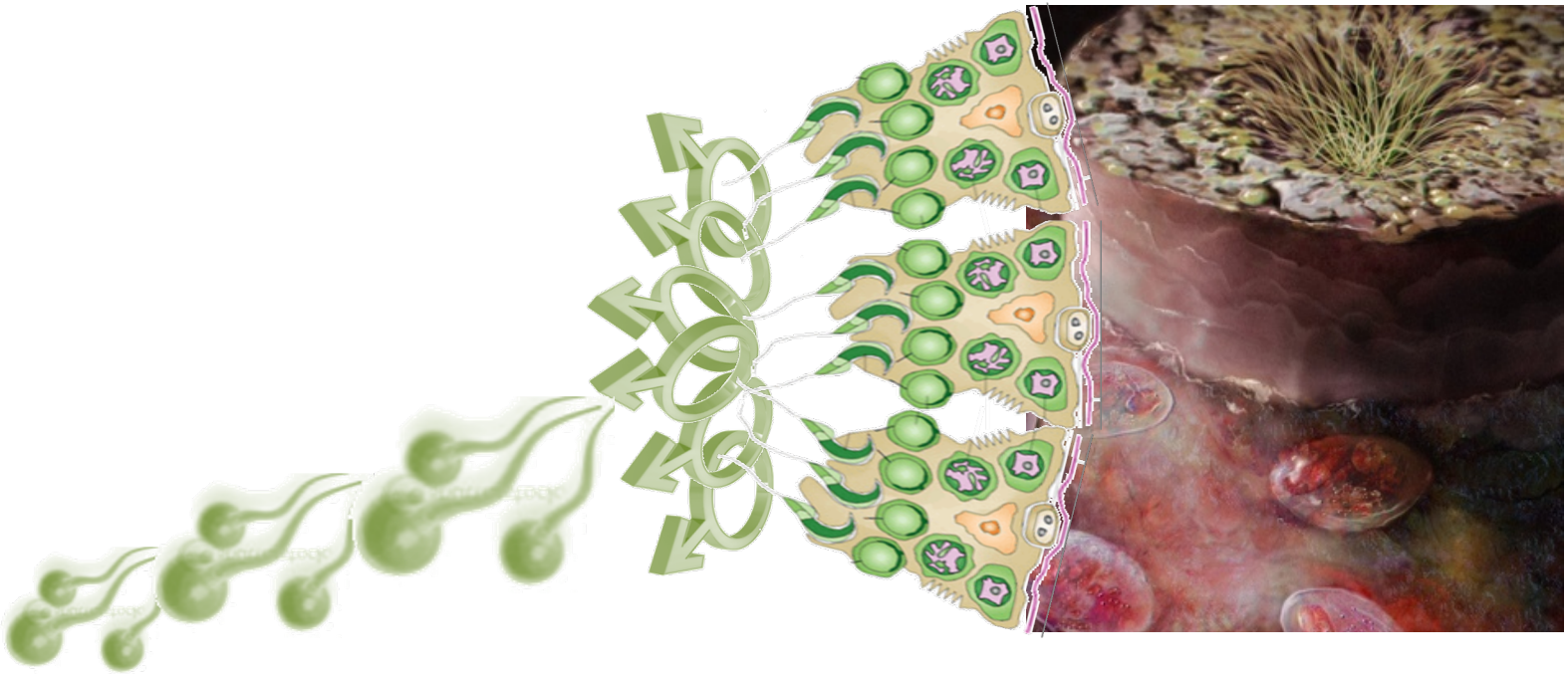
DRUGS USED IN

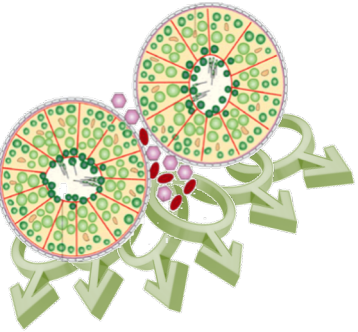
MALE INFERTILITY

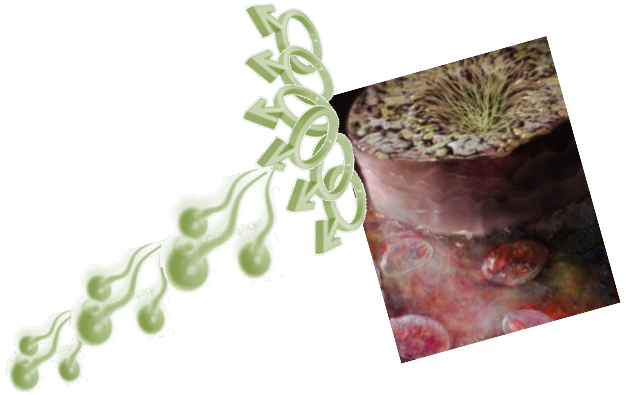


DRUGS USED IN MALE INFERTILITY

By the end of this lecture you will be able to:

- Define male infertility
- Recognize regulations contributing to male fertility & dysregulations leading to infertility
- Classify hormonal & non-hormonal therapies used in male infertility whether being emperical or specific.
