

# Regenerative Therapies for Erectile Dysfunction: Possibility or a mirage?

**Dr.M.Natesh Prabhu** M.D, FCSM, CCEBDM, ACC,  
Associate Professor – Department of Pharmacology  
DSMCH, Perambalur, Tamilnadu, India

Men's Health Consultant, Andregn Clinic, Trichy



# Learning Objectives

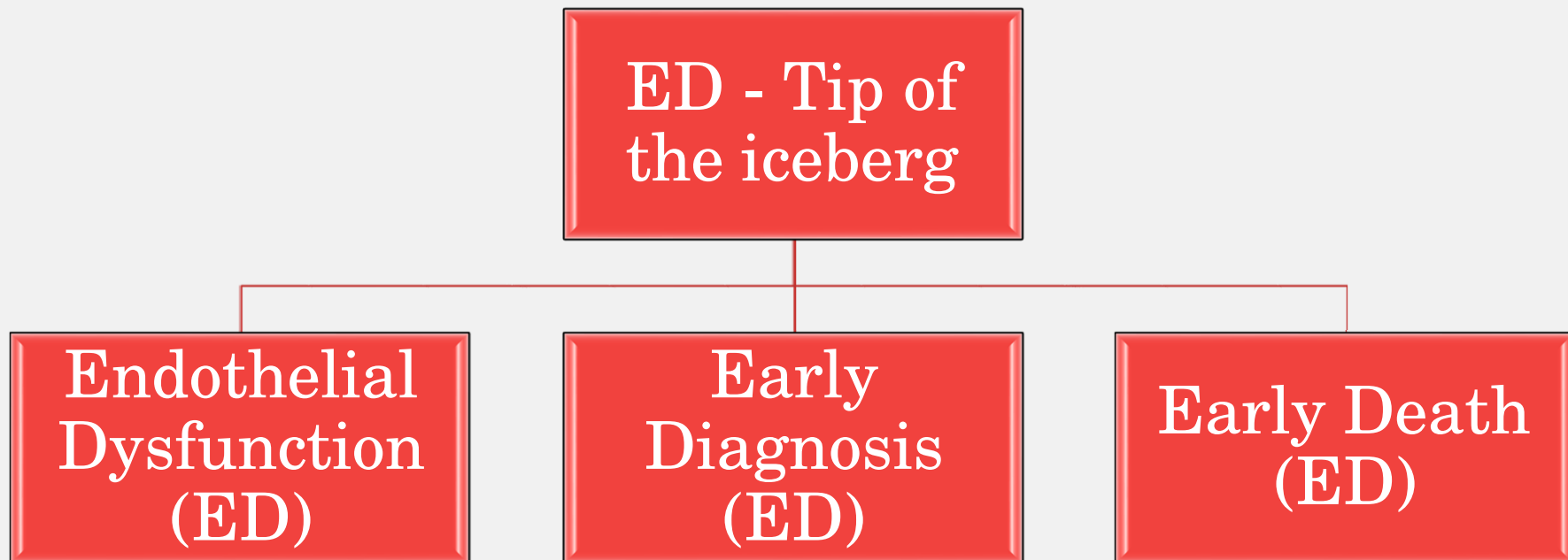
- Review penile vascular anatomy and physiology of erection
- Understand impact of Erectile Dysfunction (ED)
- Describe mechanism of Diabetes induced ED
- Know various medications for treating ED
- Understand role of Regenerative Medicine in ED

# Erectile Dysfunction



# Impact of Erectile Dysfunction (ED)

---



# Effects of ED

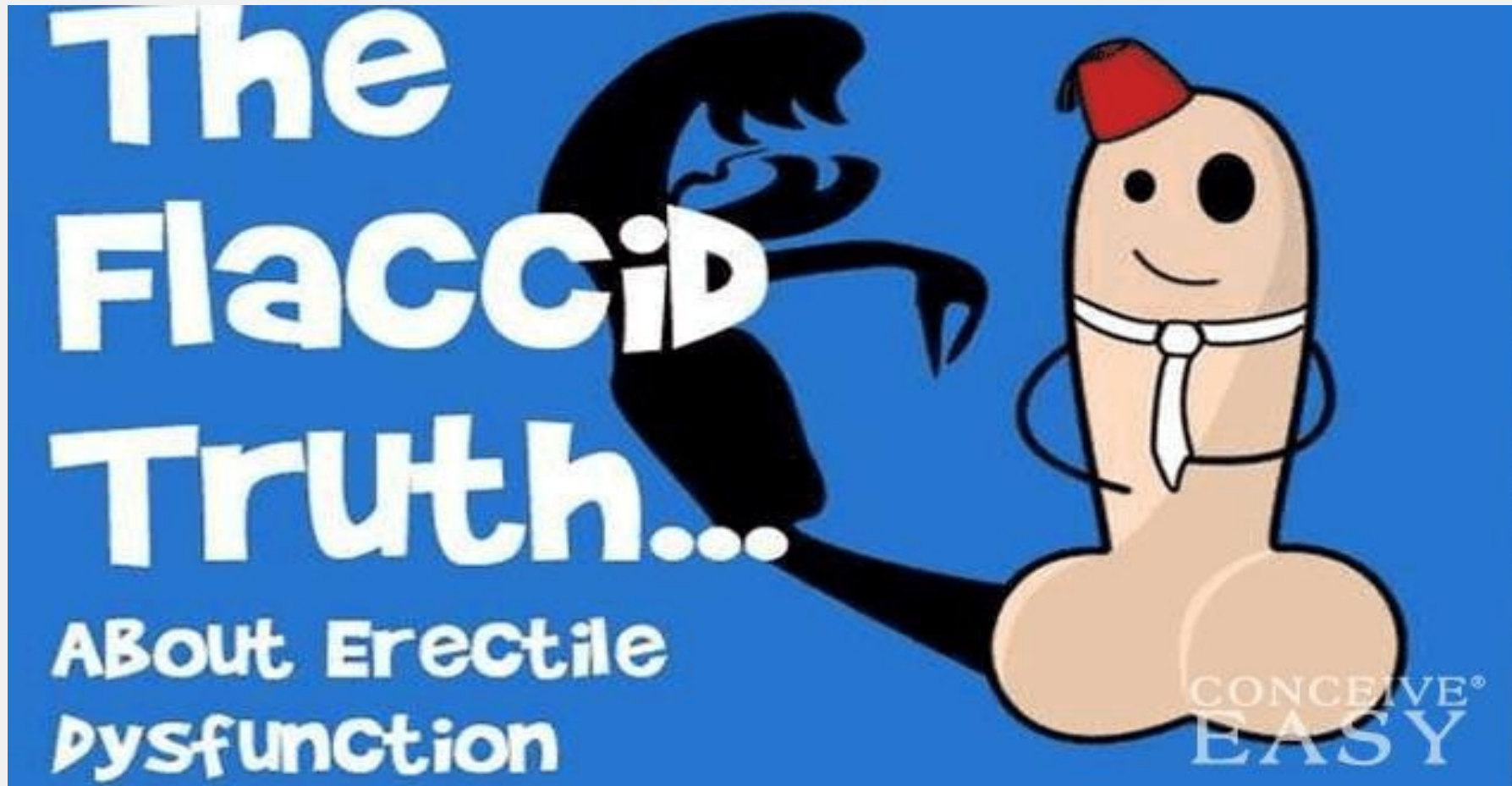
---



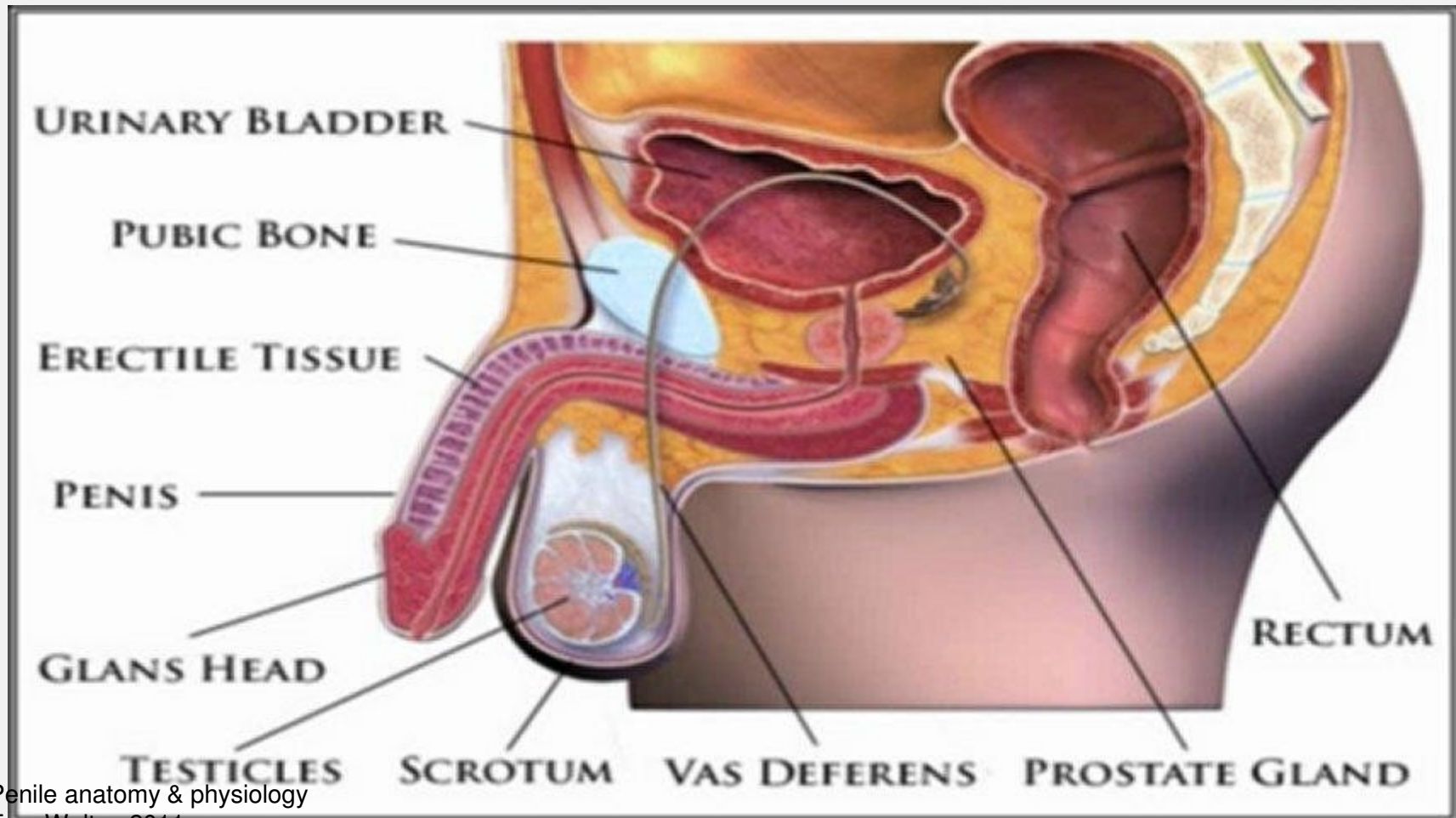
- Psychological / Emotional
- Health Concerns
  - Cardiovascular Diseases (CVD)  
*“Canary in the coal mine”*
    - Silent CAD
    - Predictive of Stroke
    - Coronary Events Risk
  - Diabetic Mellitus
    - ED is the first sign: 12% – 13%

