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Anatomy and physiology of erection and sexual response
&
Common causes and co-morbidities associated with erectile dysfunction

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Overview

- Review of the physiological basis of normal erectile function (EF)
- Identification of how various conditions exert their effects on EF, some of which may be related to the condition, or related to treatment with various medicines
- Consider risk factors associated with development of ED

What is ED?

- ‘persistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual activity’

- Erectile dysfunction is the inability of a man to get an erection of sufficient quality for sexual activity

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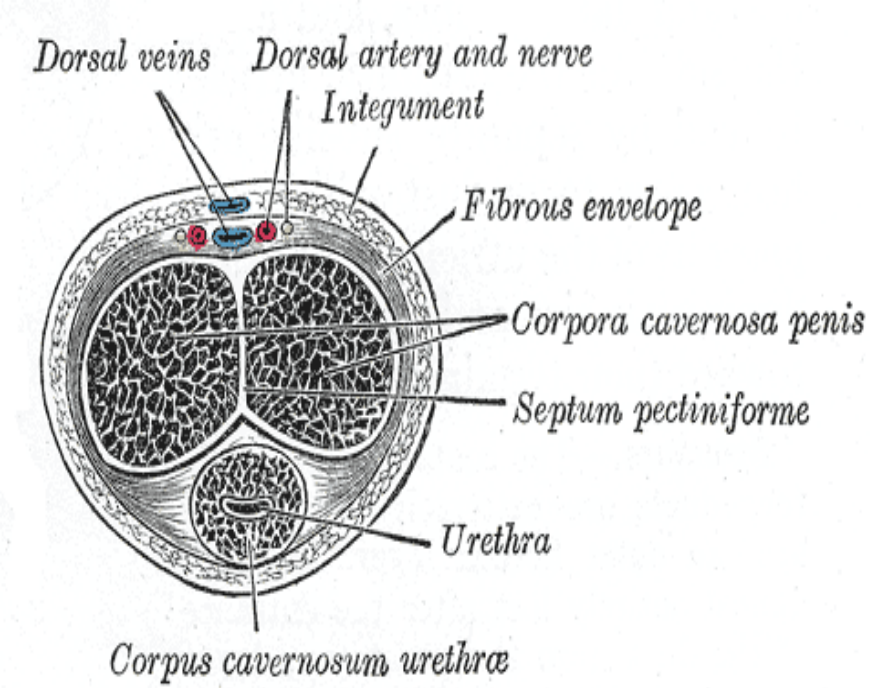
The penis

- 3 cylindrical structures - paired corpora cavernosa & corpus spongiosum (which houses the urethra) - covered by a loose subcutaneous layer and skin.
- Flaccid length is controlled by the contractile state of the erectile smooth muscle (varies considerably) - depending on emotion and ambient temperature
- Neither age nor the size of the flaccid penis accurately predicts erectile length



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Erection

- Release of neurotransmitters from the cavernous nerve terminals - relaxation of smooth muscles and the following events:
- Arterial & arteriole dilatation - increased blood flow into the expanding sinusoids
- Venous compression - reducing venous outflow
- Sinusoidal relaxation & stretching of the tunica to its capacity - occludes the emissary veins and further decreases the venous outflow to a minimum
- An increase in PO2 (to about 90 mmHg) and intracavernous pressure (around 100 mm Hg), which raises the penis from the dependent position to the erect state (the full-erection phase)
- A further pressure increase (to several hundred mmHg) with contraction of the ischiocavernosus muscles (rigid-erection phase)

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Psychogenic (supraspinal) erections

- Occur under the influence of activity in the cerebral cortex and neural impulses - origins can be localised to the thoracolumbar erection centre in the spinal cord (level T10 to L2).
- From there, impulses continue to travel to the penis, specifically the vascular network within the corpora cavernosa and spongiosum.
- In the absence of direct mechanical stimulation, erections of this type are generally initiated in response to visual, auditory, olfactory, tactile stimuli or imaginary stimuli.
- The cortex also has the capacity to suppress erection, even in the presence of mechanical stimulation, as can other psychological, environmental and emotional factors.

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Reflex erections

- The result of tactile stimuli applied to the penis or genital area - generates a simple reflex arc with the sacral erectile centre located within the sacral spinal cord (levels S2-4; the sacral erectile centre).
- May be seen in some men following partial, or complete spinal cord injuries.
- Some studies indicate that despite spinal cord injury, men may be able to achieve erections sufficient to enable penetration, even though their injuries have resulted in a lack of control over other bodily functions (Goldstein 2000) - this, however also crucially depends upon the level of injury.

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Spontaneous tumescence

- Involuntary, commonplace and a normal physiological phenomenon
- Usually occur three to four times during the night – as either nocturnal penile tumescence (NPT), or early morning tumescence (EMT)
- Tend to occur during rapid eye movement (REM) sleep, the stage in which dreaming occurs
- Coincide with reduced sympathetic nervous system activity during REM sleep (specifically the locus coeruleus in the brain stem) – when proerectile parasympathetic activity predominates
- Nutritive role - maintain regular blood-flow and oxygenation to the penis.
- Men suffering from depression, sleep disorders (including obstructive sleep apnoea), and abnormal/reduced REM phase may not experience spontaneous tumescence.
- Absence of spontaneous tumescence is also commonly used to distinguish between organic and psychological causes of erectile dysfunction.

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Haemodynamics of Erection

Corpora Cavernosa

- The penile erectile tissue (cavernous smooth muscle and smooth muscles of the arteriolar and arterial walls), plays a key role.
- In flaccid state - smooth muscles are tonically contracted, allowing only a small amount of arterial flow for nutritive purposes.
- Both corpora cavernosa separated by incomplete septum, which allows them to fill/ function in unison.

