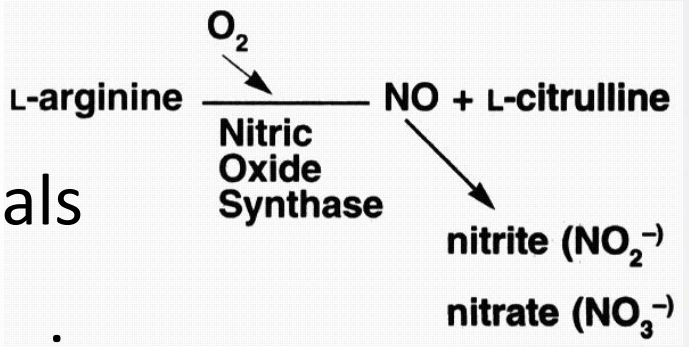
Signaling

- Leukocytes aerobically produce lactate as a byproduct of their “superoxide burst.”
- Lactate ↑ endothelial and macrophage release of VEGF and other growth factors
- HBO directly ↑ VEGF, ↑HIF-1,

↑ PDGF, ↑TGF-B in the wound.

Nitric Oxide (NO)

- O_2 + L-Arginine → NO
- Small, diffusible messenger - mediates biological processes, signals O_2 availability, vasodilator
- NO deficit in diabetic wounds, chronic hypoxic wounds, pts on steroid therapy, smokers
- ↑iNOS
- NO levels in wounds increase with HBO



Thom et al. J Neurobiol 51: 85-100, 2003

Reactive Oxygen Species (ROS)

- ROS (mostly H_2O_2) beneficial for wound healing
  - Secondary messenger molecules induce wound healing process, control inflammation
  - ↑ ROS →↑ PDGF, TGF-B, VEGF, IGF-1, EGF
  - ↑ ROS → ↑ NO

Sen, et al Wound Rep Reg 2003;11: 431-8

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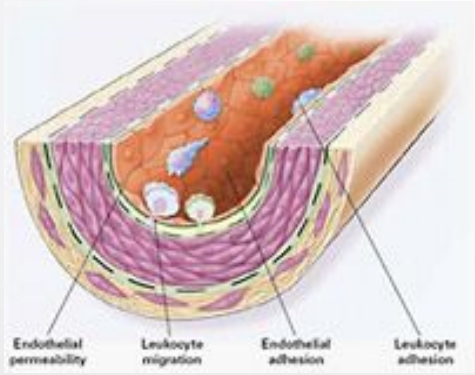
Ischemia-Reperfusion Injury

- When blood vessels loose perfusion they upregulate ICAM-1 receptors along their endothelium after about 2 hours.
- When perfusion is restored, neutrophils are attracted to the ICAM-1 receptors and are activated.

Ischemia-Reperfusion Injury

- HBO blocks adherence of neutrophils to the endothelial lining after perfusion has been restored.
- This reduces secondary inflammatory injury and neutrophil activation.



- What about oxidative stress?
- Isn't that bad?

Oxidative Stress

- <u>Free radicals are involved in normal physiology.</u>
- HBO will increase free radical synthesis
  - Superoxide ($O_2^{\cdot -}$) and H_2O_2 enzyme sources

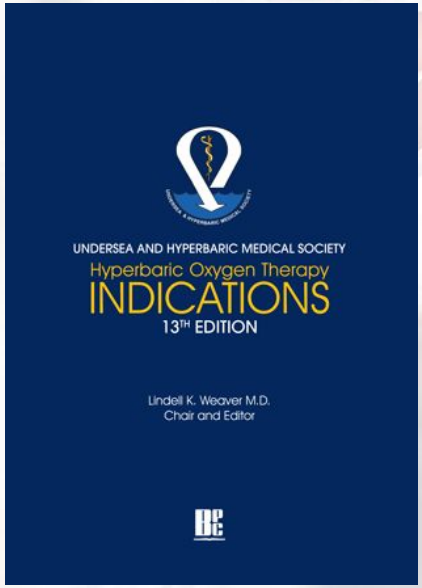
- **BUT – Cellular antioxidant defenses keep radicals 'in check' and are NADPH dependant.**

Oxidative Stress

- HBO induces production of antioxidant defenses to combat increased ROS:
  - superoxide dysmutase (SOD)
  - catalase
  - glutathione peroxidase
  - iNOS