- Expand on the mechanism of action, indications, preparations, side effects, contraindications & interactions of most hormonal therapies
- Highlight some potentialities of emperical non-hormonal therapies





MALE INFERTILITY

Definition

Inability of a male to achieve conception in a fertile woman after one year of unprotected intercourse.

Prevalence

Approximately 15-20% of all couples are infertile
In up to 50% of such cases(7.5-10%), males are responsible

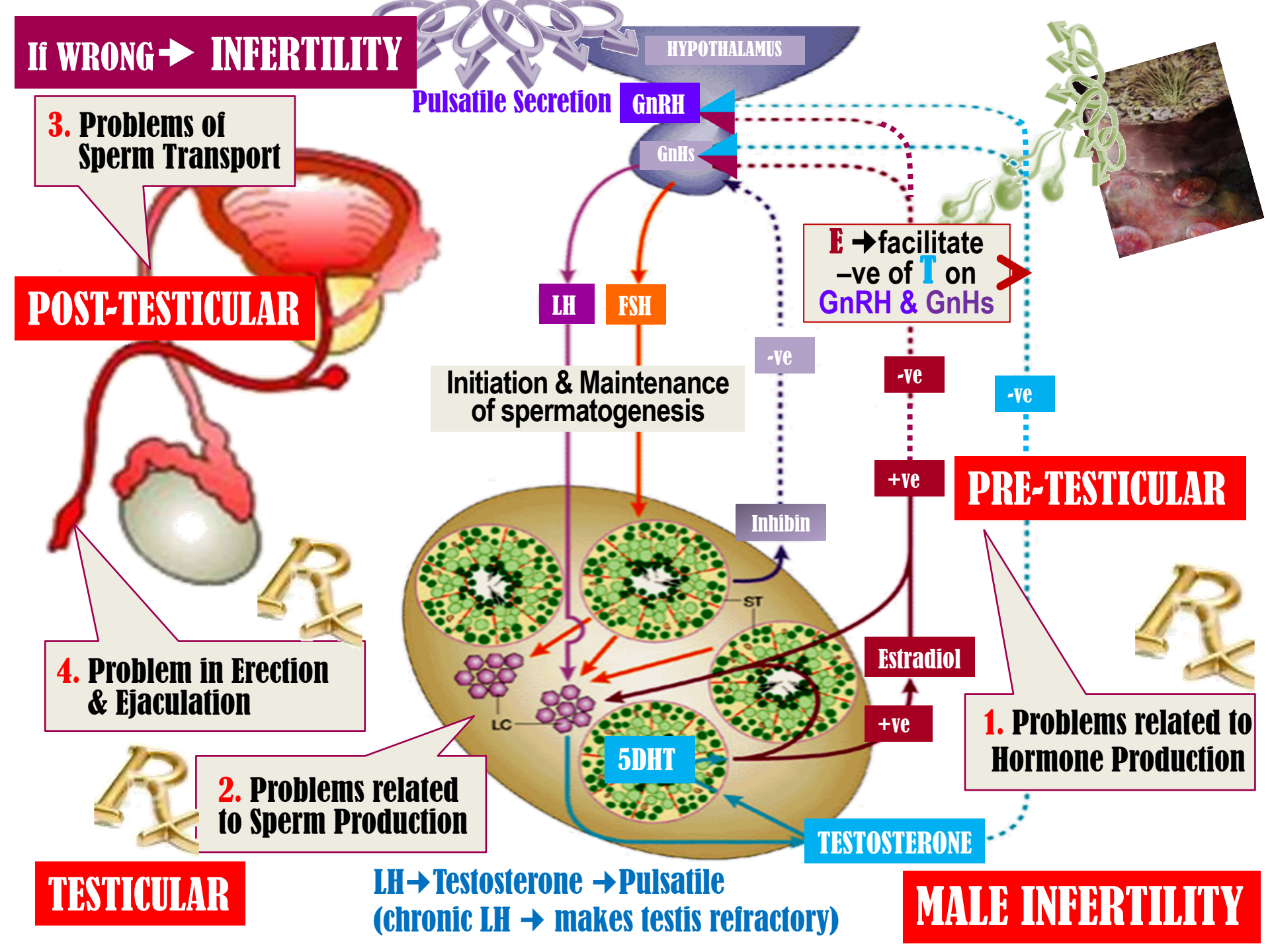
INFERTILITY vs IMPOTENCE – What is the difference?