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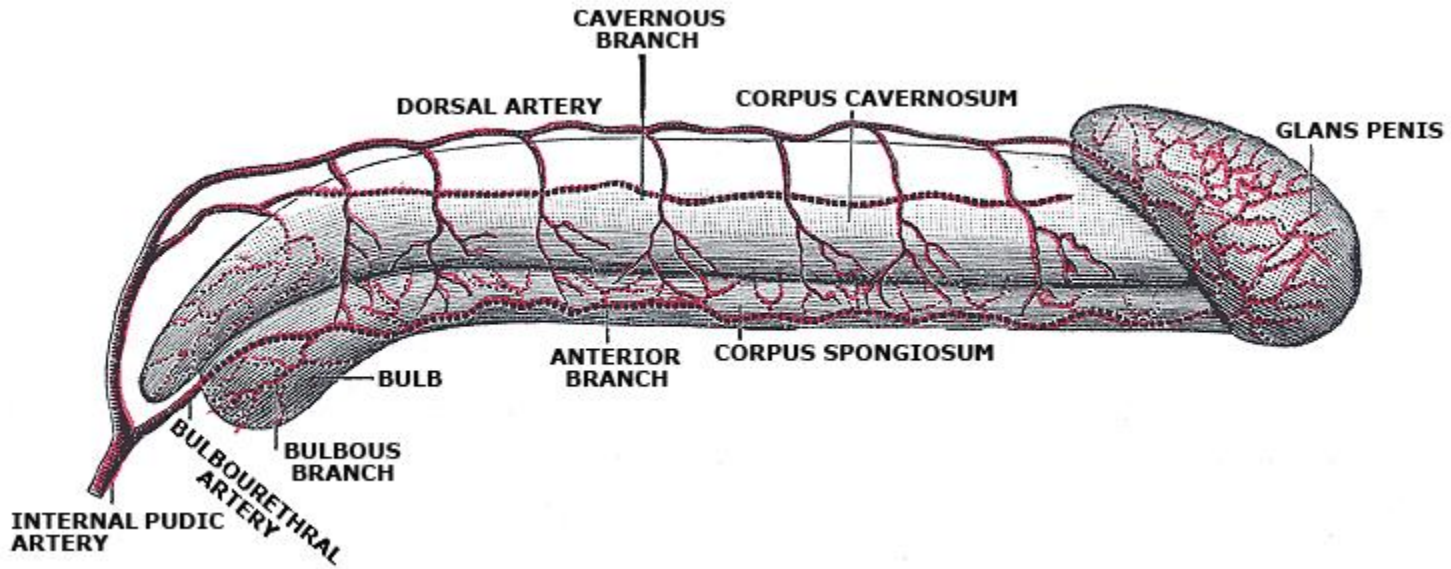
Arterial supply

- Penile blood supply - the internal pudendal artery (off internal iliac artery) → common penile artery
- 3 branches - dorsal, cavernousul and bulborethral
- Dorsal artery is responsible for engorgement of the glans during erection



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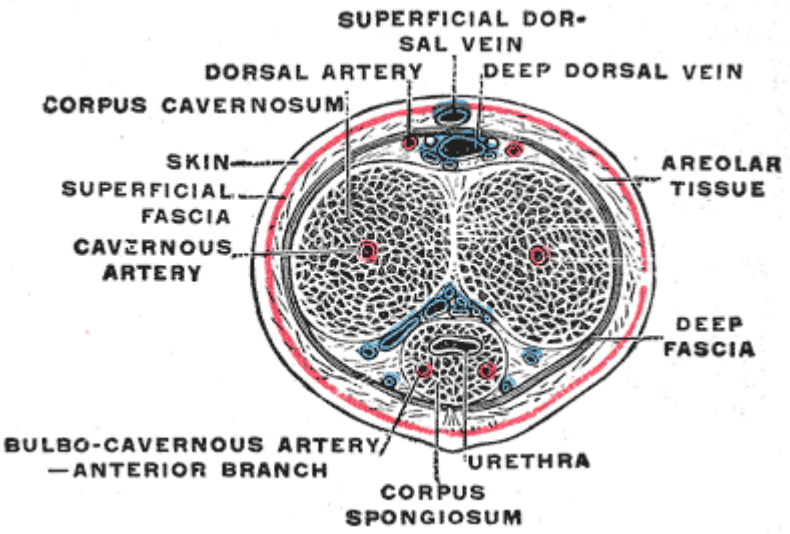
Venous supply

- Venous drainage from the three corpora originates in tiny venules leading (from sinusoids) – exit as the emissary veins