HBO Indications

HBO Indications



Hyperbaric Oxygen Therapy Indications.
13th Edition: Published 2014 by UHMS

Accepted Indications for HBO

1. Decompression Sickness
2. Air or Gas Embolism
3. Carbon Monoxide Poisoning
4. Clostridial Myositis (Gas Gangrene)
5. Acute Traumatic Ischemias
6. Enhancement of Healing In Selected Problem Wounds

Accepted Indications for HBO

7. Severe Anemia
8. Intracranial Abscess
9. Necrotizing Soft Tissue Infections
10. Osteomyelitis (Refractory)
11. Delayed Radiation Injury
12. Compromised Grafts and Flaps
13. Acute Thermal Burn Injury

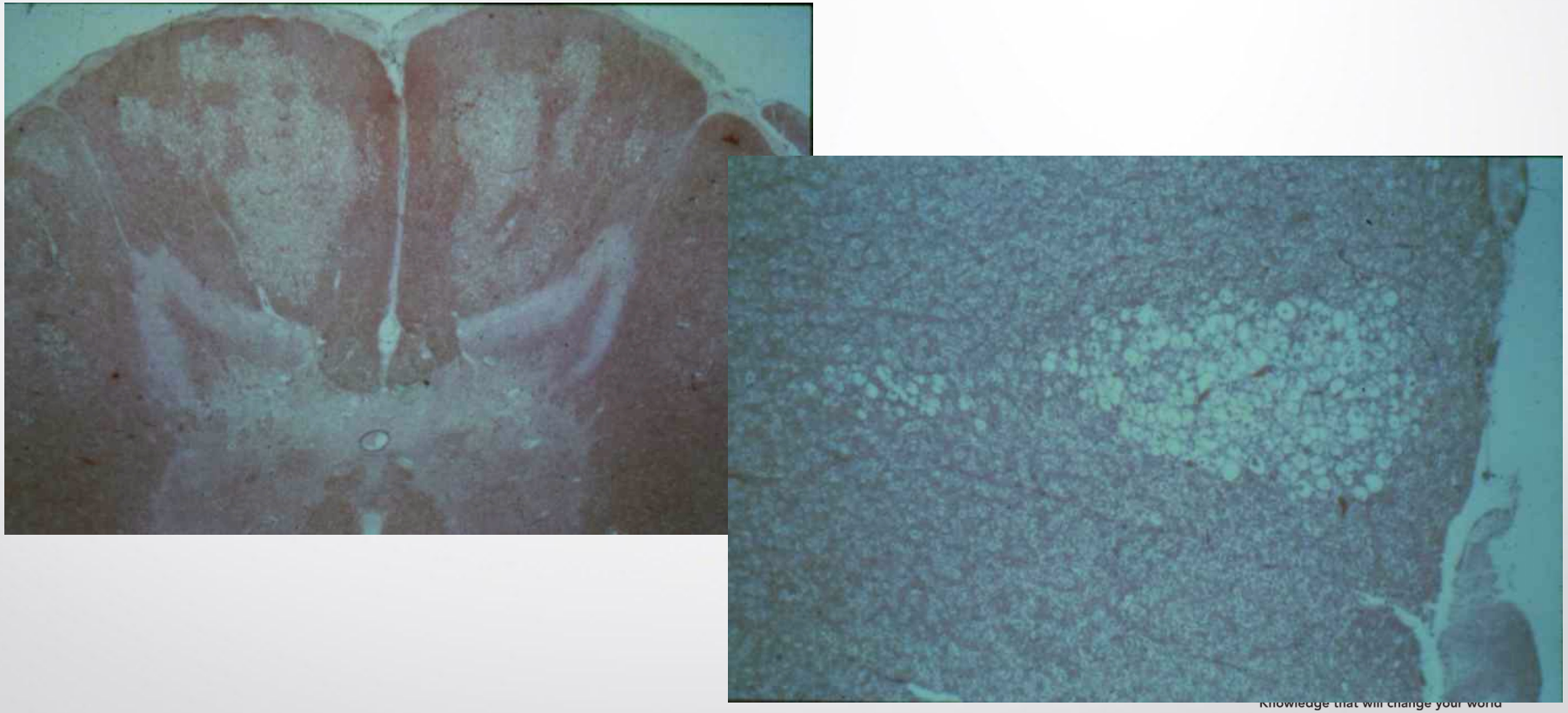
Decompression Illness

- Nitrogen accumulates in the tissue and blood in proportion to the depth and length of the dive.
- Nitrogen is biologically inert.

