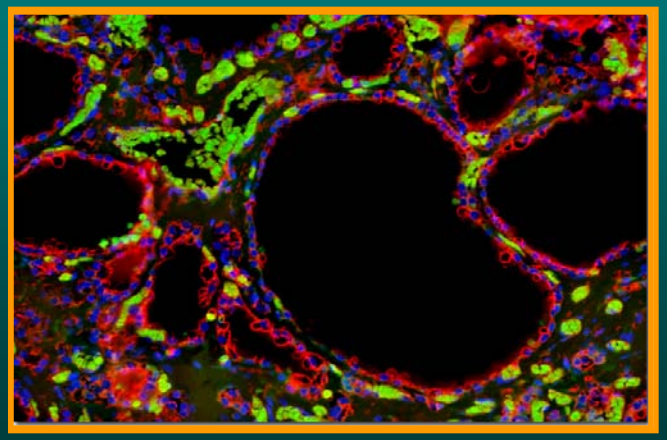
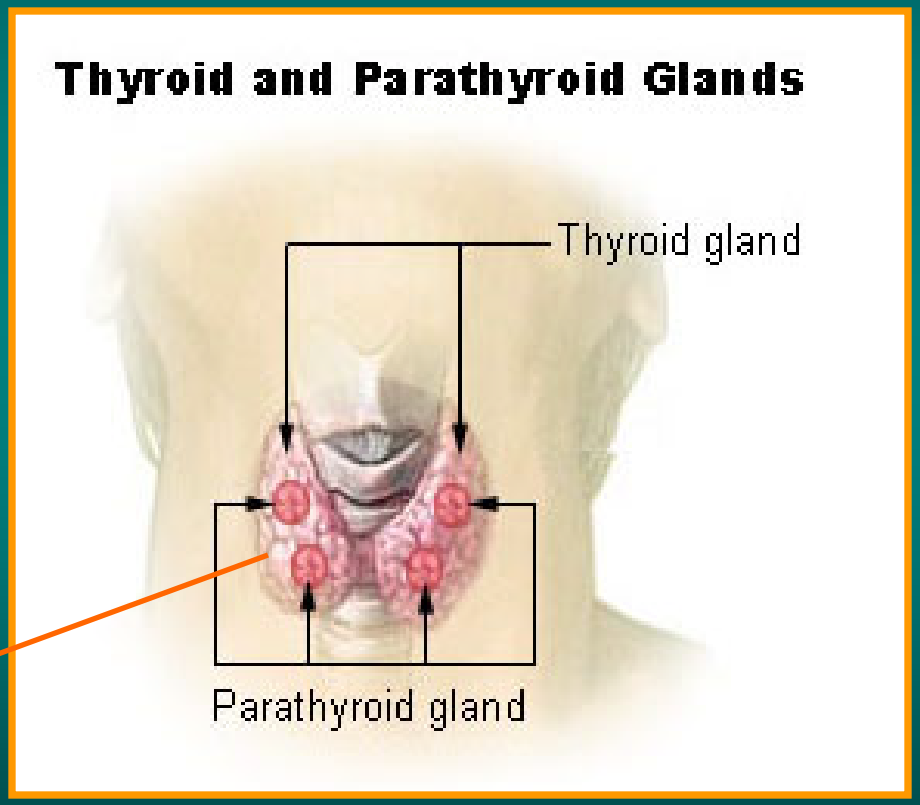
AR
and
THR

Thyroid glands

- The thyroid gland is a strongly vascularized organ
- It is located in the neck, in close approximation to the first part of the trachea.
- In humans, the thyroid gland has a "butterfly" shape, with two lateral lobes that are connected by a narrow section called the isthmus.
- Most animals, however, have two separate glands on either side of the trachea.
- Thyroid glands are brownish-red in color.