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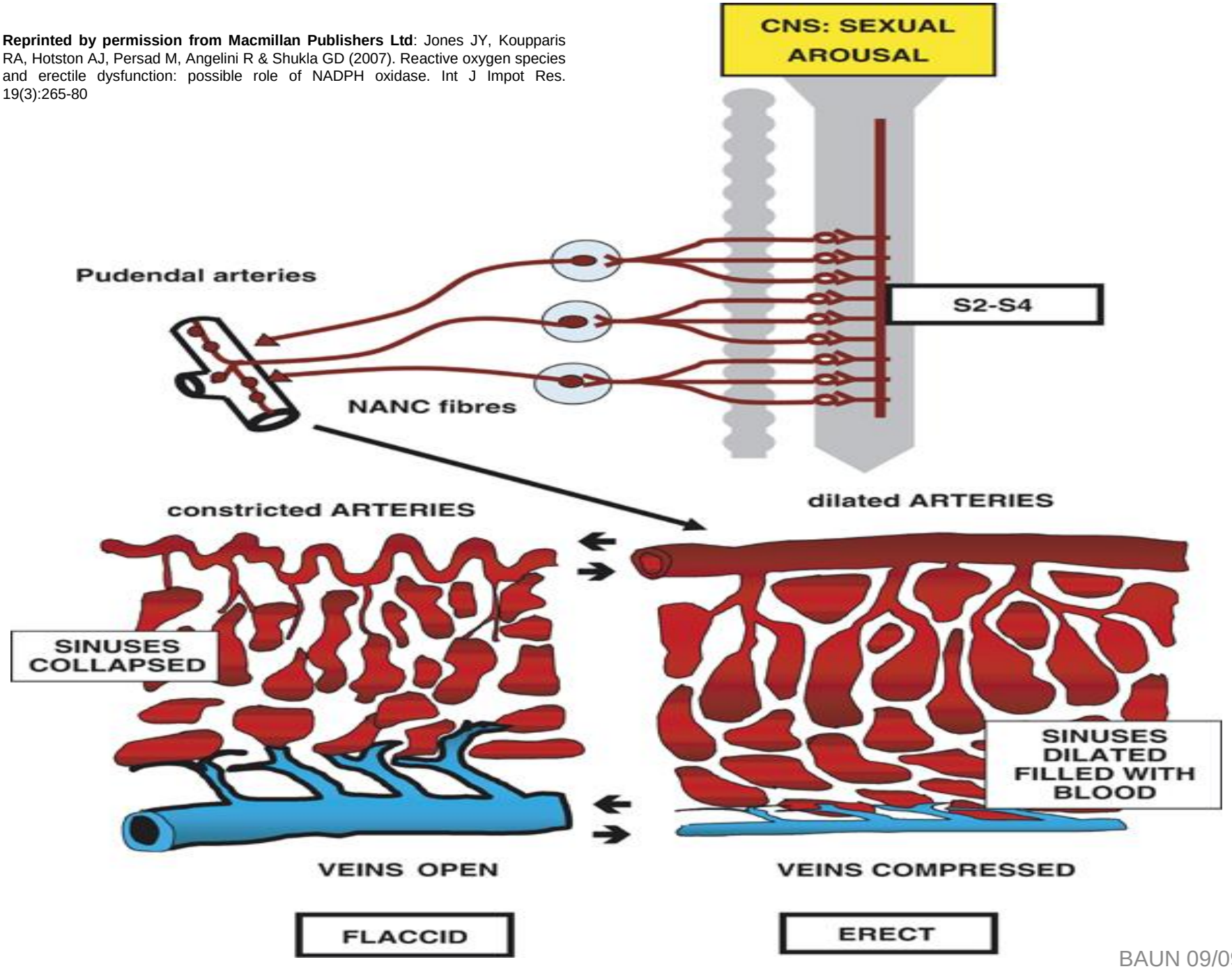

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Corpus Spongiosum and Glans Penis

- Haemodynamics of the corpus spongiosum and glans different from those of the corpora cavernosa.
- During erection - arterial flow increases in a similar manner; however, the pressure in the corpus spongiosum and glans is only ⅓ - ½ of that in the corpora cavernosa because the tunical covering (virtually absent over the glans and thin over the corpus spongiosum) ensures minimal venous occlusion.

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Neuroanatomy and Neurophysiology of Erection

Peripheral innervation of the penis is:

- Autonomic
  - Sympathetic
  - Parasympathetic
- Somatic
  - Sensory
  - Motor

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Neural Input

- In the spinal cord and peripheral ganglia - sympathetic and parasympathetic nerves merge to form the cavernous nerves, which enter the corpora cavernosa and corpus spongiosum.
- In the flaccid state, dominance of sympathetic activity keeps arterioles and smooth muscle contracted
- Erections are primarily vascular in nature BUT result from pro-erectile parasympathetic stimulation
- Causes arteriolar dilation and trabecular smooth-muscle relaxation.
- Pudendal nerve also has an input causing ischiocavernosus muscle contraction, which further increases intracavernosal pressure

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Autonomic Pathways 1

- Sympathetic pathway - originates from the T11 – L2 spinal segments
- Passes through the white rami to the sympathetic chain ganglia.
- Some fibres then travel through the lumbar splanchnic nerves to the inferior mesenteric and superior hypogastric plexuses, from which fibres travel in the hypogastric nerves to the pelvic plexus.
- In humans, T10 to T12 segments are most often the origin of sympathetic fibres projecting to the penis (sacral and caudal sympathetic chain ganglia).

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Autonomic Pathways 2

- The parasympathetic pathway - arises from neurons in the intermediolateral cell columns of sacral spinal cord (S2-S4). The preganglionic fibres pass in the pelvic nerves to the pelvic plexus, where they are joined by the sympathetic nerves from the superior hypogastric plexus.
- The cavernous nerves - branches of the pelvic plexus that innervate the penis. Other branches of the pelvic plexus innervate the rectum, bladder, prostate, and sphincters.
- The cavernous nerves are easily damaged during abdominal surgery, including radical excision of the rectum, bladder, and prostate.