Decompression Illness: Bubbles…

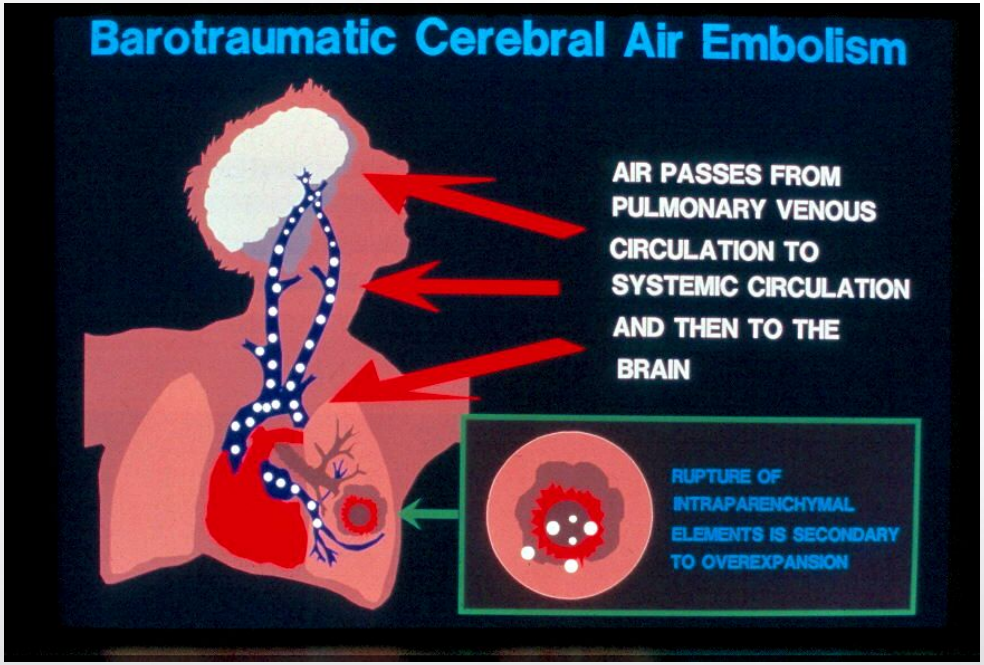
- Cause mechanical deformation of connective tissue.
- Disrupt the endothelial lining of blood vessels causing edema and inflammatory activation.
- Activates platelets, complement and leukocytes.

Bubbles can initiate Brain and Spinal Cord cell death



Arterial Gas Embolism

- Second leading cause of death in sport divers after drowning.
- Also a complication of medical procedures.



Arterial Gas Embolism

- Mechanical thrombus
- Damages endothelium

- HBO Treatment:
  - Shrinks the bubble diameter
  - Increases off gassing of the nitrogen bubble
  - Reduced secondary inflammatory damage

Carbon Monoxide

- Why is it bad?

Carbon Monoxide Poisoning

- CO binds to hemoglobin with 200 fold the affinity of oxygen.
- Activates platelet adhesion molecules which stimulate secondary inflammatory injury.
- Disrupts oxidative phosphorylation - CO binds to mitochondrial hemoprotiens and inhibits the electron transport chain.

Carbon Monoxide Poisoning

- HBO immediate effect - Displaces CO off the carboxy-hemaglobin.
  - COHb Half-life room air - 320 min
  - COHb Half-life 100% O_2 1ATA - 80min
  - COHb Half-life 100% O_2 3ATA - **23 min**
- Delayed Effect – reduces myeloperoxidation of neural tissue. (Reduces long term brain damage)

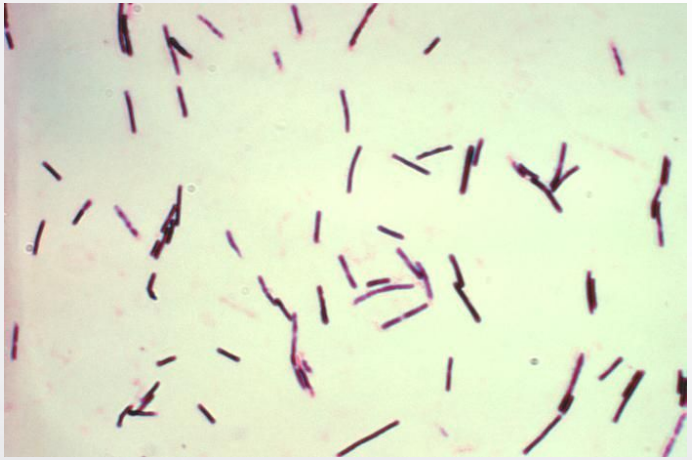

16:40

Clostridial Myositis (Gas Gangrene)