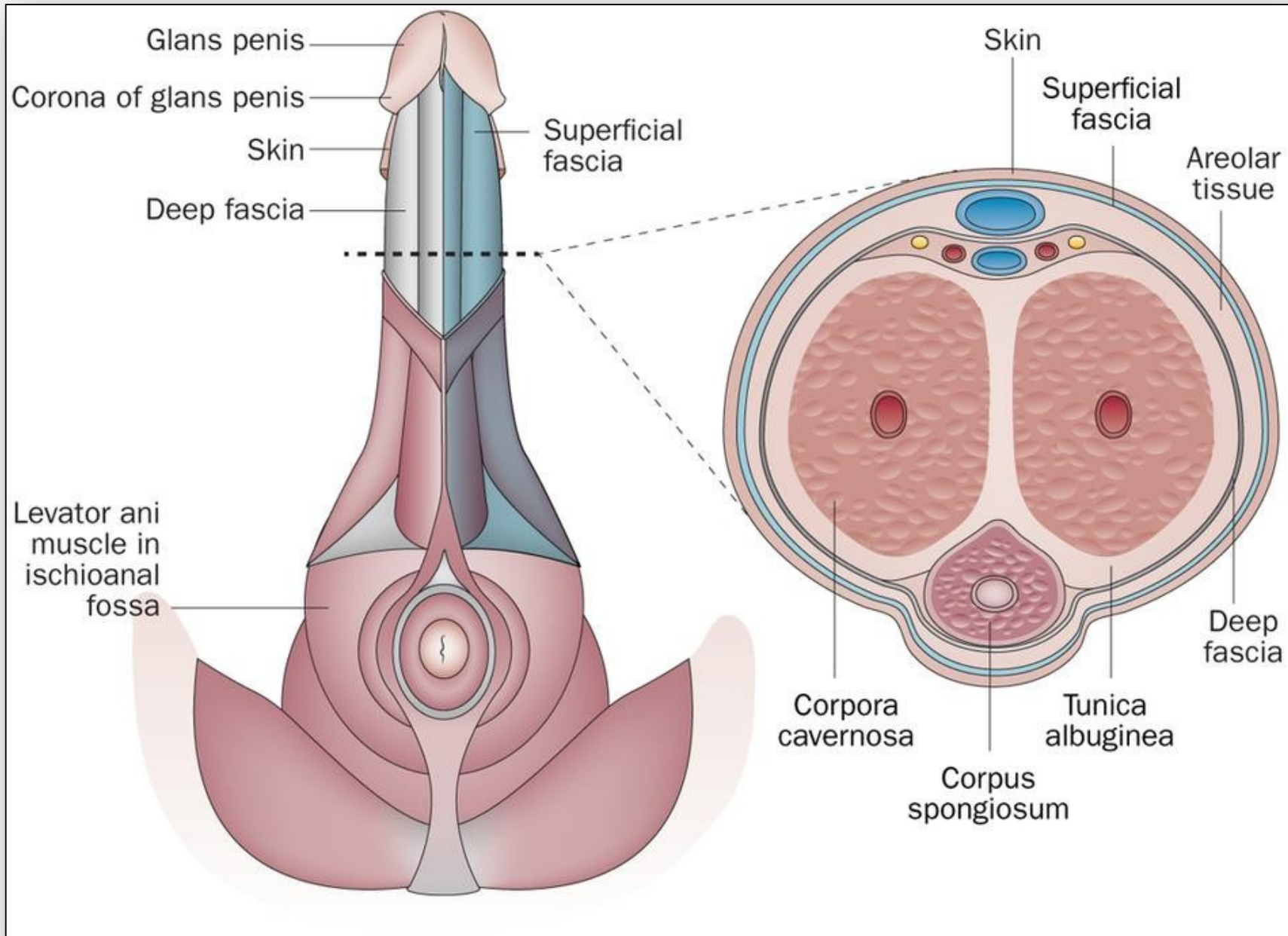
# Penis – Barometer for endothelial health

---

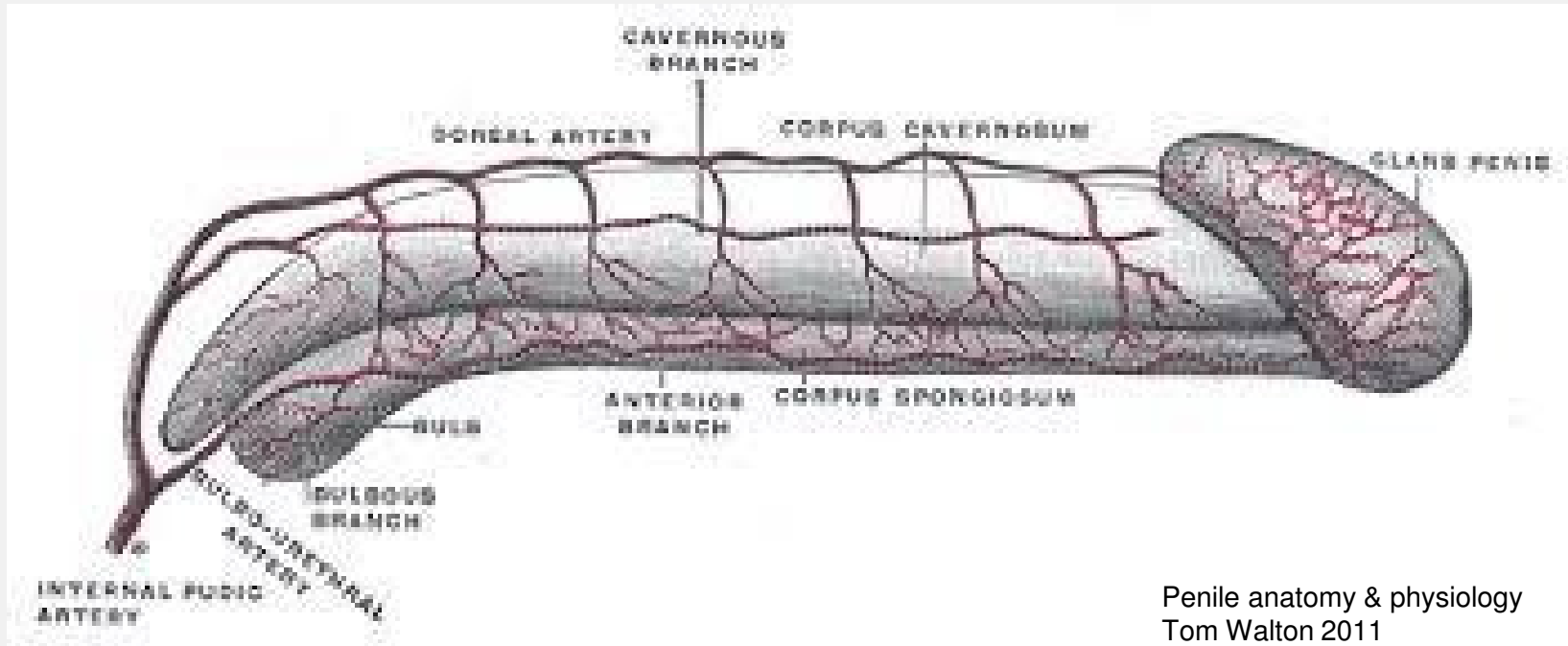
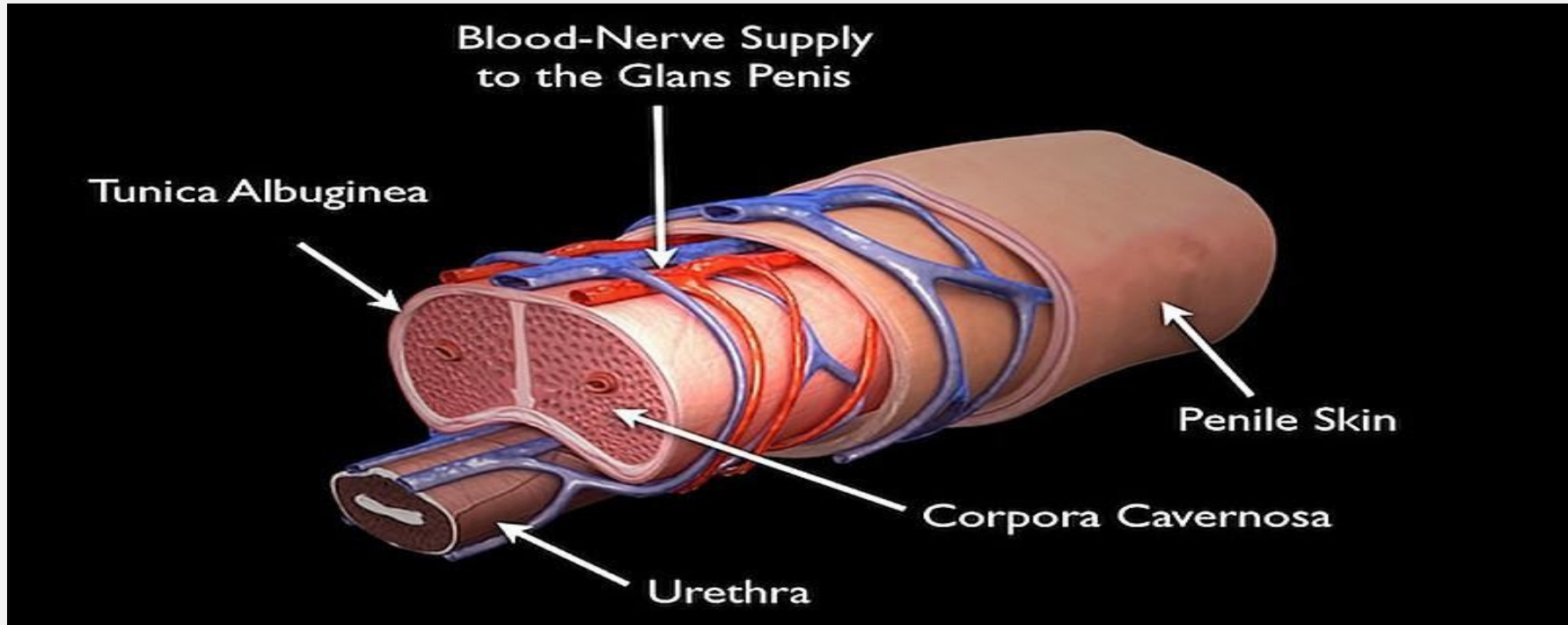