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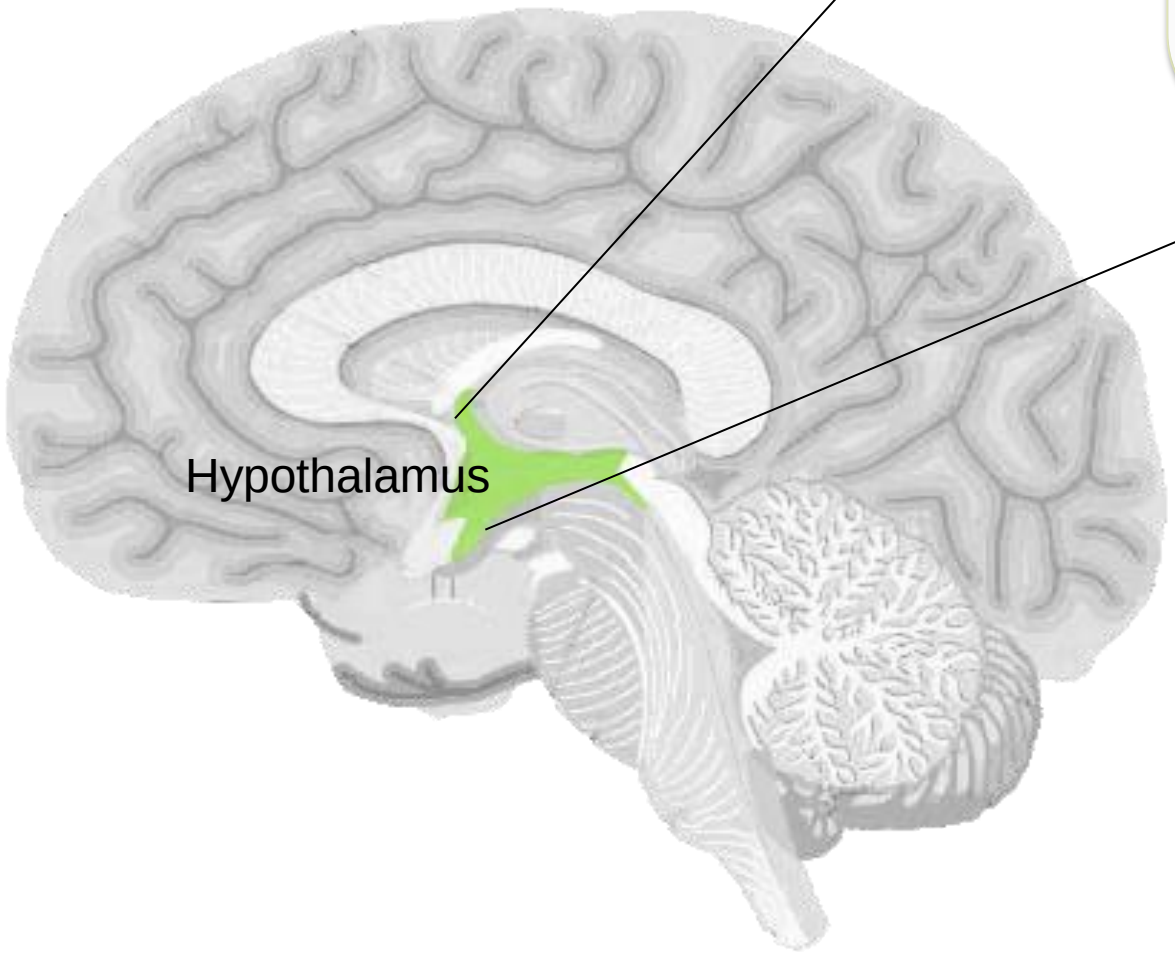
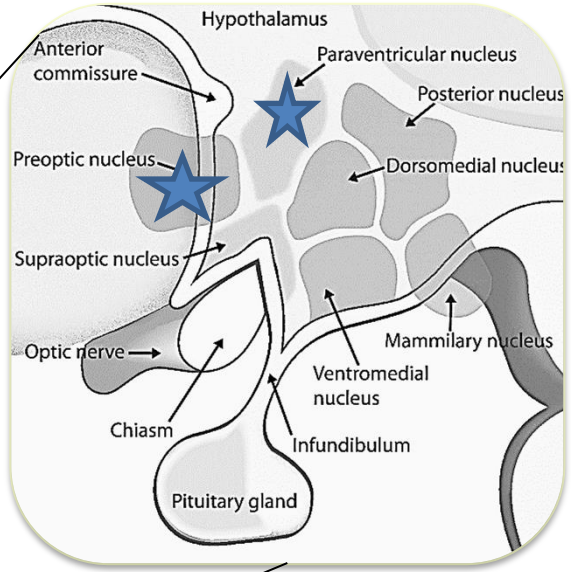
Central Control of Erections





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Central Control of Erections

- Cerebral cortex – thinking about sex
- Limbic system - how we feel about sex, how we behave sexually
- Hypothalamus - stimulation triggers arousal > orgasm

Processing of input from the senses:

- Touch - primary & secondary erogenous zones - dominant "sexual sense"
- Vision – important role
- Smell - may cause, or attenuate arousal (? role of pheromones)
- Taste – variable role
- Hearing – variable role

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Somatic Pathways

- The somatosensory pathway originates at the sensory receptors in the penile skin, glans, and urethra and within the corpus cavernosum
- The free nerve endings are derived from thin myelinated A_δ and unmyelinated C fibers
- Nerve fibers from the receptors converge to form bundles of the dorsal nerve of the penis, which joins other nerves to become the ***pudendal nerve***
- Onuf's nucleus (S2-S4) is the center of somatomotor penile innervation
- Contraction of the ischiocavernosus muscles produces the rigid-erection phase. Rhythmic contraction of the bulbocavernosus muscle is also necessary for ejaculation.

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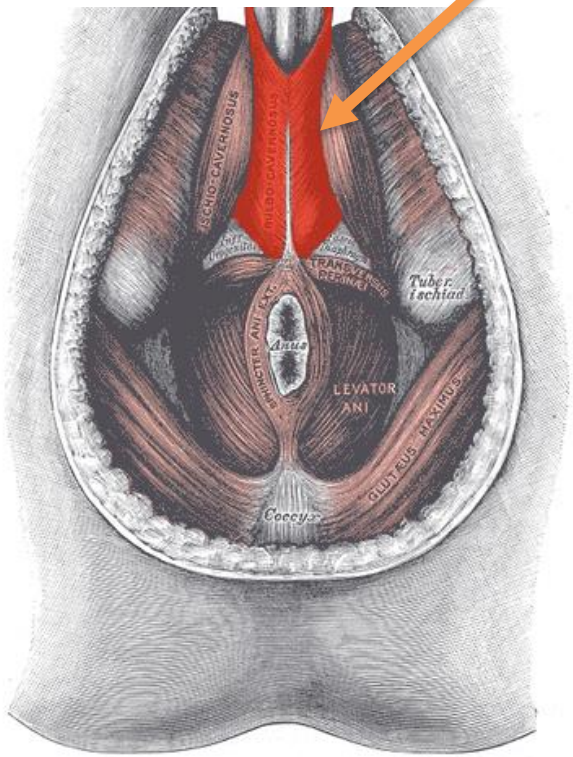
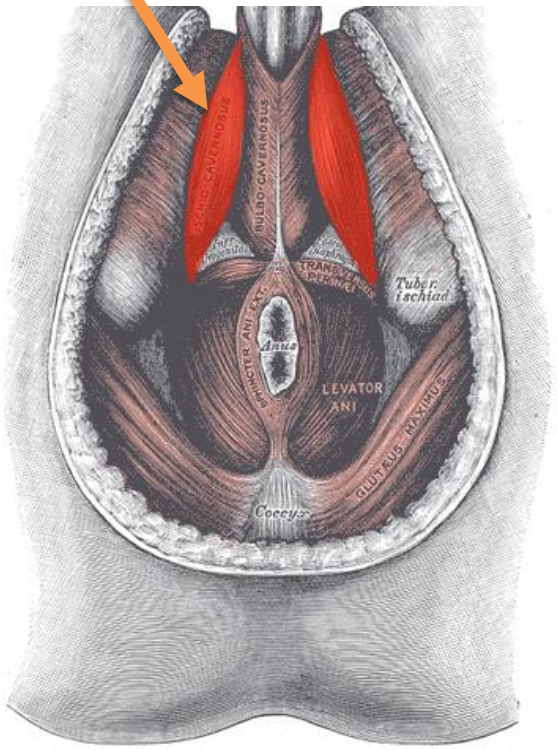
The somatic nerves are primarily responsible for sensation and the contraction of the bulbocavernosus and ischiocavernosus muscles.