- *Clostridium Perfringens* is an anaerobic gram positive rod.
- Produces α-toxin, which disrupt normal cellular function.
- Primary treatment for this disease is surgical debridement and antibiotics.
- HBO is an adjuvant treatment.

Clostridial Myositis (Gas Gangrene)

- *Clostridium Perfringens* stops replicating at PO2 of 250mmHg
- Alpha Toxin is inactivated at PO2 of 1500mmHg.



Necrotizing Fasciitis

- High mortality national average ~30%
- Surgical disease
- Compromised Host (not Always)
- HBO adjunct to Surgical/Medical management
- HBO can lower mortality and amputation rates

Enhancement of Healing In Selected Problem Wounds

The Wagner Scale of Diabetic Foot Ulcers (DFUs)

- Grade 0: Skin intact, may be deformities
- Grade 1: Superficial ulcer
- Grade 2: Ulcer reaches tendon or bone
- Grade 3: Deeper tissue, with osteomyelitis or abscess
- Grade 4: gangrene of toe or forefoot, wet or dry, infected or not

HBO Candidates in DFU

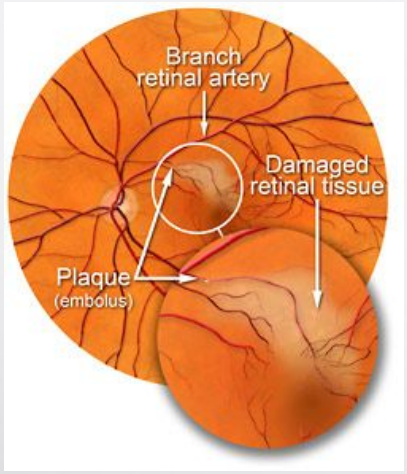
- Failure to improve after being in a wound program for more than 28 days
  - Debridement
  - Infection control
- Appropriate correction of large vessel disease
- Wagner Grade 3 or higher
- HBO reduces major amputations and speeds wound closure.

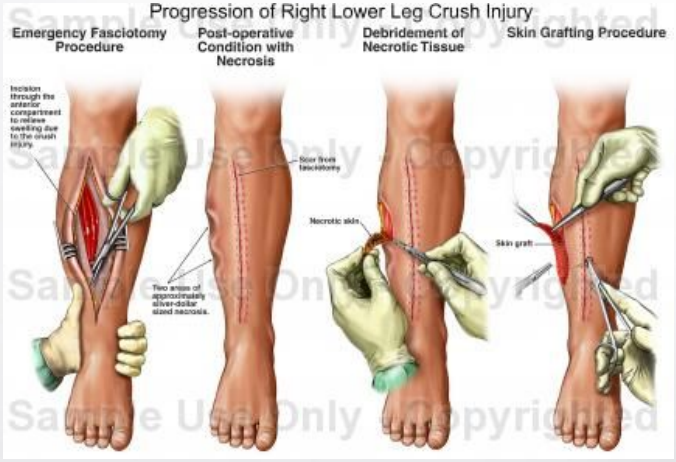
Soft Tissue and Bony Radionecrosis

- Late effect of radiation treatment
- About 3% of patients undergoing Rad Onc treatment
- Onset 6 months to 3 years after treatment
- Obliterative end-arteritis – loss of microvasculature from chronic inflammation
- Soft tissue is hypocellular and hypovascular

Acute Arterial Insufficiencies

- Central Retinal Artery Occlusion
- Crush Injury
- Compartment Syndrome
- Acute Traumatic Ischemia





Other

- Compromised Grafts and Flaps
- Acute Thermal Burn Injury
- Chronic Refractory Osteomyelitis
- Severe Anemia
- Intracranial Abscess
- Acute Sensorineural Hearing Loss

Contraindications to HBO

- Untreated pneumothorax
- Unable to equalize middle ear
- Claustrophobia
- Hemodynamic instability
- Uncontrolled Congestive heart failure
- Uncontrolled Epilepsy

