Objectives:

1. Understand the neurologic control of penile erection and detumescence including neurotransmitters release by intracavernosal nerve terminals
2. State four broad categories of erectile dysfunction and give one example for each category
3. State the mechanism of action of sildenafil (Viagra), its side effects and possible drug interactions. State two other therapies for erectile dysfunction.
4. Understand the common causes of priapism, its management, and possible consequences of extended erection.

Introduction:

1. sexual health is an important aspect to quality of life
2. male erectile dysfunction (ED) is increasing in prevalence due to the aging population

    a. approximately 10% of men over 40 report complete inability to obtain or maintain an erection
    b. up to 33% of men over 40 report occasional inability to obtain or maintain erections

3. ED may be associated with a number of important illnesses such as diabetes, hypertension, coronary artery disease or depression

    a. in some cases ED may be the presenting sign of these disorders

Neurophysiology:

1. normal sexual response requires the cerebral cortex, hypothalamus, various midbrain centers and the reticular formation to integrate cognitive, tactile, auditory, visual and olfactory stimuli
2. somatic sensory nerve fibers from the penile skin travel in the dorsal nerve of the penis to the pudendal nerve then to spinal levels S2, 3 and 4
3. the autonomic nerves responsible for erection (parasympathetic (PNS), S2-4) and detumescence (sympathetic (SNS), T10-L2) arise from the para-rectal plexus and travel together in the cavernosal nerves to enter the corpora cavernosa of the penis

    a. these cavernosal nerves lie immediately lateral to the apex of the prostate and may be injured during a radical prostatectomy

4. arterial blood flow to the corpora cavernosa is from the cavernosal artery, a branch of the pudendal artery
5. an erection is produced when PNS signals within the cavernosal nerves cause release of nitric oxide (NO) from the endothelium of the sinusoids of the corpora cavernosa
> NO stimulates the conversion of GTP to cGMP which, through a number of mechanisms, causes smooth muscle relaxation and arterial vasodilatation allowing the sinusoids to fill with blood
> the draining emissary veins are compressed against the rigid tunica albuginea as the corpora cavernosa fills, greatly reducing efferent blood flow, therefore resulting in penile tumescence
> important also, as it is used as a treatment, is that prostaglandin E1 has a vasodilatory effect, mediated by cAMP, on penile arterial vessels by causing smooth muscle relaxation
6. additional sexual stimulation initiates the bulbocavernosus reflex – the ischiocavernous muscles forcefully compress the base of the blood filled corpora cavernosa and the penis reaches full erection and hardness

    a. at this stage both the inflow and outflow of blood temporarily cease

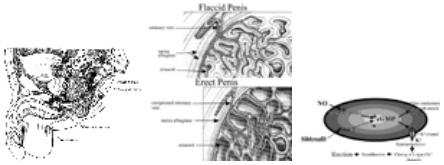
7. detumescence is a result of:

    a. sympathetic nerve terminals releasing norepinephrine (NE) causing vasocontriction
    b. the natural metabolism of NO-induced cGMP by a phosphodiesterase enzyme

        > isomers of phosphodiesterase are found in many tissues, the penile isomer is phosphodiesterase V

8. sildenafil (Viagra) is an inhibitor of phosphodiesterase V thereby prolonging the effect of NO on penile smooth muscle

    a. successful use of Viagra still requires an intact cavernosal nerve, arterial blood supply and veno-occlusive mechanism



Classification:

Psychogenic: depression, sexual phobias, strained relationship, performance anxiety, psychotic disorders

Neurogenic: stroke, diabetes, Parkinson's disease, sacral spinal cord injury, cavernosal nerve injury from radical prostatectomy or pelvic fracture

Arteriogenic: atherosclerosis in distal aorta, internal iliac or pudendal arteries (due to hypertension, diabetes, smoking)

- vascular diseases account for nearly 50% of ED in men over 50

Venogenic: Peyronie's disease

Endocrinologic: diabetes, hypogonadism, hyperprolactinemia

Drug-induced: antihypertensives (ß-blockers > HCTZ > Ca-channel blockers > ACE inhibitors), marijuana, cigarettes, antipsychotics

Patient Evaluation:

1. History must include all current medical problems, current medications and previous surgeries

a. it may differentiate between psychogenic and organic causes of ED
b. the physician should ask whether the patient has difficulty achieving an erection, whether it is suitable for penetration, whether it can be maintained for enough time for both partners to achieve sexual satisfaction
c. ask about the frequency and amount of tobacco and alcohol use
d. explore any stressors in the patients life
e. distinction should be made between diminished libido with ED and normal libido with ED
f. patients should be asked about their interest in detailed testing to determine an accurate diagnosis or whether they wish to simply try various treatments