In male infertility, the semen analysis is abnormal:

- Count is low (oligospermia)
- Sperms are absent in the ejaculate (azoospermia)
- Sperm motility is seriously affected (asthenospermia)
- Sperms are totally immobile or dead (necrospermia)

Causes of Male Infertility

1. **Idiopathic 25%** (causes unknown).
2. **Pre- testicular causes** (poor hormonal support & poor general health including:
   Hypogonadism; Drugs; alcohol; Tobacco; Strenuous riding (bicycle & horse riding); Medications (chemotherapy; anabolic steroids).
3. **Testicular causes** (testes produce semen of low quantity and/or poor quality):
   Age; Malaria; Testicular cancer; etc.
4. **Post- testicular causes** (conditions that affect male genital system after testicular sperm production):
   Vas deferens obstruction; Infection, e.g. prostatitis, T.B;
   Ejaculatory duct obstruction; Impotence.


If WRONG → INFERTILITY
HYPOTHALAMUS
Pulsatile Secretion
GnRH
GnHs
3. Problems of Sperm Transport
POST-TESTICULAR
E → facilitate –ve of T on GnRH & GnHs
LH
FSH
-ve
-ve
-ve
Initiation & Maintenance of spermatogenesis
+ve
PRE-TESTICULAR
Inhibin
ST
LC
Estradiol
+ve
5DHT
TESTOSTERONE
4. Problem in Erection & Ejaculation
1. Problems related to Hormone Production
2. Problems related to Sperm Production
TESTICULAR
LH → Testosterone → Pulsatile
(chronic LH → makes testis refractory)
MALE INFERTILITY

DRUG TREATMENT OF MALE INFERTILITY

Needs 3 months before semen quality changes

HORMONAL THERAPY

SPECIFIC

Hyperprolactinemia → *DA_2 Agonists*

Hypothyroidism → *Thyroxine*

Congenital Adrenal Hyperplasia → corticosteroids

Glucocorticoids excess → correct levels

EMPERICAL

- **Idiopathic** → *Androgens, Antiestrogen, GnH (FSH)*
- **Euogonadotrophic Hypogonadism** →
  (↓T only) Antiestrogens (SERMs & Aromatase Inhibitors)
- **Hypogonadotrophic hypogonadism** → 2ndry Hypogonadism (Hypothalamo-Pituitary)
  (↓T & ↓ FSH / LH)
  Pulsatile GnRH, hMG, hCG, Androgens, Clomiphene

- **Hypergonadotrophic Hypogonadism** (Testicular dysfunction) → 1ry Hypogonadism (↓T &↑LH) *Assisted Reproduction (no treatment)*

NON-HORMONAL THERAPY

EMPERICAL

Premature Ejaculation → *SSRIs (e.g. fluoxetine "Prozac")*

Infection of testes, prostate &UTI → *Antibiotics*

- *Antioxidants; e.g. vit. E, vit. C*
- *Zinc Supplements*
- *Folic acid*
- *L-Carnitine*