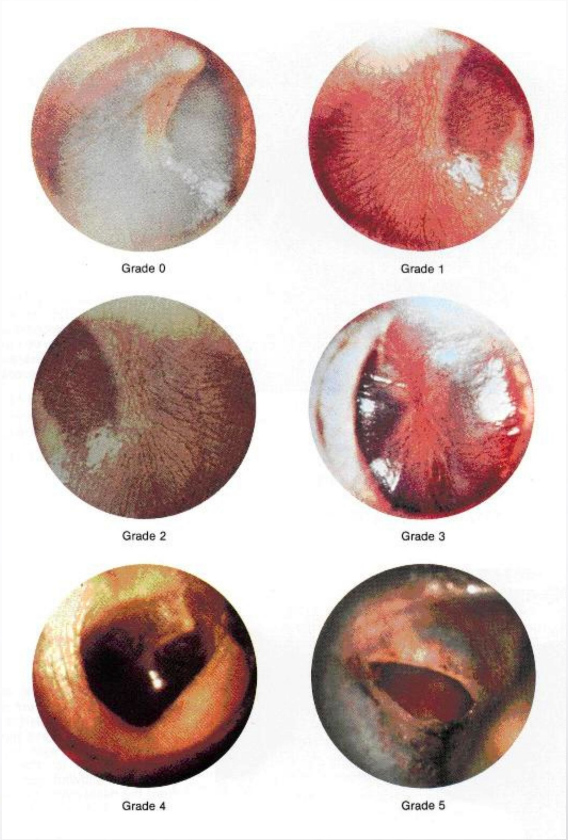
Toxic and Overdose effects

Pressure Related

Oxygen Related

Pressure related complications

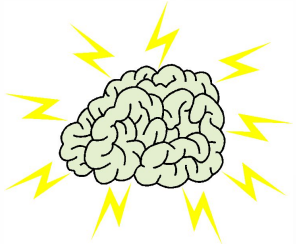
- Tympanic membrane trauma
- Hypoglycemia
- Pneumothorax (rare)