	Organic	Psychogenic
Onset	Gradual	Acute
Nocturnal erection	Poor/absent	Normal
Circumstances	Global	Situational
Course	Constant	variable

2. Physical examination must include:

a. blood pressure measurement
b. a peripheral vascular exam
c. DRE to examine the prostate as well as anal tone and perianal sensation
d. exam of the testicles for size
e. exam of the penis for Peyronie's plaque
f. assessment of secondary sexual characteristics

- low serum testosterone (T) may be suspected by atrophic testes and/or loss of secondary sexual characteristics
- examination of the prostate (DRE and PSA level) must be carried out to screen for prostate cancer if supplemental testosterone is to be given

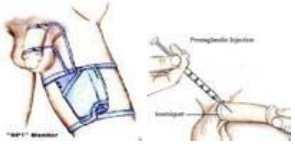
3. **Laboratory tests** should include:

a. fasting blood glucose or HgA1c as ED may be the presenting complaint of diabetes
These other tests may be appropriate depending on the history and physical exam
b. morning T, LH and prolactin are indicated patients with diminished libido or physical signs of hypogonadism
c. nocturnal penile tumescence testing may be used to detect nocturnal erections and may be helpful in distinguishing organic from psychogenic causes

- this test involves placing an elastic monitoring band around the base of the penis which the patient wears for 2-3 consecutive nights
- if an erection occurs, the duration and degree of tumescence is recorded
- normal nocturnal erections indicate a high likelihood of psychogenic ED

d. injection of prostaglandin (PGE1 – Caverject) directly into one of the corpora cavernosa is one of the most commonly used tests

- if penile blood flow and the veno-occlusive mechanism are adequate then an erection should occur in a few minutes
- the patient should judge the quality of the erection and decide if he is satisfied using Caverject as a treatment



Treatment:

1. **sildenafil** therapy works in many men with mild to moderate ED regardless of the etiology of ED

a. it is a potent inhibitor of phosphodiesterase type 5, the enzyme in the corpora that breaks down cGMP, so the effect of cGMP is lengthened
b. the patient should be counseled that sexual stimulation is still required to produce an erection
c. the effect begins approximately one hour after ingestion and may last as long as 24 hours (the drug effect not the erection)
d. numerous studies have documented that Viagra is safe in men with known coronary artery disease but there is a potentially severe interaction with nitroglycerine or other nitrates resulting in profound hypotension
e. Viagra should never be prescribed to men who require nitroglycerine frequently or those who take nitrates daily for control of angina
f. known side effects include: headache, nausea, and a blue haze in the peripheral vision
> the visual disturbance is transient and probably results from partial inhibition of phosphodiesterase type 6 located in the retina
g. Viagra is available in 25,50,100 mg tablets
h. the starting dose should be lower in those men with pre-existing liver or renal disease
i. men who fail to respond to 100 mg are not likely to respond to a higher dose
> Men who fail sildenafil treatment should be referred to a urologist for further evaluation if they are prepared to consider more invasive therapies

2. injection therapy with **prostaglandin E1** (e.g. Caverject):

a. with a small syringe the man injects one side of his penis with PGE1
b. if the vasculature within the corpora cavernosa is healthy, the use of injectable agents is almost always effective
c. the main adverse effects are a painful erection, priapism or scarring at the site of injection

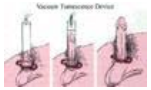
3. intraurethral therapy with **PGE1**:

a. a suppository is inserted into the urethral meatus
b. is effective in some men and may be an option for men unwilling to

perform the injections

4. **vacuum devices**:

a. a plastic cylinder is placed over the penis and used to create a vacuum and draw blood into the penis
b. after an erection is achieved a constricting band is placed at the base of the penis
c. it is effective in 60-90% of patients and can maintain an erection for up to 30 minutes
d. these are generally safe but can produce: hematomas, pain, numbness, absent or painful ejaculation
e. many men lose interest in these devices because of the preparations that are necessary, lack of easy transportability and inability to hide the ring



5. penile implants:

a. semirigid system:

i. matching cylinders are implanted into the corpora cavernosa which provide enough rigidity for penetration
ii. drawbacks: cosmetic appearance, need for surgery and destruction of erectile mechanism during surgery

b. multicomponent inflatable system

i. 2 cylinders in the corpora cavernosa, a pump in the scrotum and a reservoir usually in the fascia of the lower abdomen
ii. remains functional for 7-10 years before replacement is needed
iii. patient satisfaction with these devices is very high