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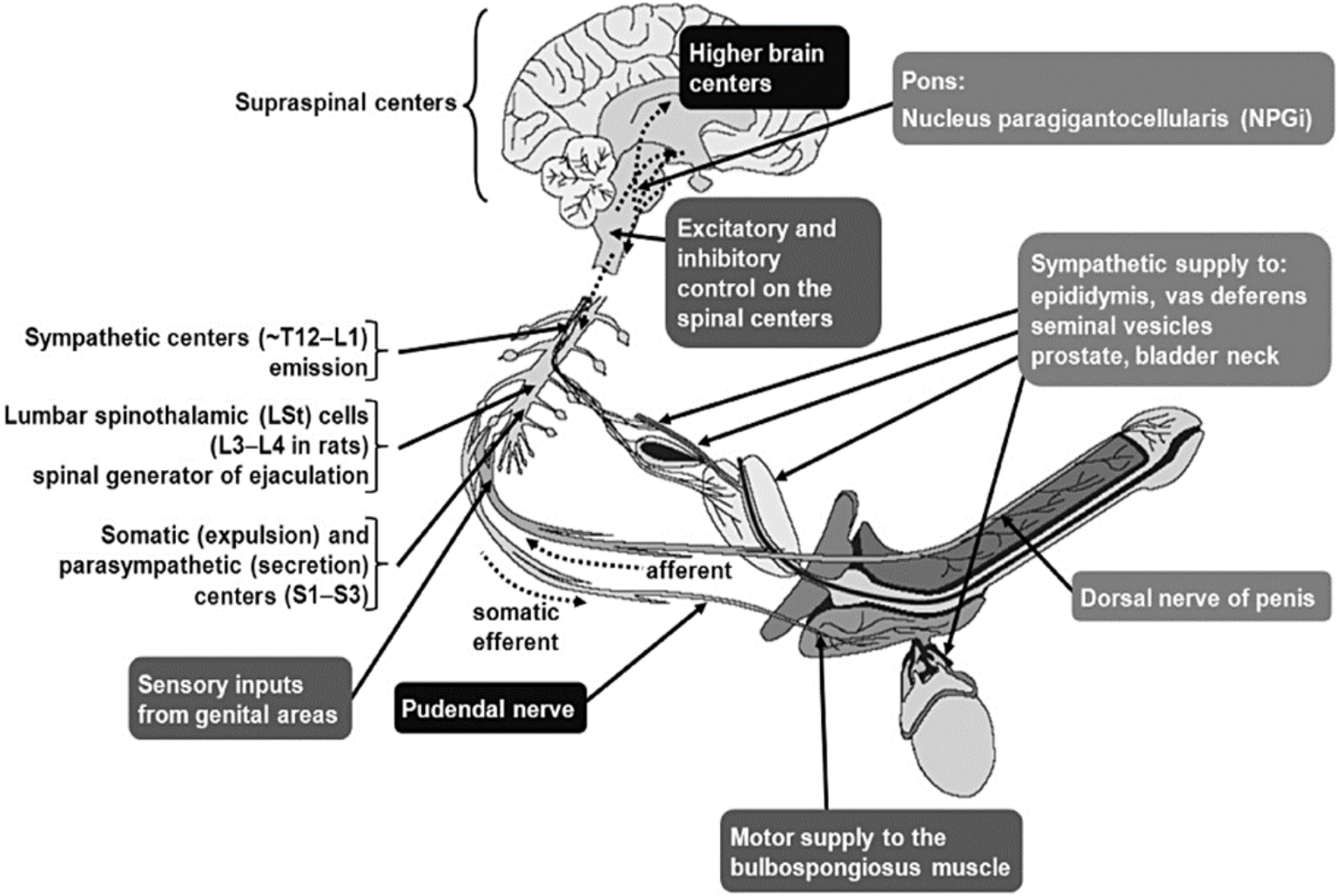
Neurophysiology of Erection