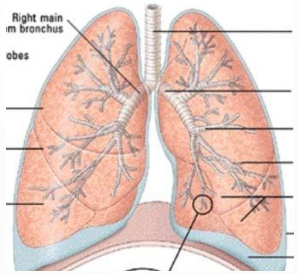


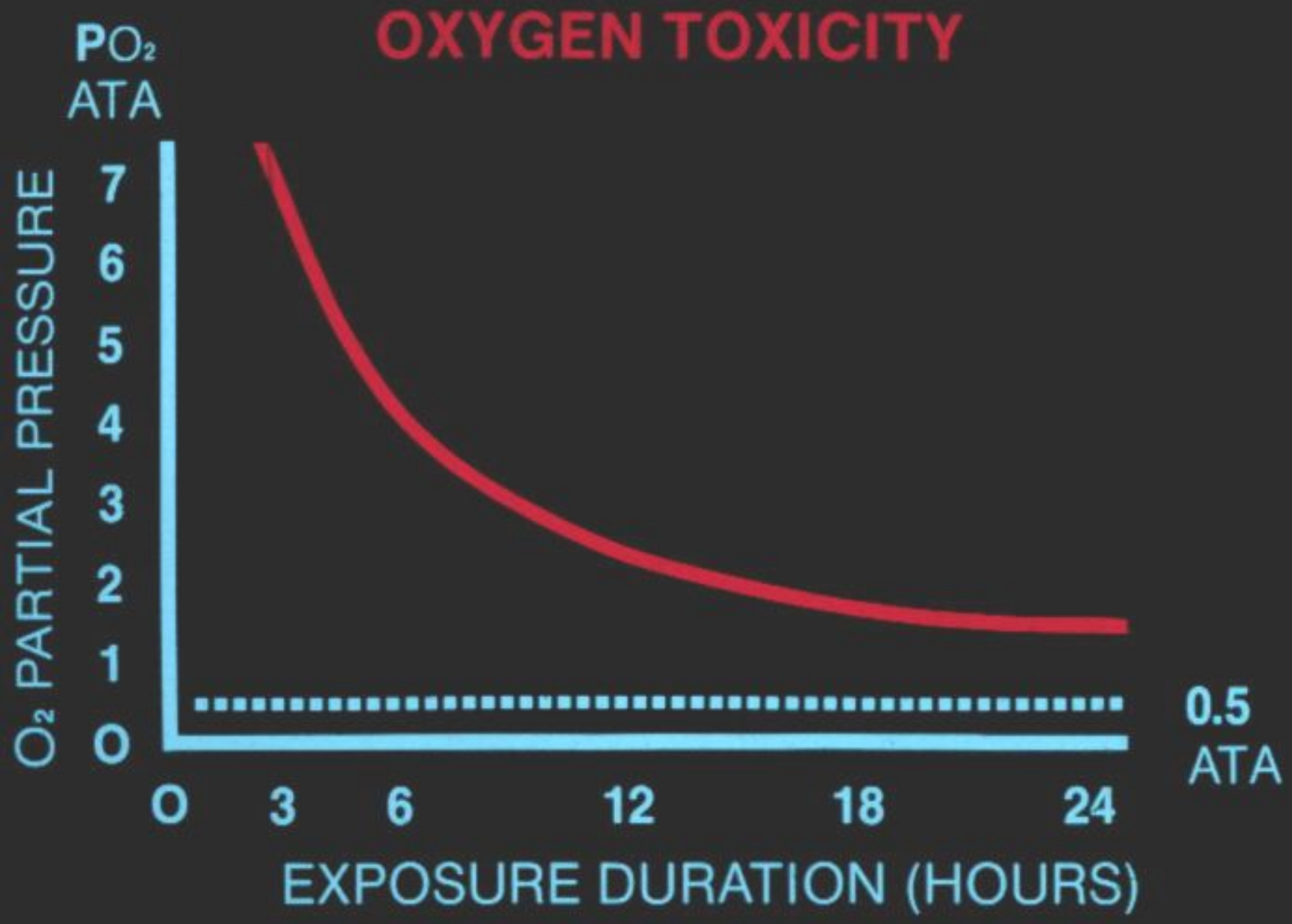
Teed Scale

Oxygen related complications

- Central nervous system
  - Seizures
- Pulmonary
  - Pulmonary toxicity
- Ophthalmologic
  - Temporary myopia
  - Cataracts






OXYGEN TOXICITY
PO2
ATA
O2 PARTIAL PRESSURE
7
6
5
4
3
2
1
O
0.5
ATA
O
3
6
12
18
24
EXPOSURE DURATION (HOURS)
J.M. Clark (1974)

Boy dies from burns suffered when Florida hyperbaric chamber exploded

Powered by CDNN - Cyber Diver News Network

June 15, 2009

LAUDERDALE-BY-THE-SEA, Florida — The 4-year-old boy injured in the explosion of hyperbaric chamber that killed his grandmother died Thursday.

Francesco Martinisi's family had brought him to the United States from Italy for medical treatment that could not be easily obtained at home. On May 1, the hyperbaric chamber in which he was receiving therapy at a clinic in Lauderdale-by-the-Sea exploded.

The boy's grandmother, Vincenza Pesce, 62, died of her injuries a day after the blast at the Ocean Hyperbaric Oxygen Neurologic Center. Francesco, seriously burned, was taken to Jackson Memorial Hospital in Miami.

"This is the tragic end of a very sad story that should never have happened," said Russell S.

A hyperbaric chamber explosion in Florida killed a 4-year-old boy and his grandmother. Such chambers are often used to treat potentially fatal scuba diving injuries.

The Broward Sheriff's Office said the Miami-Dade Medical Examiner's Office would

Does HBO cause cancer?

- Fear is that oxygen and increased free radicals would increase recurrence rate.
- Numerous studies on humans, animals, and tumor cell lines. NONE showed enhanced cancer growth by HBO.

You can now…

- Define hyperbaric oxygen therapy.
- Understand the mechanisms of action.
- Identify diagnoses HBO is indicated for.
- Review potential complications of HBO.

Hyperbaric Medicine Program

- Delayed Radiation Injury
  - Bone/Soft Tissue
- Selected foot ulcers in diabetics
- Chronic refractory osteomyelitis
- Decompression Illness
- Compromised skin grafts and flaps

Located at:

1813 6th Ave South

Birmingham, AL 35249

- For referrals or questions, please do not hesitate to contact the clinic.

- Main: (205) 996-9261
- Fax: (205) 996-9280
- Emergencies 24/7: (205) 934-6478 (MIST)

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- mvandernoot@uabmc.edu