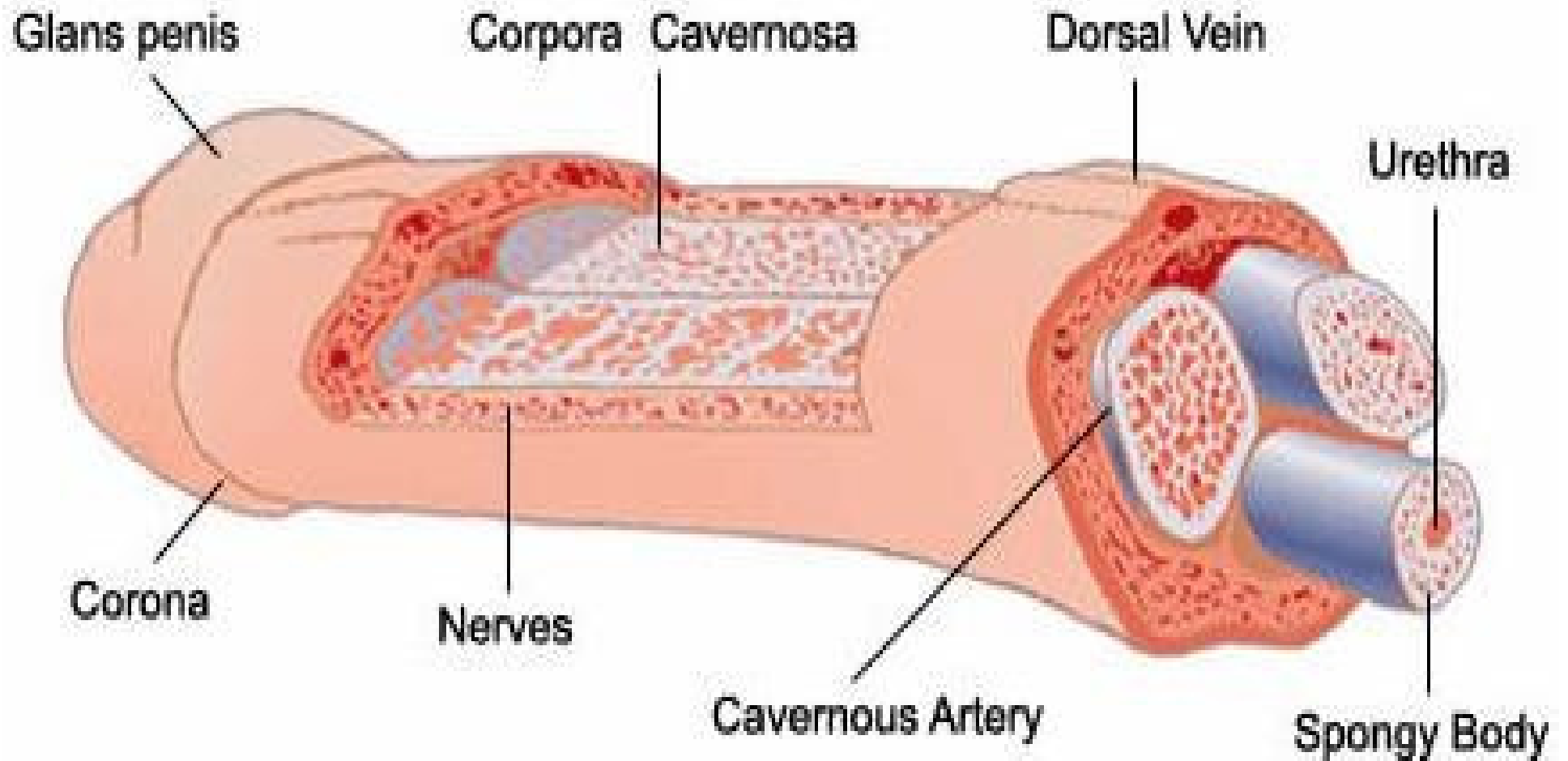
# Vascular Anatomy











# Components of Erection

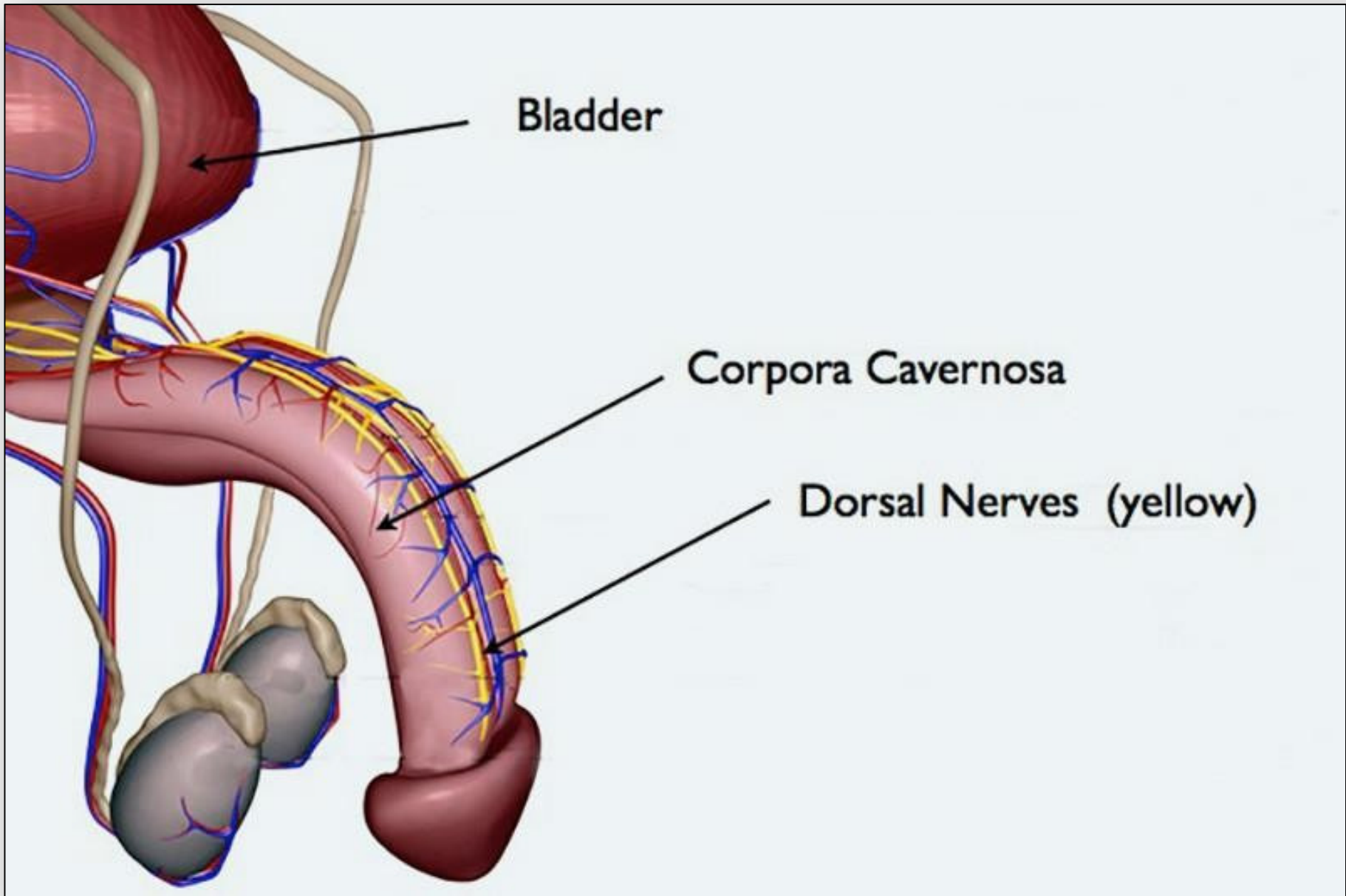
---

## Central

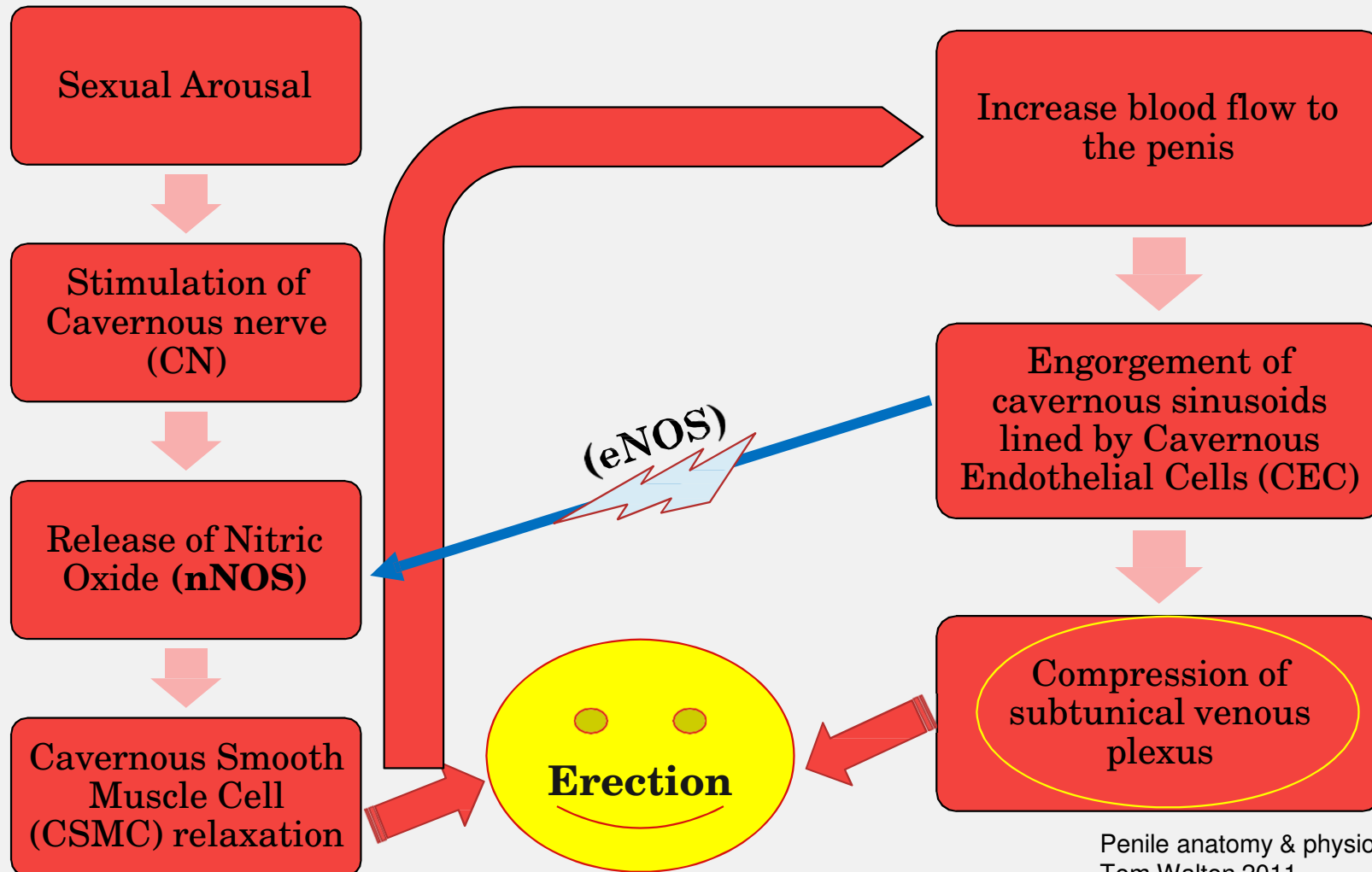
- Dopamine

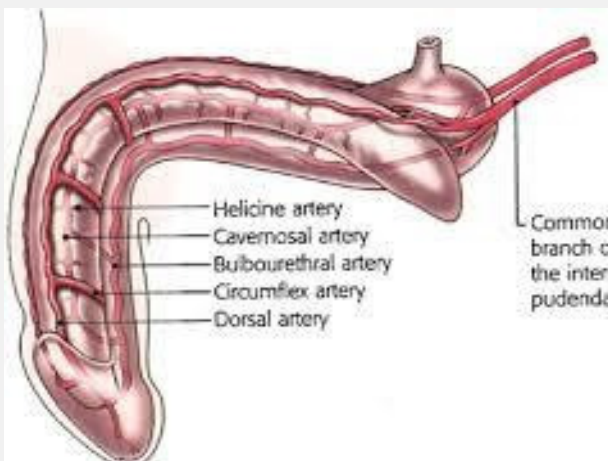
## Peripheral

- Hormonal
- Vascular
- Neural
- Smooth Muscle

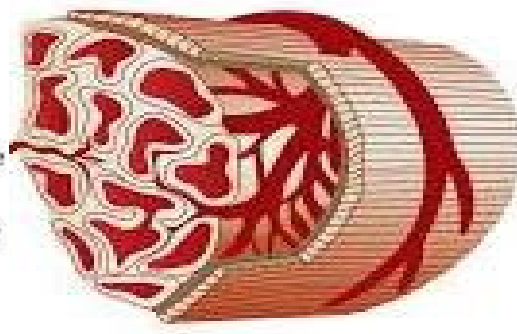


# Physiology of Erection

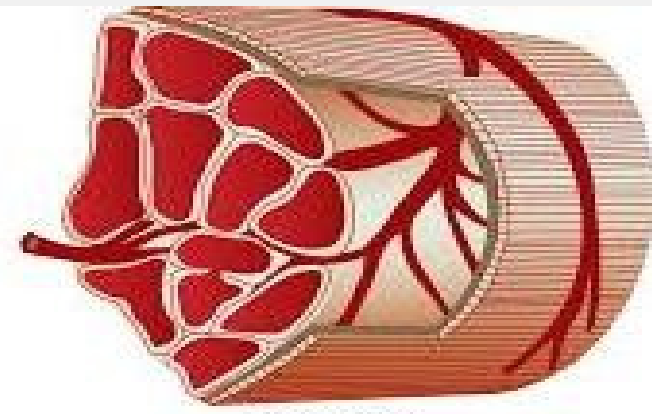




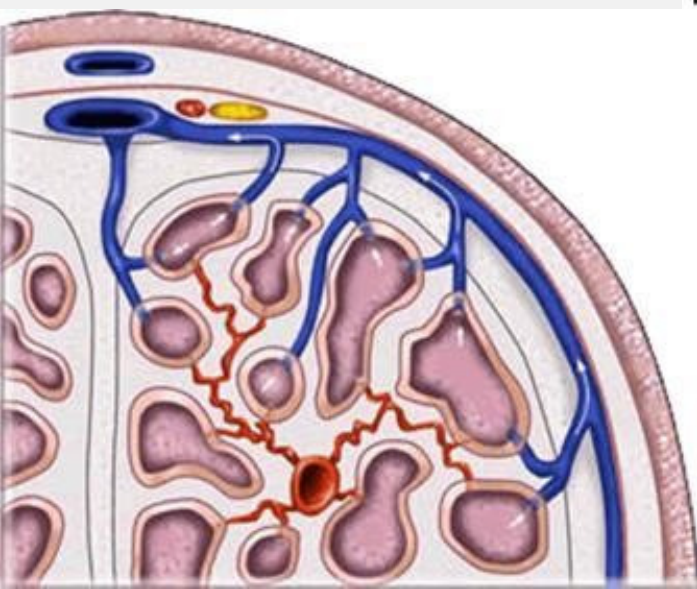
Common penile branch of the internal pudendal artery



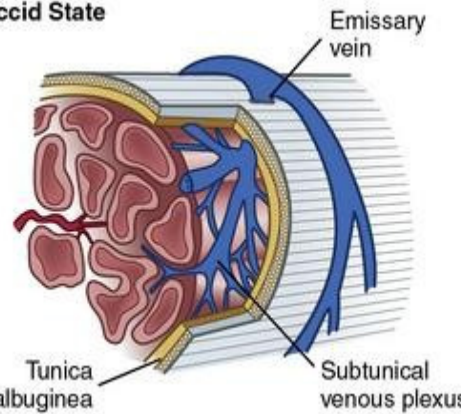
Flaccid State



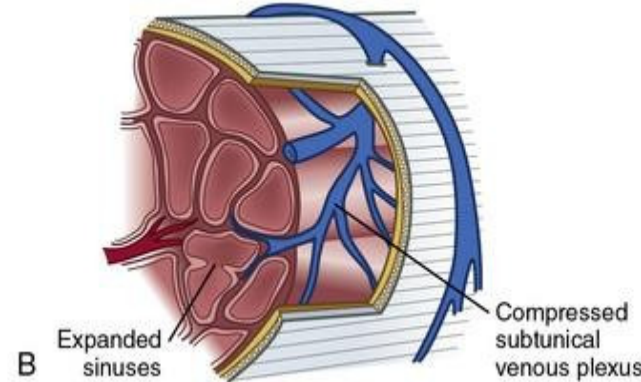
Erectile Phase



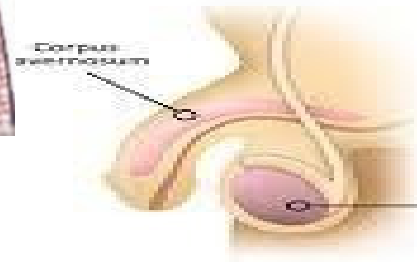
Flaccid State



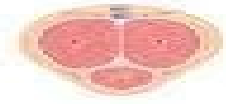
Erect State



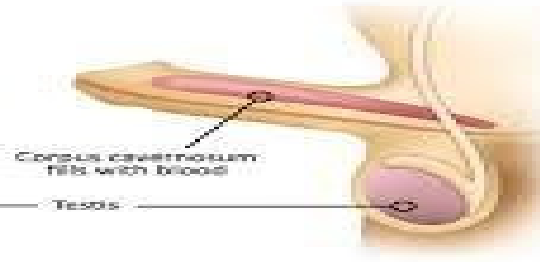
FLACCID PENIS