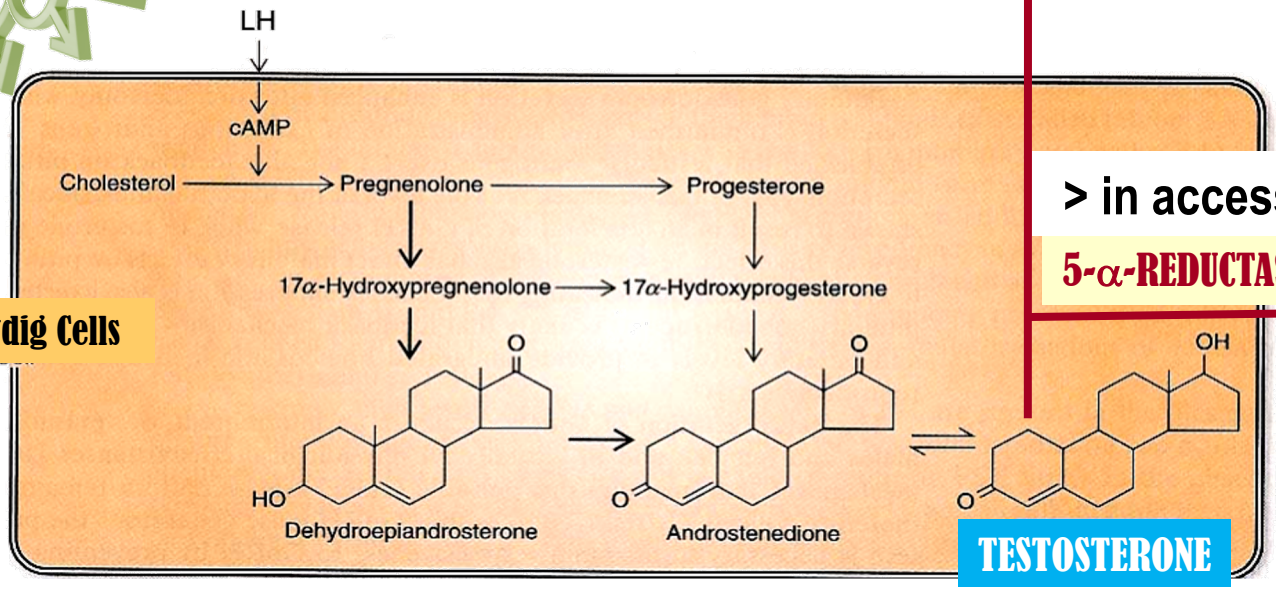
SPECIFIC

Erectile Dysfunction → *PDE 5 inhibitors, e.g., sildenafil (viagra),vardenafil (levitra), tadalafil (cialis)*

Drugs Used in the Treatment of Male infertility

1. Testosterone and synthetic androgens
2. Antiestrogens
   - SERMs e.g., clomifene (also called clomiphene), tamoxifen
   - Aromatase inhibitors e.g., Anastrazole
3. GnRH agonists (hypothalamic amenorhea)
4. GnH together with hCG (pituitary failure)
5. Non- hormonal therapy (antioxidants, zinc, folic acid, etc.).