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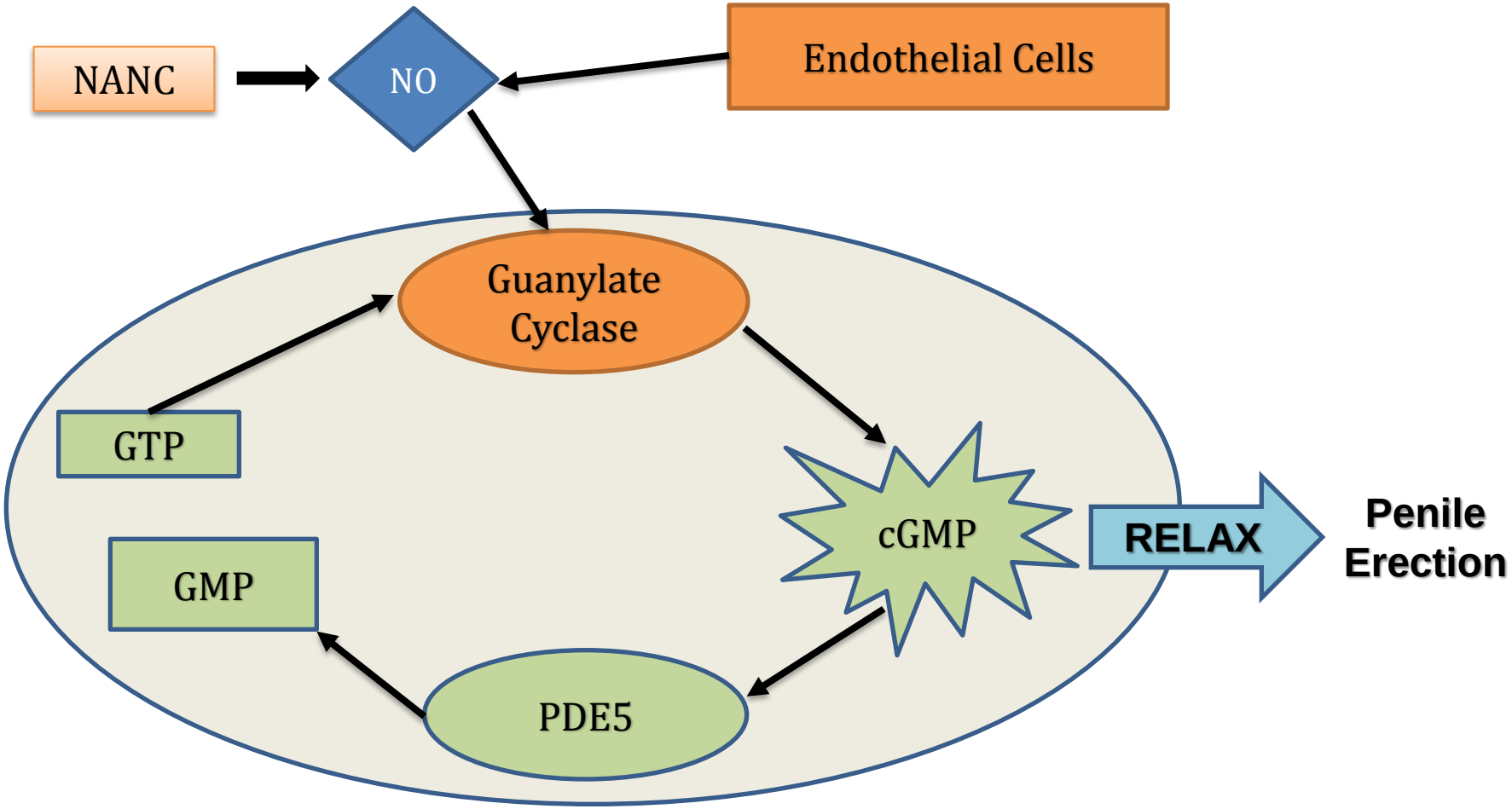

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Summary

- Relaxation of the cavernous smooth muscle = key to penile erection.
- NO-release initiates the erection process & helps maintain erection - released from parasympathetic nerve terminals
- Parasympathetic nerve terminal also releases acetylcholine (Ach) - stimulates vascular endothelium to also release NO
- NO stimulates the production of cGMP in smooth muscle cells.
- Cyclic GMP activates protein kinase G, which causes potassium channels to opens and calcium channels to close.
- Low cytosolic calcium favours smooth muscle relaxation.
- The smooth muscle regains its tone when cGMP is degraded by phosphodiesterase – this underpins the action of PDE5Is

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Flaccidity and Detumescence

- Background partial contaraction of intracorporeal smooth muscle influenced by three factors:
    1. Intrinsic myogenic tone
    2. Adrenergic neurotransmission
    3. Endothelium-derived contracting factors such as angiotensin II, $PGF_{2\alpha}$, and endothelins
- α-Adrenergic nerve fibres and receptors - norepinephrine = principal neurotransmitter to control penile flaccidity and detumescence
- Detumescence and return to flaccid state – also result of ↓ NO release, the breakdown of cyclic guanosine monophosphate (cGMP) by phosphodiesterases, or sympathetic discharge during ejaculation
- Endothelin - potent vasoconstrictor produced by the endothelial cells, may be a mediator

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Sexual Response Cycles

- **Kaplan**
  - Desire
    - Distinct (not required)
  - Excitement
  - Orgasm
- **Masters & Johnson**
- Excitement Phase Vasocongestion, myotonia, flush
- Plateau Phase
- Orgasm Phase
- Resolution Phase
- Refractory period

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THE SEXUAL RESPONSE

- Masters and Johnson: four phases

- Excitation:
  - Vasocongestion: pelvic area receives more blood in general, in particular to genitals.
    - penile erection
    - scrotal sac thickens, elevates
    - sex flush (can happen later)
    - heart rate, respiration rate gradually increase
    - generalized myotonia

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THE SEXUAL RESPONSE

- Plateau:
  - continued vasocongestion
  - Heart rate, respiration rate and blood pressure continue to increase
  - Perspiration
  - Increased myotonia
  - Cowper's glands secrete fluid through tip of penis
  - scrotum even higher and testicles bigger

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THE SEXUAL RESPONSE

- Orgasm:
  - Males: spinal reflex triggers two phases:
    - contraction of seminal vesicles, vas and prostate (emission: fluid in urethral bulb)
    - contraction of urethra and penis: expulsion: semen expelled
      - ➢ Sensation experienced = Ejaculatory Inevitability

- Accompanied by increased heart rate, blood pressure and breathing rate
- Intense myotonia

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THE SEXUAL RESPONSE

Resolution phase

- The resolution phase (Refractory period) occurs after orgasm
- Subsidence in any sex-flush and a feeling of relaxation, blood pressure drops and the body recovers from excited state
- During this time man is unable to orgasm again (refractory period)
- Associated with production of oxytocin & prolactin centrally (Exton et al., 2001).
- The duration of recovery, commonly referred to as the post-ejaculatory recovery time (PERT) and the intensity of the refractory period can be very short in younger men, whereas in mid-life and in older men, it can last for as long as a few hours, or days (Exton et al., 2001).