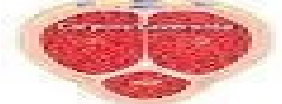
FLACCID



ERECT PENIS



ERECT



# What's happening during Erection?

---

Interplay between Neural – Vascular –  
Smooth Muscle interplay

- Intact Cavernous Nerve
- Healthy Endothelium
- nNOS / eNOS
- Symphony

Penis is a vascular organ

# Causes of Erectile Dysfunction

---



Psychogenic

---

Hormonal

---

Iatrogenic – Post RP/RT

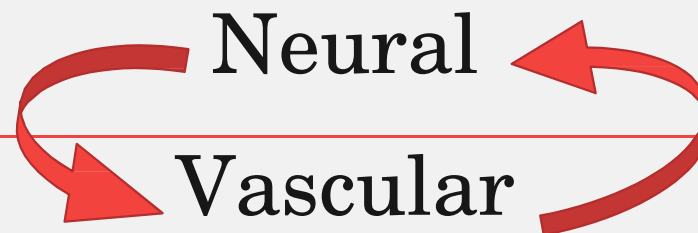
---

Drug Induced – *Propranolol, Thiazides...*

---

Developmental

---





# Diabetes induced ED

---

- Oxidative Stress (Free radicals)
- Advanced Glycation End products (AGE)
- Neural Growth Factor Deficiency
- Protein Kinase C (PKC) dysfunction
- Tissue Remodeling

# DM induced ED

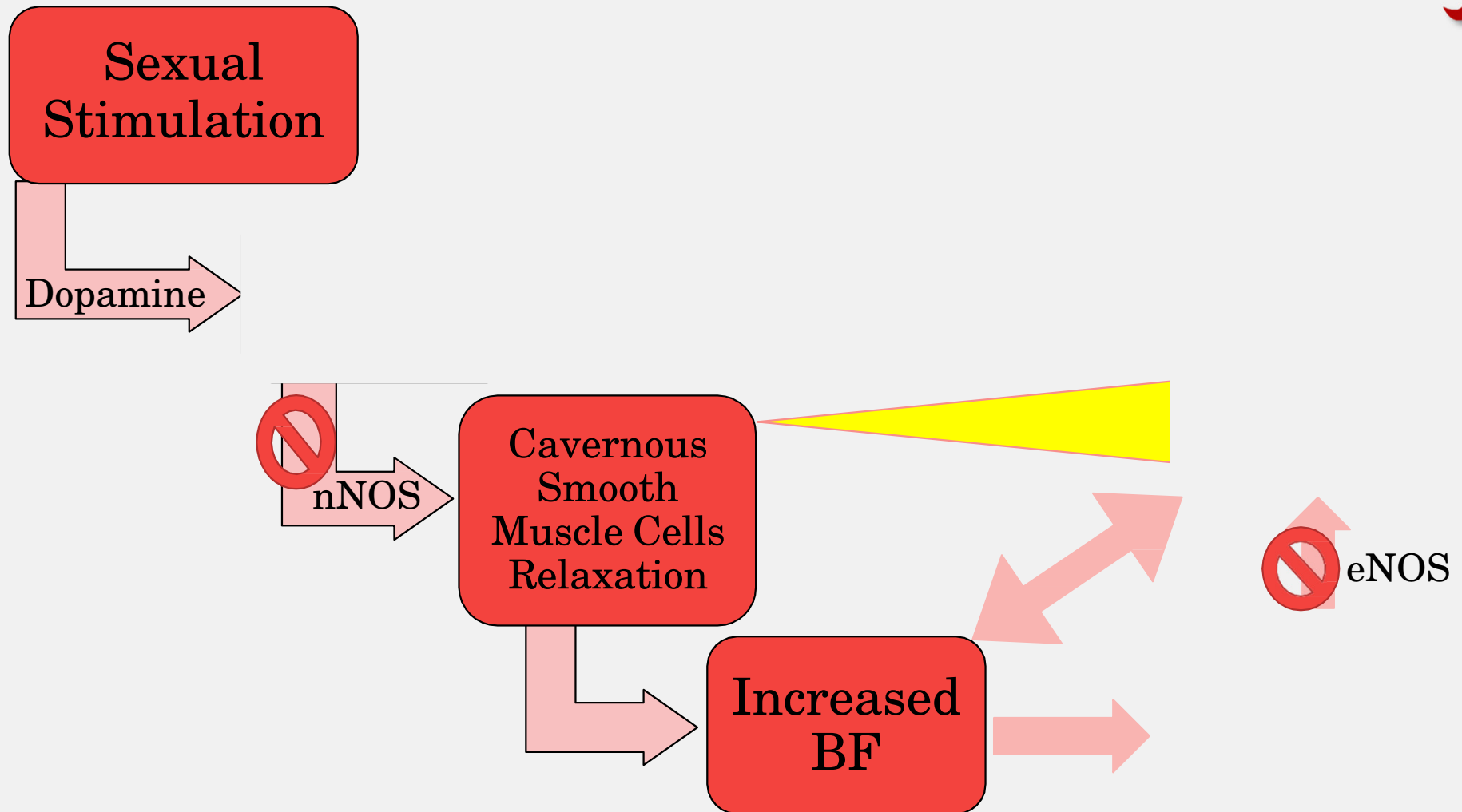
**Cavernous Nerve Apoptosis** →  
Decrease Penile CN Content