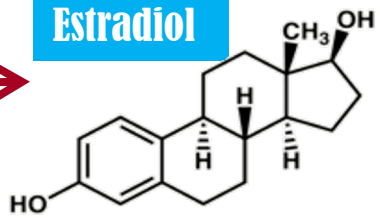
1.Testosterone



> in brain, bone, liver, adipose tissue

AROMATASE

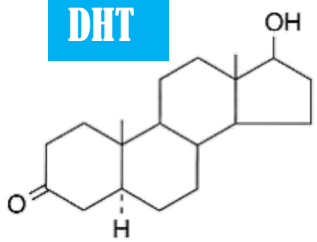
Estradiol



> in accessory sex organs

5-α-REDUCTASE

DHT



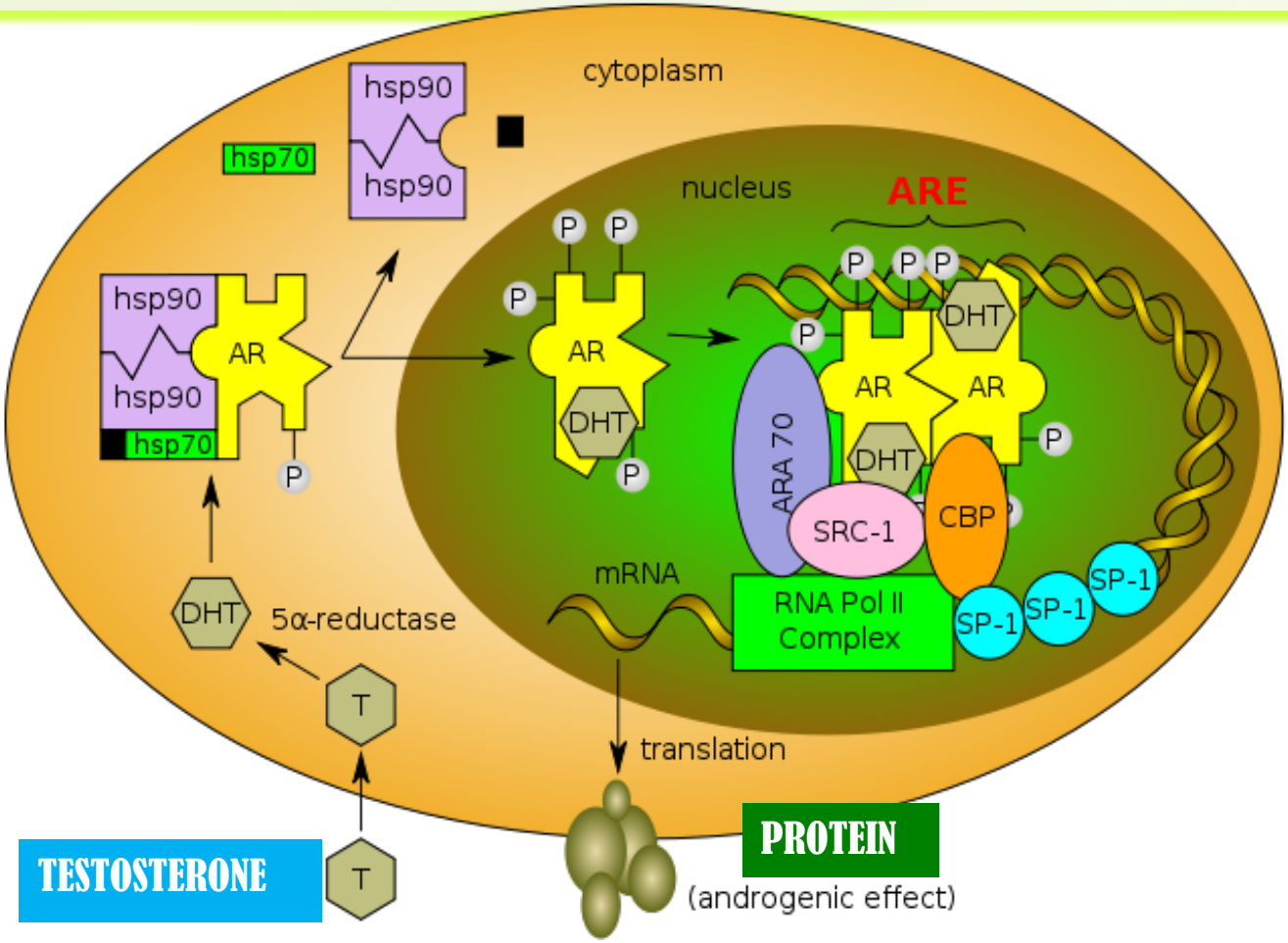
Principle male sex hormone produced in testis (> 95%), small amount in adrenals.

It follows a circadian pattern➔⬆in early morning & ⬇in evening

Mechanism of action of testosterone

A. Prostate and seminal vesicles

Testosterone is converted by α-reductase to DHT



B. Bones and Brain

Testosterone is metabolized by c-p450 aromatase to estradiol .

Bones: estradiol accelerates maturation of cartilage into bone leading to closure of the epiphysis & conclusion of growth.