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Psychogenic and Psychiatric causes

Two possible mechanisms have been proposed:

- ❖ Exaggeration of the normal suprasacral inhibition, leading to direct inhibition of the spinal erection centre by the brain
- ❖ Excessive sympathetic outflow, or elevated peripheral catecholamine levels

- Stress/PTSD
- Anxiety
- Loss of attraction to partner
- Relationship difficulties
- Psychosis
- Depression

Clues differentiating psychogenic from organic causes

- Psychogenic
  - Sudden onset
  - Situational
  - Normal spontaneous erections (nocturnal & EMT)
  - Normal erection with masturbation
  - Relationship problems
  - Significant life event
  - Anxiety, depression,fear
- Organic
  - Gradual onset
  - All situations
  - Reduced or absent spontaneous erections (nocturnal & EMT)
  - No erections with masturbation
  - Penile pain

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Relationship Difficulties

- Current relationship status
- Length of relationship
- Previous sexual partners and relationships
- Partner issues e.g. painful intercourse/menopause/long-term illness

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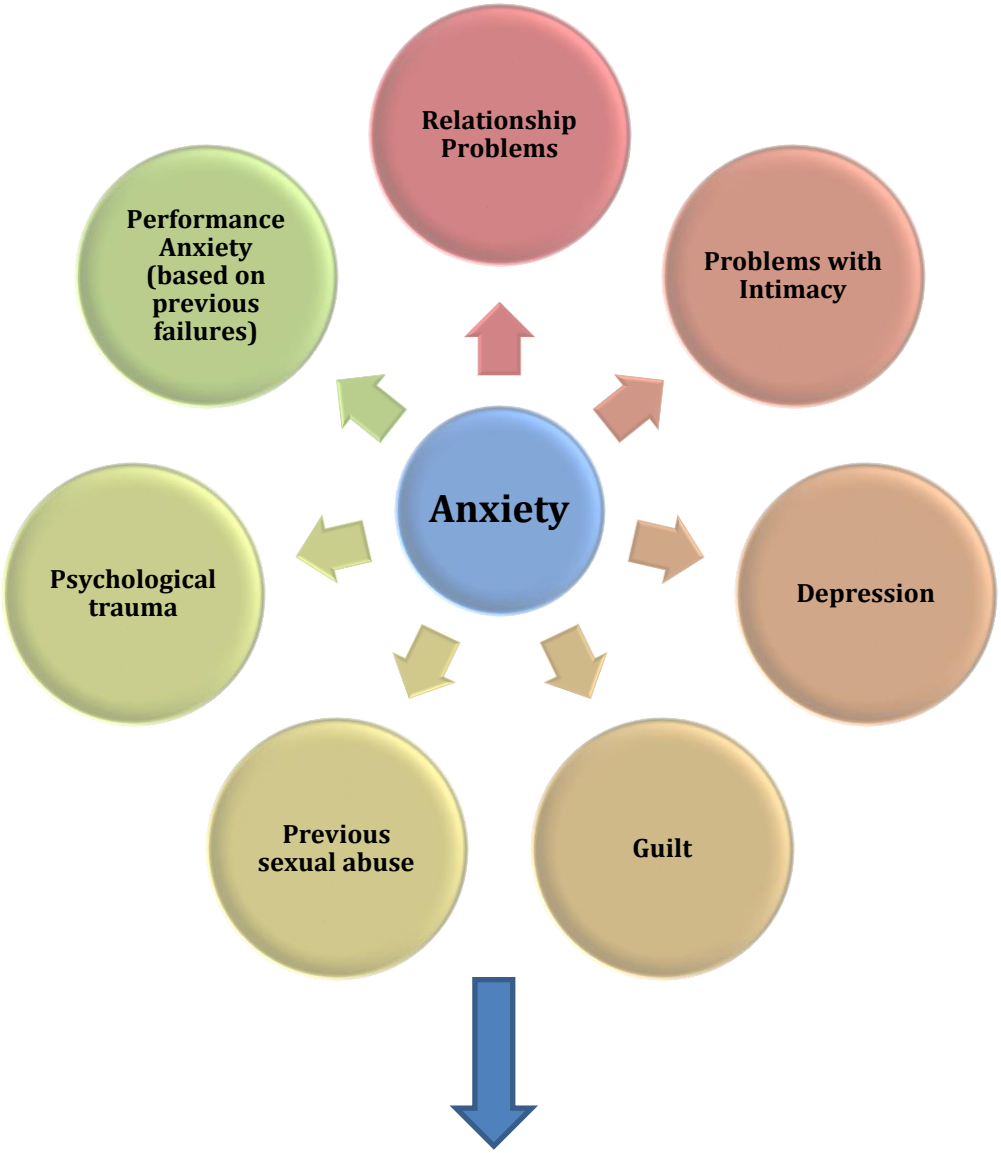

Psychogenic ED

Reproduced from Carson C,Holmes S,Kirby R. Fast Facts-Erectile Dysfunction. Oxford: Health Press Limited; 2002 : 33

Prevalence (literature)

- 52% of men have ED (40-70 years of age)
- 8% of 40 year old men; 40% of 60 year old men
- Estimate in UK is 2.3 million
- Worldwide prevalence of erectile dysfunction around 177 million cases - has been predicted to double (and reach 322 million cases by the year 2025).
- De Berardis, et al. (2005) decreased QoL in men with Type 2 DM
- ED can be the first presentation of cardiovascular disease. The average time between onset of ED and 1st cardiac event is 3 ½ years

What does this mean for practice?