- No Nitric Oxide
- No Relaxation of CSMC

**Cavernous Endothelial Cell Apoptosis**

**Higher apoptotic index in the  
Cavernous Smooth Muscle Cells**

# What is lost in diabetes?



# Erectogenic Agents

## Injectable – Intracavernous

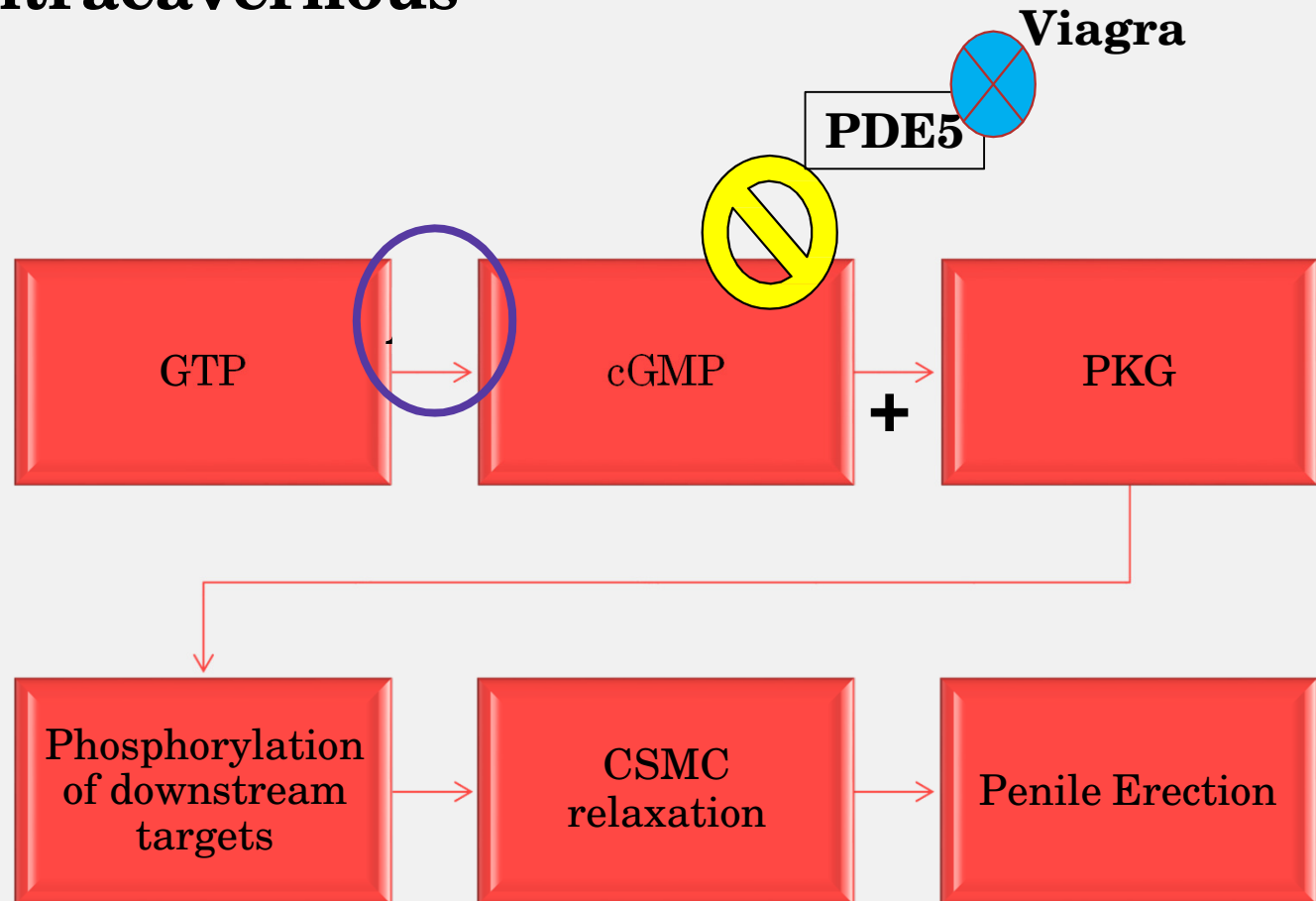
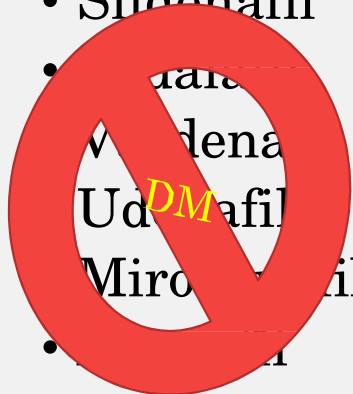
- Papaverine
- Pentolamine
- Alprostadil