Brain: estradiol serves as the most important feedback signal to the hypothalamus (esp. affecting LH secretion).

Pharmacological effects of Testosterone

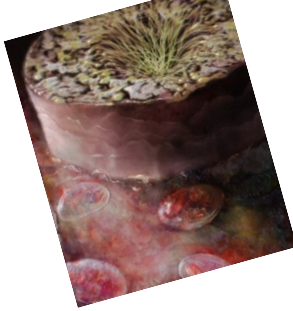
Testosterone has virilizing and anabolic effects

- **Virilizing effects**
  - Gonadotropin regulation
  - Spermatogenesis
  - Sexual dysfunction
  - Sexual restoration and development
- **Protein anabolic effects**
  - Increased bone density
  - Increased muscle mass
  - Increased red blood cell mass

← Testosterone & Synthetic Androgens

←Anabolic Steroids
Un approved use

Kinetics of Testosterone



Ineffective orally (inactivated by 1st pass met.)➔ *I.M* or *S.C.*

Skin patch & gels…. are also available

- Binds to Sex Hormone Binding Globulin [SHBG]
- t1/2 = 10 –20 min
- Inactivated in the liver.; 90% of metabolites ➔excreted in urine.
- Disadvantages: Rapidly absorbed, rapidly metabolized (Short duration of action).

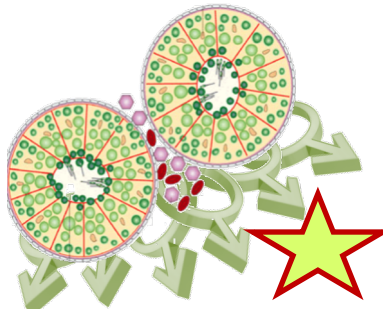
Synthetic Androgens

- Less rapidly metabolized & more lipid soluble ► increasing its duration of action.

Derived from Testosterone

- Esters; propionate, cypionate ➔in oil for **IM**; every 2-3 weeks
- Other derivatives as Methyltestosterone, Danazol ➔ given **Orally;** daily

Derived from DHT; Mesterolone ➔ given **Orally;** daily



Mesterolone More safe and can be given in ↓ testosterone or in 2ndry hypogonadism.

Why???

1. Not aromatised into estrogens → no –ve of GnHs → encourages natural testosterone production → spermatogenesis is enhanced.

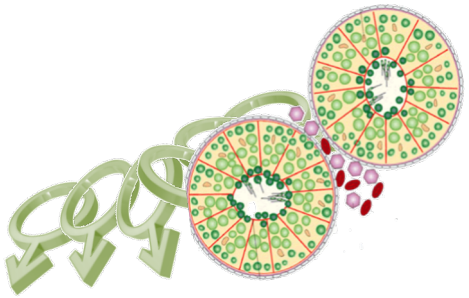
2. Unlike other oral synthetic androgens it is not hepatotoxic.

INDICATIONS

1. ANDROGENS

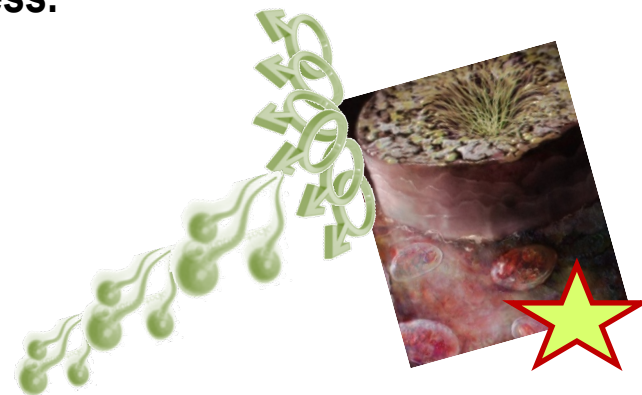
As Testosterone Replacement Therapy (TRT)

- Therapy for androgen deficiency in adult male infertility.
- In delayed puberty with hypogonadism
  ➔ give androgen slow & spaced for fear of premature fusion of epiphyses ➔ short stature.