- Incidence of ED is >1:10
- On average, it takes 3.5 - 6.6 years for patients to seek advice
- On average, relationships change within 6 months of a sexual dysfunction
- Patients do not know the words to use to ask for help
- Evident silence in discussing sexual problems
- Little or no advertising of Men's health - is it an agenda item?
- Patients are devastated by ED (or the implications of ED)

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Risk Factors for ED

- General health status
- Diabetes mellitus
- Cardiovascular disease
- Concurrence of other GU diseases
- Psychiatric or psychological disorders
- Chronic diseases
- Smoking
- Medications
- Hormonal factors also serve as well-defined risk factor-associated conditions

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Endocrine causes of ED

- Antiandrogen therapy
- Pituitary Abnormalities
- Hyperthyroidism
- Hyperprolactinaemia
- Hypogonadism
  - Raised SHBG
  - Raised Prolactin
  - Low testosterone

If two consecutive testosterone results are 12nmol/L or less (provided blood taken between 09.00 and 11.00):

Endocrine opinion

Drugs associated with ED

- Antihypertensives
  - β blockers
  - Thiazides
  - Centrally acting drugs
- Antidepressants
  - Tricyclics
  - MAO inhibitors
  - SSRIs
- Anticholinergics
  - Atropine
- Antipsychotics
  - Phenothiazines
- Anxiolytics
  - Benzodiazepines
- Psychotropic drugs
  - Alcohol
  - Opiates
  - MDMA/Amphetamines
  - Cocaine
  - Tobacco

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ED and Coronary Artery Disease

- Generalised atherosclerosis
- Penile arteries smaller than coronary arteries
- ED pre-dates coronary artery disease
- Man with ED and no cardiac symptoms is a cardiac patient until proven otherwise
- Increased peripheral vascular resistance
- Enhanced basal and myogenic tone has been observed in arteries

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Arteriogenic Cause of ED

- Reduced arterial perfusion, increased peripheral vascular resistance & enhanced basal and myogenic tone may collectively contribute
- Common risk factors
    - IHD/Hypertension
    - Smoking
    - Diabetes
    - Hyperlipidaemia
    - Peripheral vascular disease
    - Blunt perineal or pelvic trauma – leading to focal stenosis
    - Pelvic irradiation
- Long-distance cycling is also a risk factor – causes vasculogenic and neurogenic changes

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Cavernous (Venogenic)

- **Degenerative changes** (aging, Peyronie's disease and diabetes) or traumatic injury to the tunica albuginea (e.g. penile fracture) - impairs the compression of the subtunical and emissary veins.
- **Loss of elasticity of the penile sinusoids** associated with increase in collagen deposition & reduction in fibre elasticity - may be seen in diabetes, hypercholesterolaemia, vascular disease, penile injury, or aging.
- **Veno-occlusive dysfunction** may result from a variety of pathophysiologic processes: degenerative changes to tunica, fibroelastic structural changes, insufficient relaxation of trabeculae, and venous shunting (venous leak).

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Neurogenic causes of ED

- Any central lesions of brain, especially MPOA, PVN, hippocampus - these are important integration centres
- Spinal trauma - nature, location, and extent of injury largely determines EF
- Pelvic surgery/radiotherapy → Neuropraxia
- Myelodisplasia (spina bifida)
- Multiple sclerosis
- Intervertebral disc lesion
- Peripheral neuropathies
  - Inherited neuropathies
  - Diabetic neuropathy
  - Alcohol
  - HIV

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What to assess?

- Is it erection trouble or premature ejaculation?
- How long has there been a problem
- What precipitated it? (if known)
- Do you get erections in the morning/night-time
- Are you still intimate with your partner
- Can you penetrate?
- What treatment have you tried?
- Correct treatment/dosing?

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Hypertension

- Hypertension is an independent risk factor for ED
- Cardiovascular complications such as ischemic heart disease and renal failure are associated with even higher ED prevalence
- ED may be compounded by treatments given to manage hypertension (nitrates, beta blockers, etc.) & some treatments may be an absolute contraindication (e.g. patients taking nitrates)

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Diabetes Mellitus

- Common chronic disease, affecting 0.5% to 2% worldwide
- In 12% of diabetic men, deterioration of sexual function can be the first symptom
- Prevalence of ED is three times higher in diabetic men (28% versus 9.6%)
- Causes vascular and neurogenic changes

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Chronic Renal Failure

- Erectile dysfunction can be seen in up to 40–80% of haemodialysis patients.
- ED in CKD is multifactorial - includes decreased arterial blood flow, venous leakage, altered penile smooth muscle function, hormonal disturbances, side effect of medications and neurogenic changes.
- Uremia decreases NO bioavailability

Rathi, M., & Ramachandran, R. (2012). Sexual and gonadal dysfunction in chronic kidney disease: pathophysiology. Indian journal of endocrinology and metabolism, 16(2), 214.

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History

- Medical/Surgical/Mental Health
- Medication
- Smoking
- Alcohol
- Recreational drug use

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History (continued)

- Detailed description of problem, is it ED?
- Causative factors
- Sexual desire/libido
- Ejaculatory disorders
- Impact on quality of life and on relationship
- Expectations of treatment

And finally…..

- Sexual activity demands energy
- Approximately 3-5 METs are needed for ‘normal’ sex
- Equates to mowing a small lawn or climbing 2 flights of stairs
- If you cannot do either, you are not fit enough for sexual activity

Summary

- ED is very common
- Identify it early & any potential risk factors – makes treatment ‘easier’
- Ask – no-one else will
- Aggressive management (where possible) to regain sexual self confidence & prevent neuropraxia
- May herald future major cardiac/cerebrovascular event – seek onward referral, advice & intervention