## MUSE

- Alprostadil

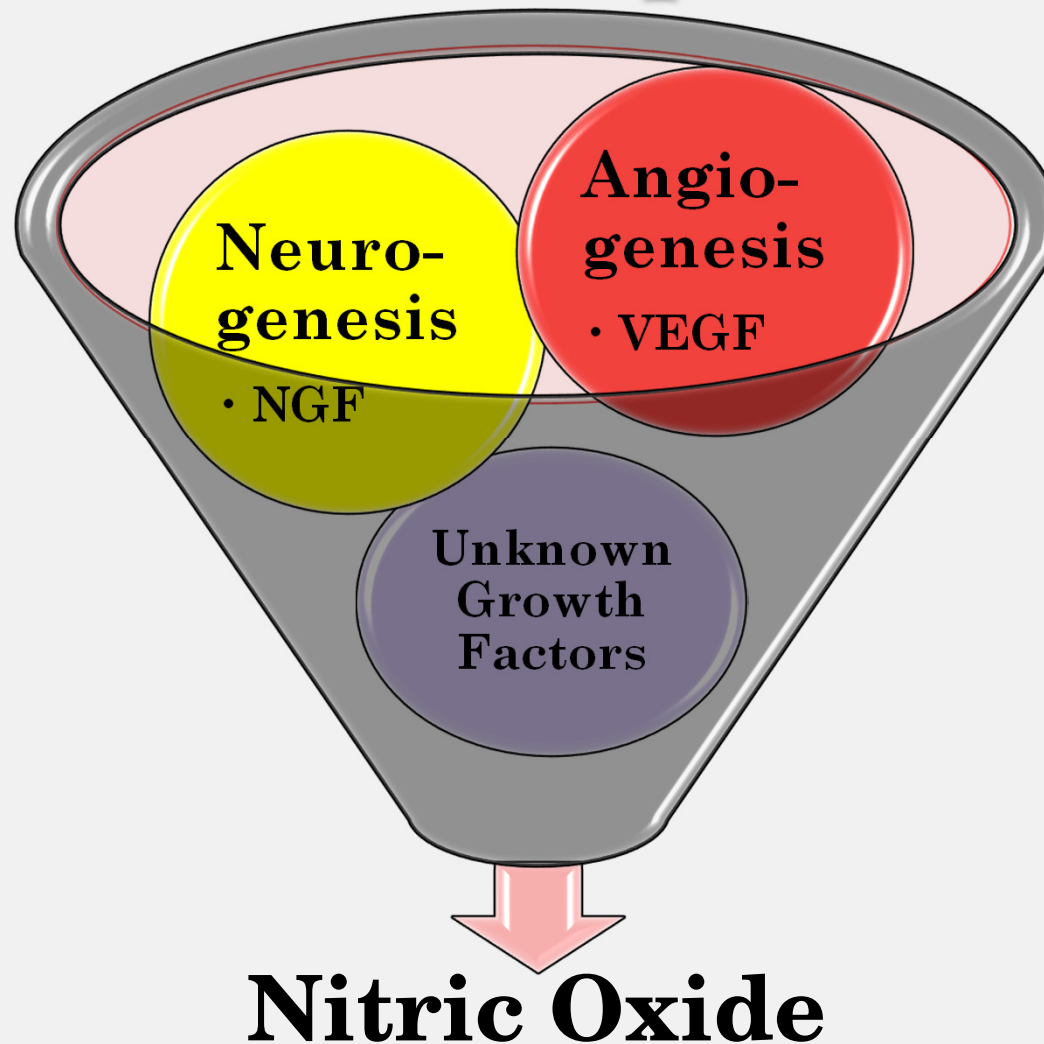
## Oral

- Sildenafil
- Tadalafil
- Vardenafil
- Udenafil
- Mirodenafil
- Lodenafil

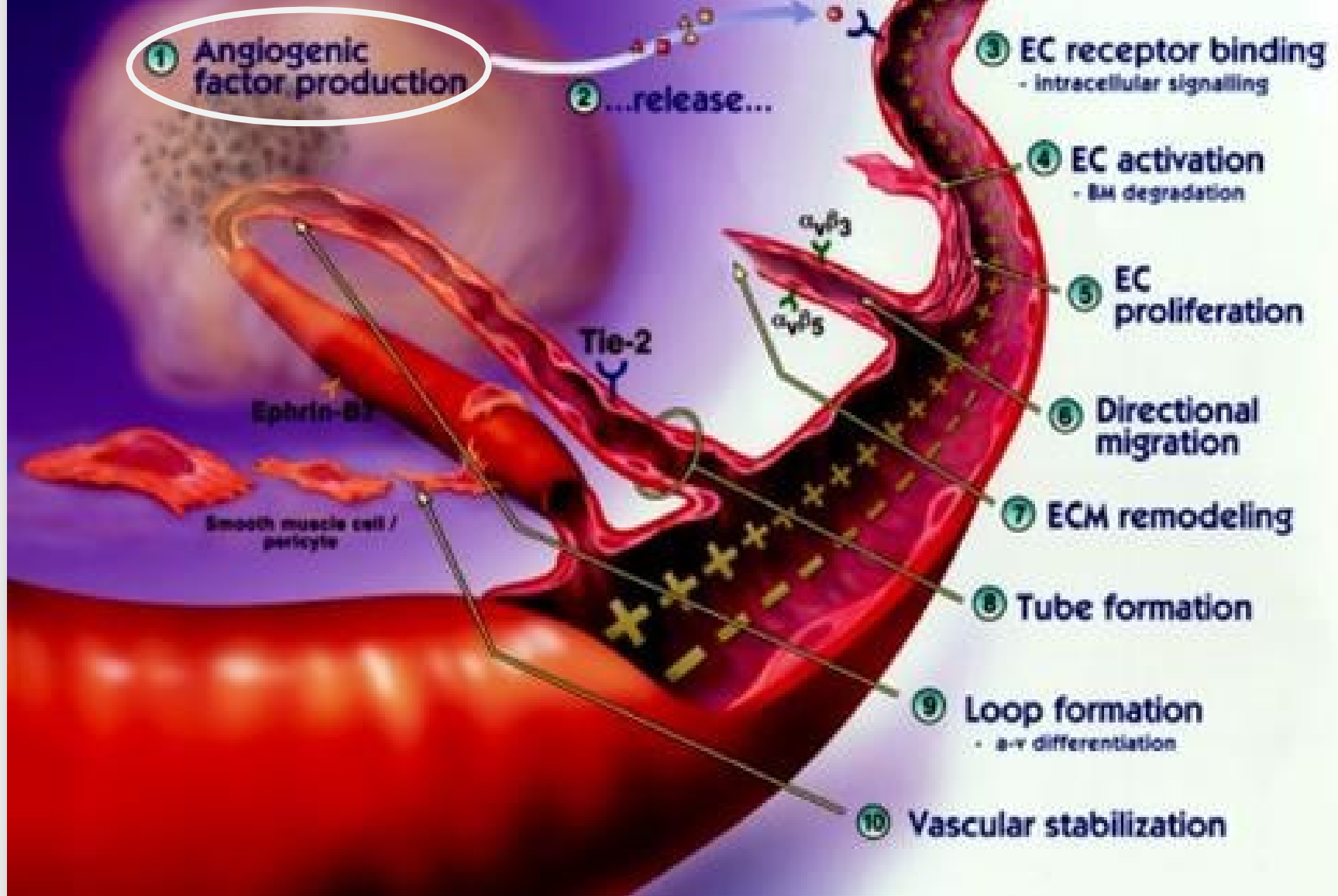


# What is needed in Diabetic ED patients?

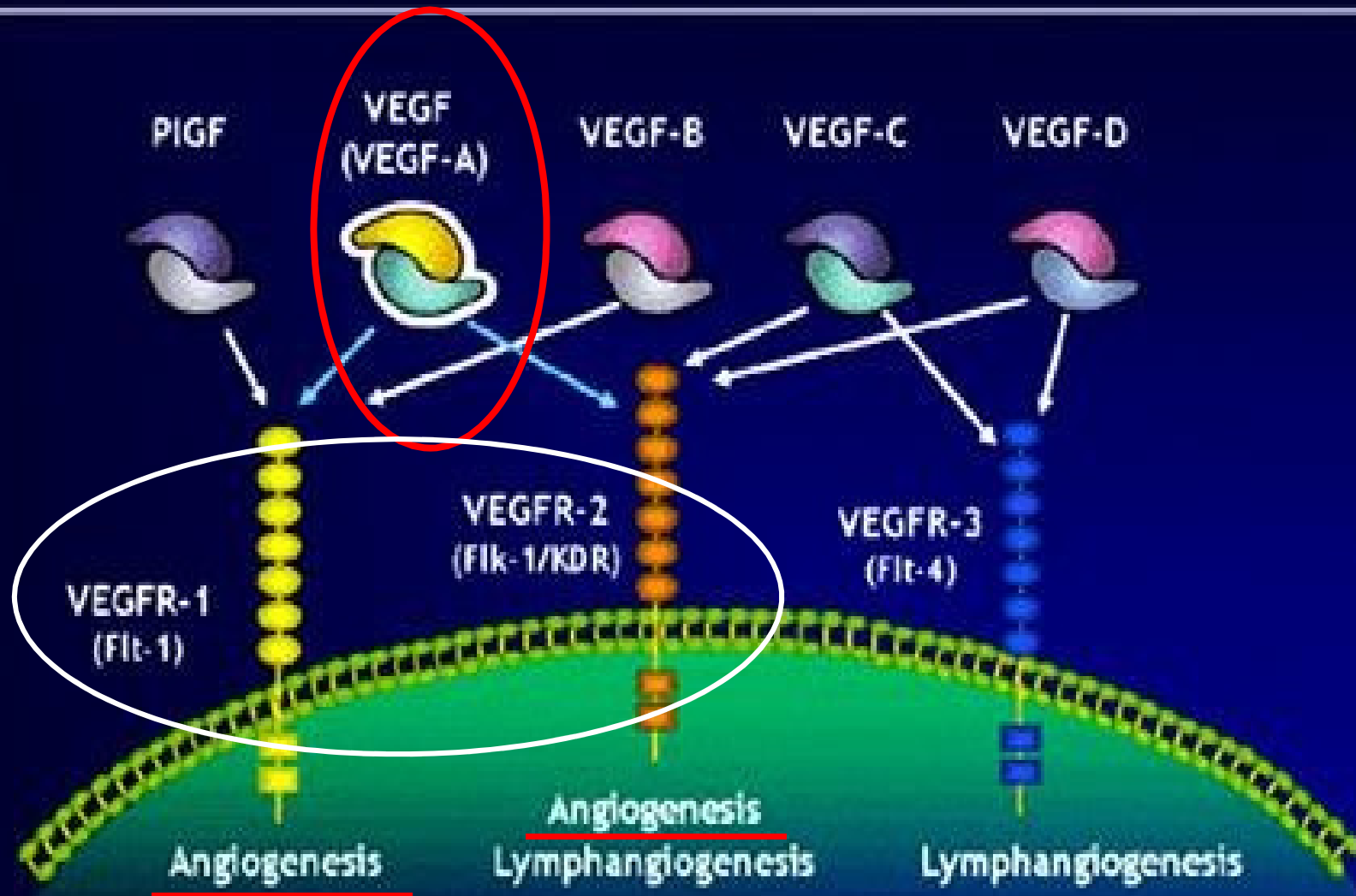
---



# Angiogenesis: Cascade of Events



# The VEGF Family and Its Receptors

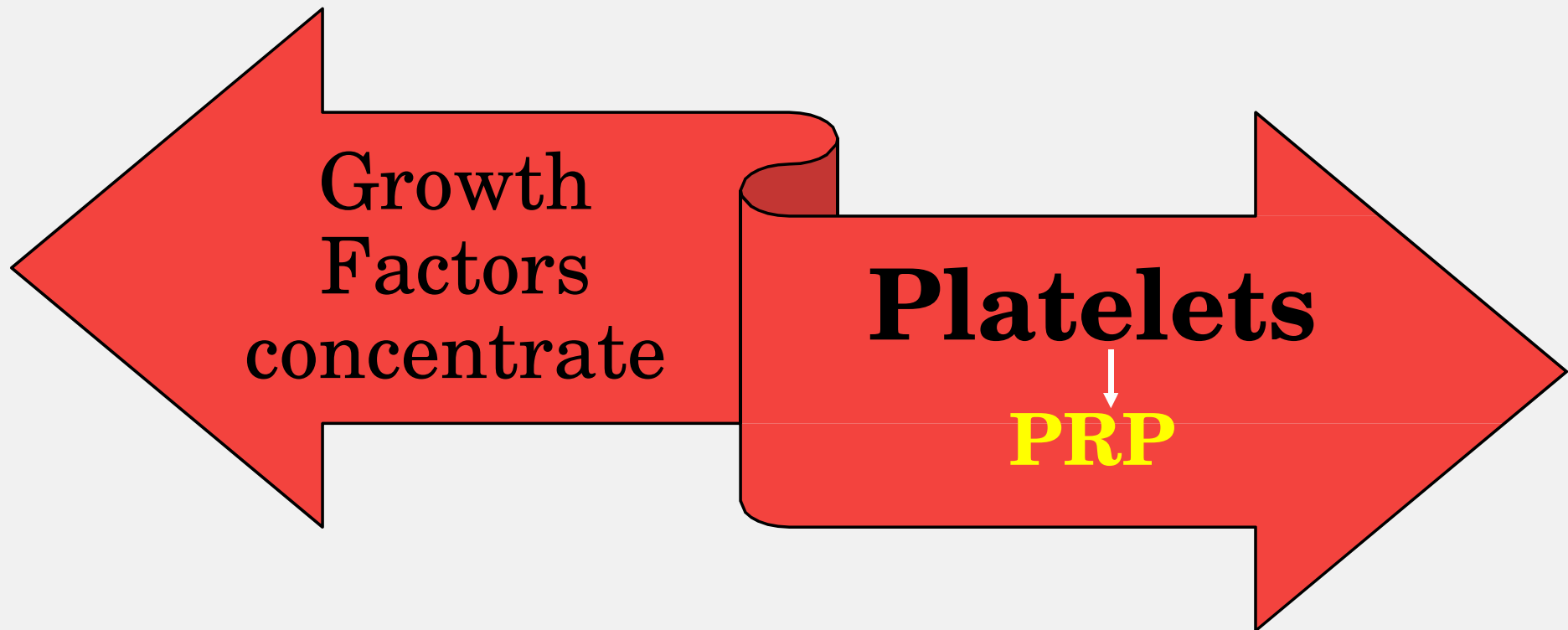


PlGF = placenta growth factor.