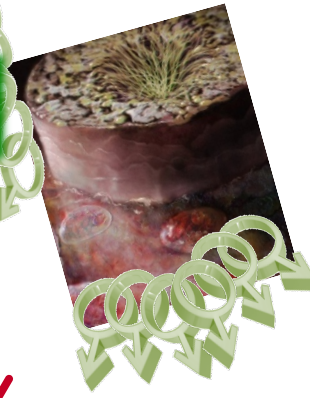


Adverse effects of Androgens

- Excess androgens (if taken > 6 wks) can cause impotence, decreased spermatogenesis & gynecomastia.
- Alteration in serum lipid profile: ↓HDL & ↑LDL, hence, ↑risk of premature coronary heart disease.
- Polycythemia (increase # of RBC) → ↑risk of clotting.
- Salt & water retention leading to edema.
- Hepatic dysfunction; ↑ aspartate amino transferase levels , ↑alkaline phosphatase, ↑ bilirubin & cholestatic jaundice.
- Hepatic carcinoma (long term use)
- Behavioral changes; physiologic dependence, ↑ aggressiveness.
- Premature closing of epiphysis of the long bones.
- Reduction of testicular size



Testesterone



Contraindications

- Male patients with cancer of breast or prostate
- Severe renal & cardiac disease → predispose to edema
- Psychiatric disorders
- Hypercoagulable states
- Polycythemia

Interactions

+ corticosteroids → oedema

+ warfarin → ↓metabolism → ↑ bleeding

+ insulin or oral hypoglycemics → hypoglycemia

+ propranolol → ↑ propranolol clearance → ↓efficacy

2. Antiestrogens

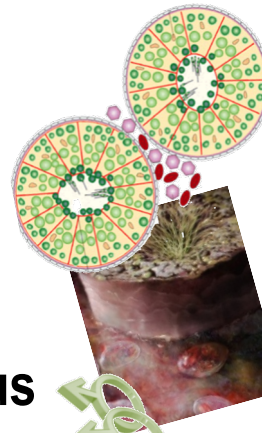
Because estrogens ➔ –ve feedback on hypothalamus ➔↓ GnRH pulse & pituitary responsiveness to GnRH, so antiestrogens ➔↑ GnRH & improve its pituitary response.

2.a. SERMs Tamoxifen, Clomiphene

Tamoxifen

Clomiphene

Both drugs can induce libido & bad temper in men

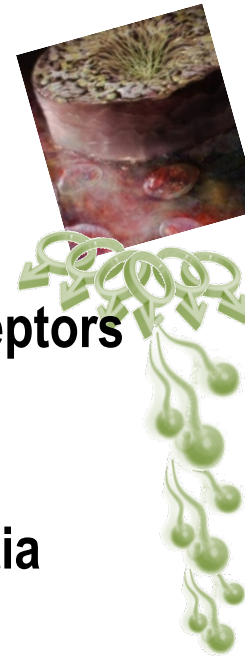


2.b. Aromatase Inhibitors Anastrozole

Blocks conversion of testosterone to estrogen within the hypothalamus

(All are used for inducing spermatogenesis when sperms count is low)

3. GnRH



Used in hypothalamic dysfunction

Given as Pulsatile GnRH therapy using a portable pump.

Exogenous excess of GnRH ➔ down-regulation of pituitary GnRH receptors & ↓ LH responsiveness.

ADRs; Headache, depression, generalized weakness, pain, gynecomastia and osteoporosis.

4. GnHs

Used in 2ndry hypogonadism (FSH or both FSH &LH absent) ➔↑ spermatogenesis hMG combined with hCG.

ADRs; Headache, local swelling (injection site), nausea, flushing, depression, gynecomastia, precocious puberty.

hMG, Human Menopausal Gonadotrophin; hCG, Human Chorionic Gonadotrophin

5.Non-HORMONAL THERAPY

Sometimes is very promising, to improve sperm quality and quantity.

Antioxidants Protect sperm from oxidative damage(e.g. vit. E,C)

FOLIC ACID

Plays a role in RNA and DNA synthesis during spermatogenesis & has antioxidant properties.

ZINC

Plays an important role in testicular development, sperm production & sperm motility.

L-CARNITINE

Highly concentrated in the epididymis & is important for sperm maturation and motility.