Thyroid glands

• **Thyroid epithelial cells - the cells responsible for synthesis of thyroid hormones - are arranged in spheres called *thyroid follicles*.**

• **The follicle lumen is filled with a thick colloid which predominantly contains thyroglobulin.**

• **Thyroglobulin is a highly glycosylated protein of two subunits, each of 330 kDa. The subunit contains 115 tyrosine residues. This way, the thyroid gland maintains a large reservoir of potential hormone.**

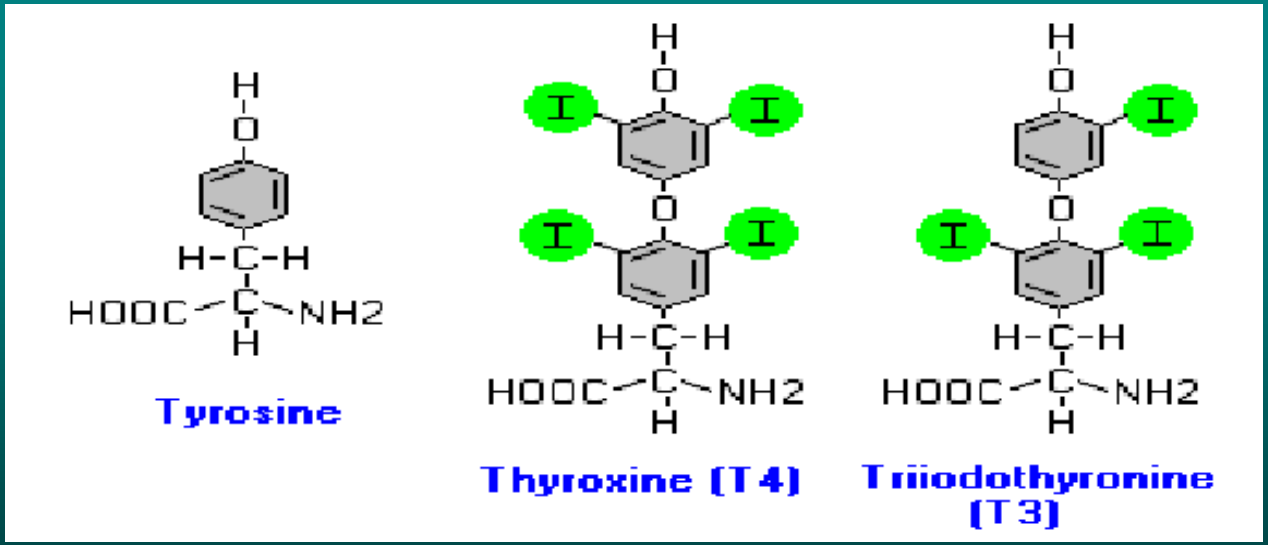
Thyroid hormones

• Thyroid hormones are derivatives of the amino acid tyrosine bound covalently to iodine. The two principal thyroid hormones are:

  • **thyroxine** (known also as **T4** or L-3,5,3',5'-tetraiodothyronine; major form released from the gland)

  • **triiodothyronine** (**T3** or L-3,5,3'-triiodothyronine).

• Although both T3 and T4 are important for normal growth and development and energy metabolism, **T3 is ~10 times more active ligand of THR than T4.**



Thyroid hormones are basically two tyrosines linked together with the critical addition of iodine at three or four positions on the aromatic rings.