# External source of these growth factors?

---





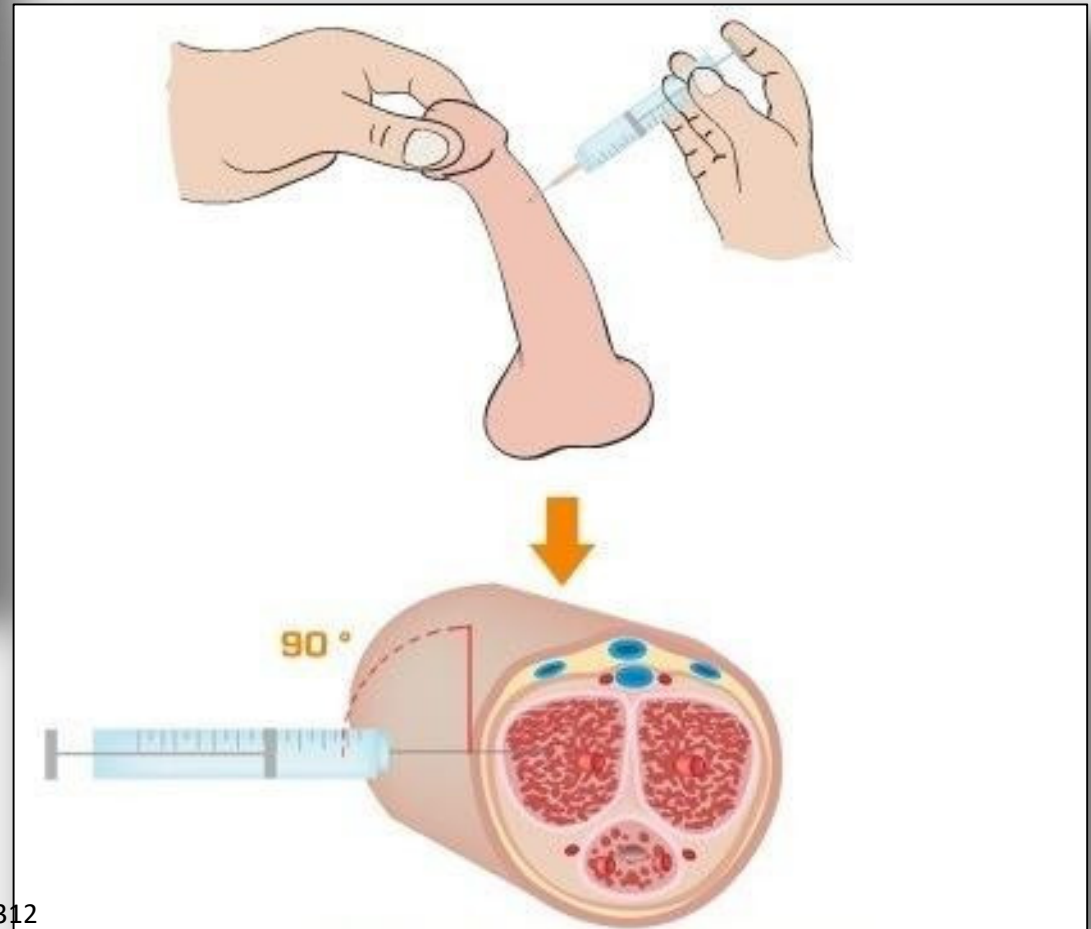
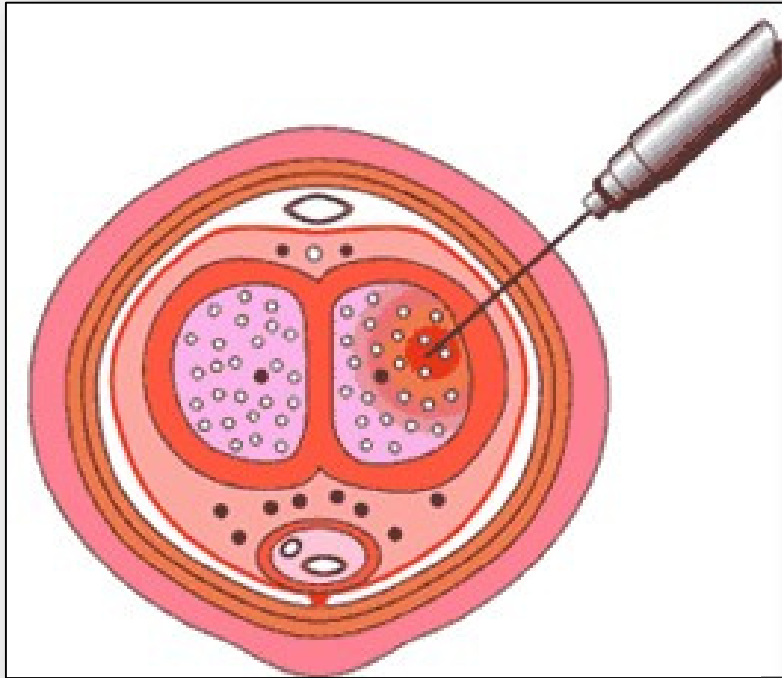
# Platelet Dynamics



**The intact endothelial lining inhibits platelet activation by producing –**

**Nitric Oxide, endothelial-ADPase, and PGI<sub>2</sub> (Prostacyclin)**

# Intracavernous Injection of PRP Priapus (P)– Shot



# Variability in the efficacy of PRP



Lack of standardization of preparation

External Activation vs Internal activation dilemma

- CaCl<sub>2</sub>/ Bovine thrombin
- Collage Type 1
- Free thawing
- CaCl<sub>2</sub> + Autologous thrombin

Lack of growth factors quantification

No follow up with objective evidence

Selection of PRP injection sites

# Objective Evidence

---

## Improvement in ICP

- CN stimulation

## Vascular Doppler

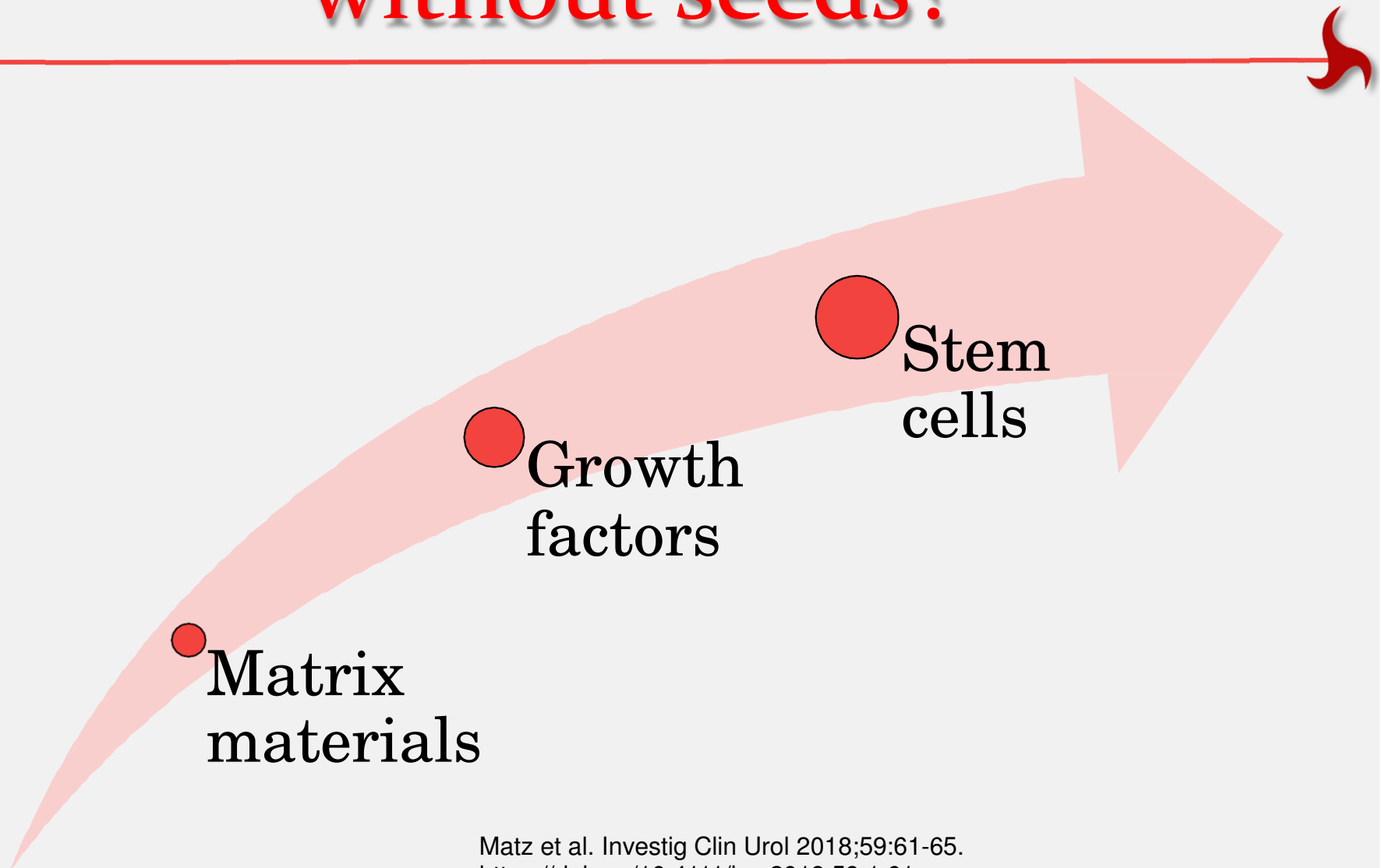
- Pre & Post treatment
- Angiogenesis

## International Index of Erectile Function

- IIEF-5 Questionnaire

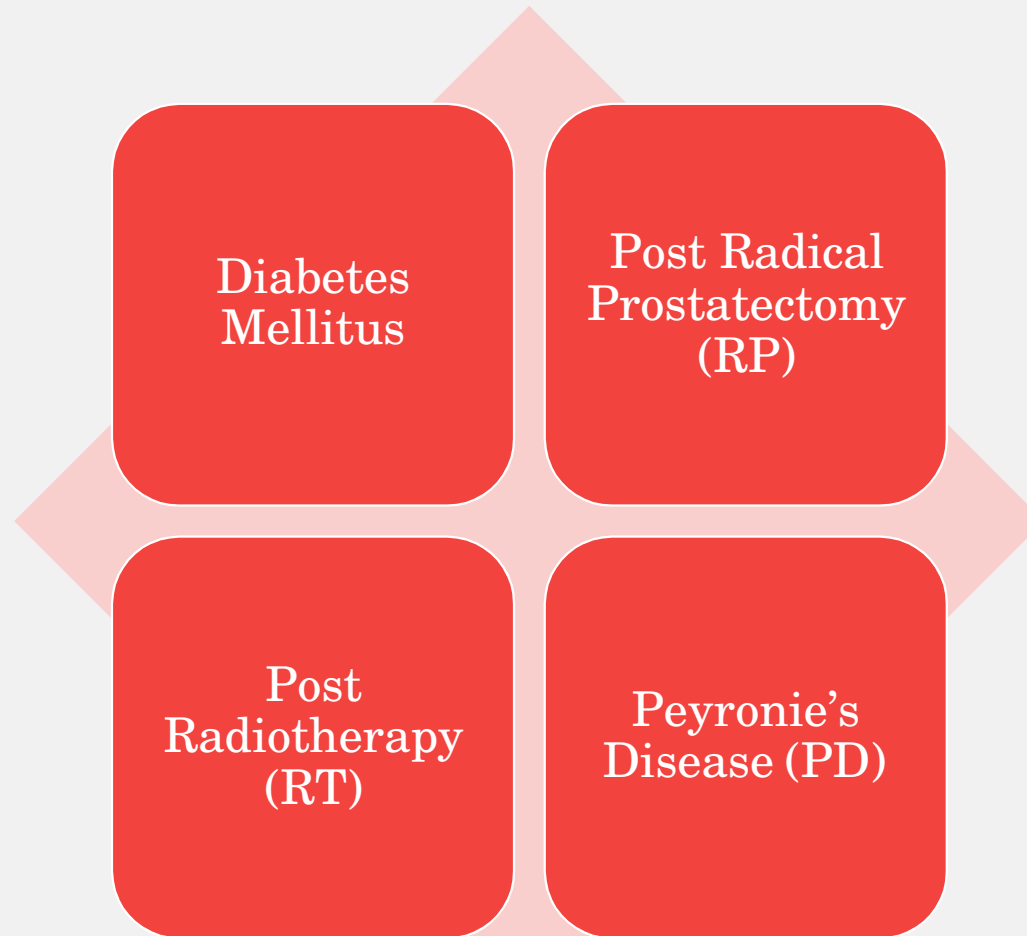
# How good are fertilizers without seeds?