Priapism:

1. the presence of a persistent, usually painful erection
2. it is frequently idiopathic, but also associated with some systemic diseases and intercavernosal injections
3. priapism is a persistent erection of the corpora cavernosa originating from disturbances to the mechanisms that control detumescence
4. the corpora spongiosum and surrounding urethra remain flaccid
5. two types of priapism are described:

a. arterial high-flow priapism is usually secondary to a rupture of a cavernous artery and unregulated flow into the lacunar spaces

i. this is rare and is usually secondary to penetrating penile trauma or a blunt perineal injury (straddle injury)

b. veno-occlusive priapism is usually due to full and unremitting corporeal veno-occlusion

i. prolonged veno-occlusive priapism results in fibrosis of the penis and a loss of the ability to achieve an erection – it is a urologic emergency!
ii. patients with sickle cell disease are prone to veno-occlusive priapism – this not uncommonly occurs in children with sickle cell disease
iii. arterial priapism is not associated with fibrotic change

Causes:

Arterial high-flow priapism:

1. genitourinary trauma:

    a. intercavernosal injections
    b. straddle injuryies

2. drugs:

    a. cocaine (especially crack cocaine)

Veno-occlusive priapism (low flow):

1. malignancy:

    a. genitourinary malignancies are most commonly associated
    b. hematological malignancies (e.g. leukemia, multiple myeloma)
    c. metastases are less commonly associated with priapism

2. hypercoagulable state:

    a. sickle cell disease
    b. polycythemia
    c. total parenteral nutrition
    d. Fabry's disease
    e. dialysis
    f. vasculitis

3. drugs:

    a. intercavernosal injection
    b. intraurethral pellets
    c. antidepressants
    d. cocaine (especially crack cocaine)
    e. alcohol
    f. antihypertensives
    g. antipsychotics

4. neurogenic:

    a. spinal stenosis
    b. medullary trauma

Treatment:

1. any patient with an erection for longer than 4 hours should receive therapy for priapism, but most will respond to conservative measures including:

    a. use of ice packs to the perineum
    b. walking up stairs – it is thought the mechanism is related to an arterial steal phenomenon
    > if these measures do not work quickly the patient should go to the hospital

2. permanent histological damage is seen in veno-occlusive priapism at 24 hours

3. treatment of high-flow priapism is not emergent because penile tissue does not become ischemic and the risk of permanent injury is much less than with veno-occlusive priapism
4. pharmacolgic interventions:

    a. corporeal injection of a-adrenergic agonists: counteract smooth muscle relaxation
    b. corporeal injection of methylene blue: inhibits guanylate cyclase, but is short lived and priapism may reccur

5. surgical ligation of the fistula may be required for treatment of high-flow priapism with the potential complication of long-term impotence
6. selective embolization with a catheter seems to be effective for high-flow priapism with few long-term complications
7. emergent therapy for veno-occlusive priapism often involves drainage of the corpora cavernosa with a large gauge needle
8. therapy for priapism secondary to sickle cell disease includes: hydration, alkalinization, analgesia, blood transfusions to decrease the concentration of Hb S

Patient Evaluation:

History:

High Flow	Low Flow
not painful	painful
well oxygenated corpora – adequate arterial flow	ischemic corpora – inadequate arterial flow
soft erections	rigid erection
may be sexually active	inactive sexually and no desire
initiated usually with straddle injury	no history of trauma
may be chronic in nature at presentation	usually present to ER within hours
low risk of permanent erectile dysfunction	high risk of long-term erectile dysfunction
rarely caused by medication	frequently associated with substance abuse or vasoactive penile injections

Physical:

1. presence of priapism should be confirmed with the finding of erect or semierect penis, with a flaccid glans penis
2. examine for evidence of trauma to the genital region
3. examine for signs of a systemic disease that predisposes to priapism

Work-up:

1. CBC and reticulocyte count to identify priapism associated with blood disorders
2. coagulation profile and platelet count
3. urinalysis (for multiple myeloma, cocaine use???)
4. corporeal blood gases to distinguish between high-flow and veno-occlusive priapism
a. veno-occlusive will have low oxygen, high carbon dioxide and low pH
5. in patients with high-flow priapism, selective angiography may be required in order to identify the site of the fistula
6. penile Doppler testing may be necessary to differentiate high-flow from low-flow priapism