---



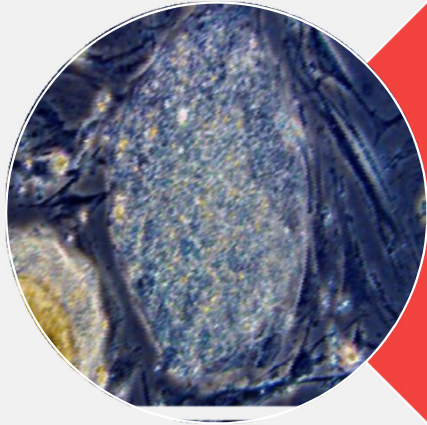
# Role of Stem Cells in Ed

---

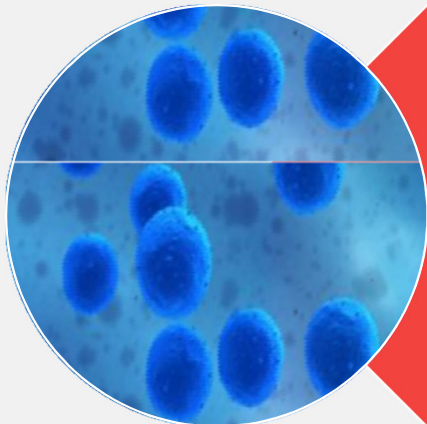


# Types of stem cells

---



Embryonic Stem Cells (ESC)



Adult Stem Cells (ASC)

- Hematopoietic Stem cell (HSC)
- Neural Stem Cell (NSC)
- Epithelial Stem Cell (ESC)
- Mesenchymal Stem Cell (MSC)

# DM induced ED

---



- **Diabetes**

- Oxidative Stress (Free radicals)
- Advanced Glycation End products (AGE)
- Neural Growth Factor Deficiency
- Protein Kinase C (PKC) dysfunction
- Tissue Remodeling

- **Cavernous Nerve Apoptosis** → Decrease Penile CN Content

- No Nitric Oxide
- No Relaxation of CSMC

- **Cavernous Endothelial Cell Apoptosis**

- Higher apoptotic index in the CSMC of diabetic Rat



# Stem Cells in DM induced ED

---

- MSCs – VSF
- BMSC – BMMNC - SkMSC
- Preclinical Stage – Few Clinical Studies
  - IHC / IF
    - CEC
    - CSMC
    - CN
- Injection
  - Intra cavernous
  - Periprostatic
  - MPG



# Stem Cells in DM induced ED

## Improvement in ICP

- Not sufficient to maintain intercourse
- Short term follow-up: One Study – 1 Yr
- Non – characterized SCs
- Need of low dose PDE5 inhibitors (Sildenafil, Tadalafil, etc.)

# Stem Cells in DM induced ED

---

## Differentiation Vs Paracrine Effect

- Can't be traced at the site of injection
- Dye difficulties
- Blockade of adrenomedulline / CXCL5 / Anti – VEGF antibodies
- Intra-MPG vs IC injection vs IV injection

## Human trials in Denmark has shown positive results

- Improvement / Regaining morning erections
- IIEF questionnaires – Venous doppler – Rigiscan
- Stempeutics – yet to start Phase II trial for DM issue with ED

# Autologous bone marrow derived stem cell transplantation for Type 2 Diabetes

---



- Targeted approach
  - Gastroduodenal artery (superior pancreaticoduodenal artery), splenic artery, gastroduodenal artery and peripheral intravenous route - under fluoroscopic guidance.
- T2DM >5 years
- Triple drug failure receiving insulin (0.7 U/Kg/day), metformin
- 15 months of follow-up
  - **Reduction in mean insulin requirement & HbA1c**
  - **Improvement in glucagon stimulated C-peptide levels & Homeostasis Model Assessment - $\beta$  & QOL scores.**

# Stem Cells in Post – RP & Post – RT

---

## Nerve Sparing RP

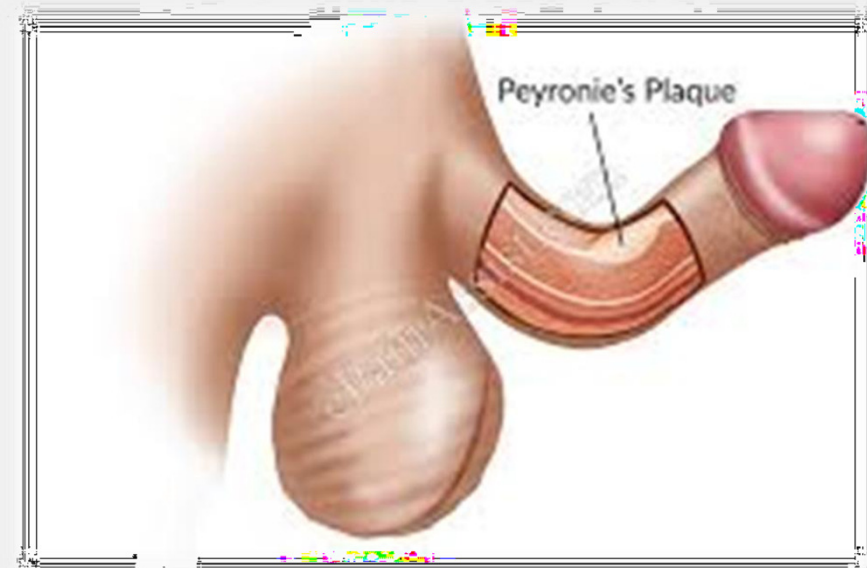
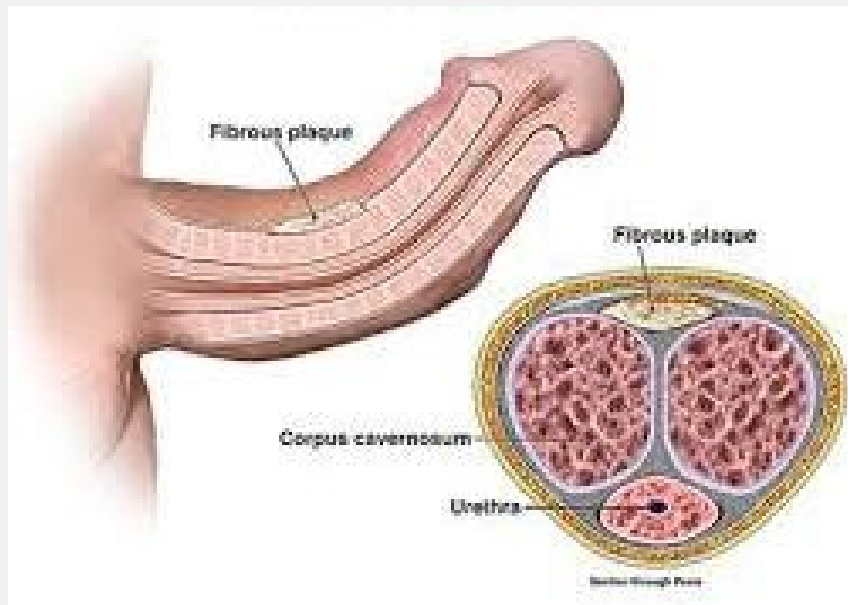
- Inadvertent damage → Subtle
- No Nitric oxide
- No engorgement of penis → Hypoxic Penile tissue
- CSMC replace by collagen

## Preclinical

- Transection / Crush injury of CN / Radiation
- Grafted SC (POLG – SIS – Hydrogel)
- Transfection / Transduction (K<sup>+</sup> Channel)

# Stem Cells in Peyronie's Disease (PD)

- Fibrous Plaque in Tunica Albugenia (TA)
- Not Exactly ED



# Stem Cells in Peyronie's Disease (PD)

---

## Preclinical – Mice / Rats

- Injury to TA
  - Acute / Chronic
- Injections of TGF –  $\beta$
- Transplantation of grafted SC
  - MSCs
  - BMMNC
  - BMSC

# References

1. Gretchen M. Erectile Dysfunction. Primary Care: Clinics in Office Practice. Volume 46, Issue 2, June 2019, Pages 249-255 <https://doi.org/10.1016/j.pop.2019.02.006>
2. Tom Walton. Penile anatomy & physiology. 2011
3. Diniz et al. Ionic Channels as Potential Therapeutic Targets for Erectile Dysfunction: A Review. Frontiers in Pharmacology 2020; 11: 1120 doi: 10.3389/fphar.2020.01120
4. Yiou et al. Stem-cell therapy for erectile dysfunction. Biomed Mater Eng. 2017;28(s1):S81-S85  
DOI 10.3233/BME-171627
5. Ching-Shwun Lin. Advances in Stem Cell Therapy for Erectile Dysfunction. Advances in Andrology. 2014.  
<http://dx.doi.org/10.1155/2014/140618>
6. Alonso, Isis. (2008). Role of somatostatin receptors in angiogenesis. <http://hdl.handle.net/1822/9050>
7. Scott et al. Sex Med Rev Volume 7, Issue 2, April 2019, Pages 306-312  
<https://doi.org/10.1016/j.sxmr.2018.12.006>
8. Matz et al. Investig Clin Urol 2018;59:61-65. <https://doi.org/10.4111/icu.2018.59.1.61>
9. Bratu et al. Erectile dysfunction post-radical prostatectomy - a challenge for both patient and physician. Journal of Medicine and Life. 2017 Jan-Mar;10(1):13-18. <http://dx.doi.org/10.1016/j.eururo.2015.09.026>
10. Bhansali, et al. Efficacy of autologous bone marrow-derived stem cell transplantation in patients with type 2 diabetes mellitus. Stem Cells Dev Dec 2009.1407-1416



# References

11. Yiou et al. Safety of Intracavernous Bone Marrow-Mononuclear Cells for Postradical Prostatectomy Erectile Dysfunction: An Open Dose-Escalation Pilot Study *European Urology*, 2016; 69 (6); 988-991  
<http://dx.doi.org/10.1016/j.eururo.2015.09.026>
12. Jalkut et al. Peyronie's Disease: A Review *Rev Urol*. 2003 Summer; 5(3): 142–148.
13. Mousa et al. *Intractable & Rare Diseases Research* 2020 ; 9 (1): 10-13 doi: 10.5582/irdr.2019.01130

**BE LIKE THE  
STEM CELL**

---

**DIFFERENTIATE  
YOURSELF  
FROM OTHERS**