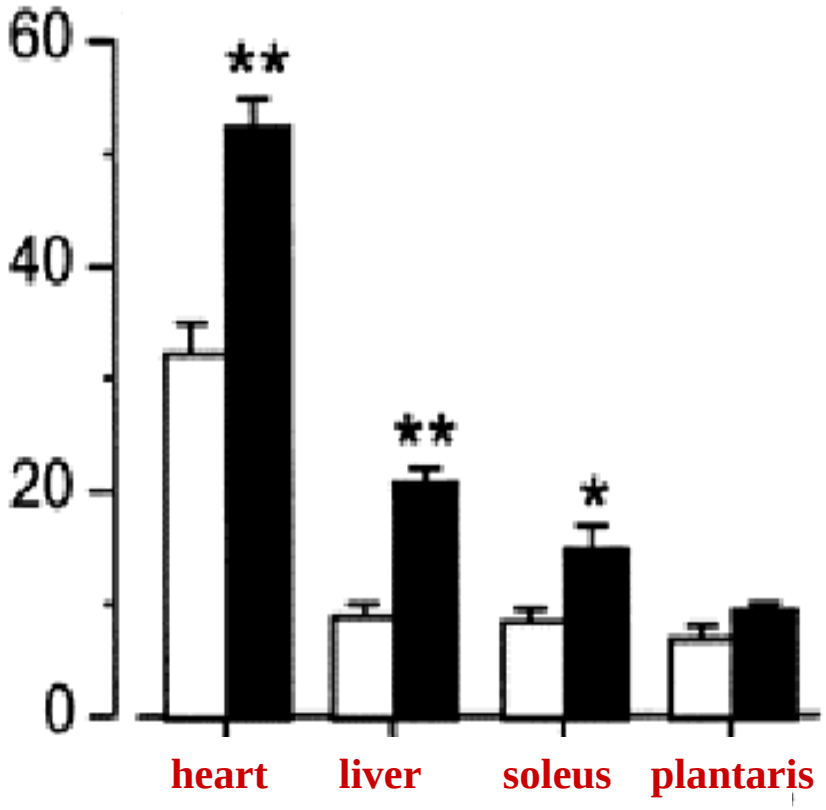
Physiologic effects of thyroid hormones

- It is likely that all cells in the body are targets for thyroid hormones.
- Thyroid hormones have profound effects on many "big time" physiologic processes, such as development, growth and metabolism.

Metabolism:

- Thyroid hormones stimulate diverse metabolic activities in most tissues, leading to an increase in basal metabolic rate.
- One consequence of this activity is to increase body heat production, which seems to result, at least in part, from increased oxygen consumption and rates of ATP hydrolysis.
- Thyroid hormones induce expression of UCP-1

Mitochondrial ATP production in control (open bars) and hyperthyroid (filled bars) in rats.



Physiologic effects of thyroid hormones

Growth:

- **Thyroid hormones are clearly necessary for normal growth in children and young animals, as evidenced by the growth-retardation observed in thyroid deficiency.**

Development:

- **A classical experiment in endocrinology was the demonstration that tadpoles deprived of thyroid hormone failed to undergo metamorphosis into frogs.**

Rana temporaria

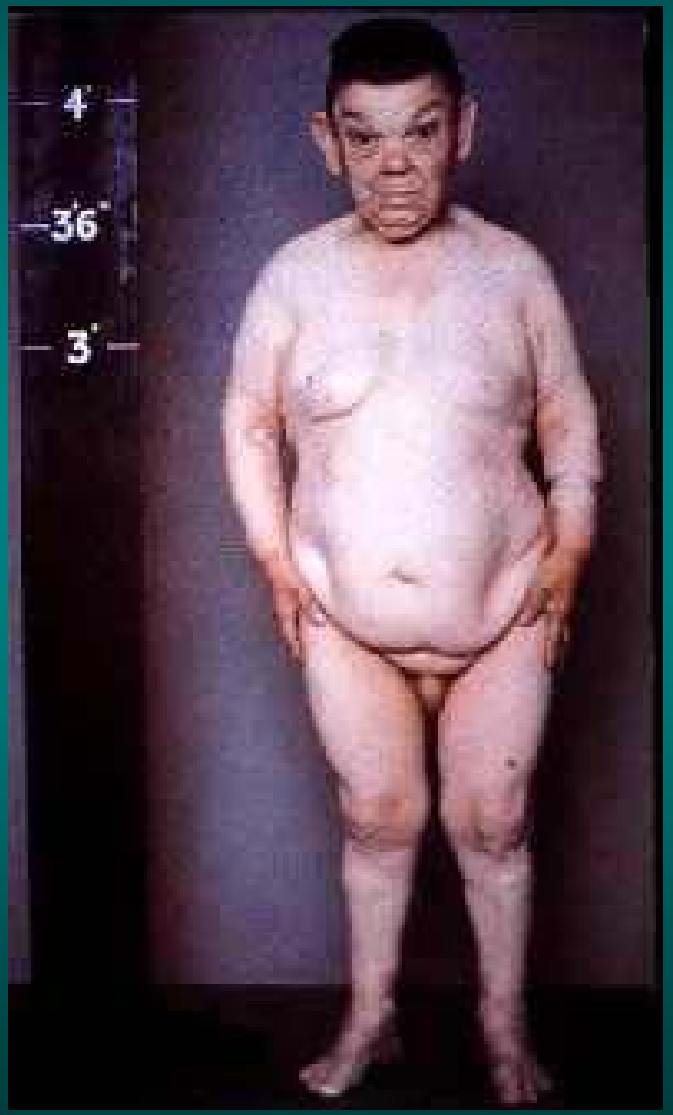
Xenopus laevis

Rot-Nikcevic & Wassersug, J Exp Biol 2004.

Physiologic effects of thyroid hormones

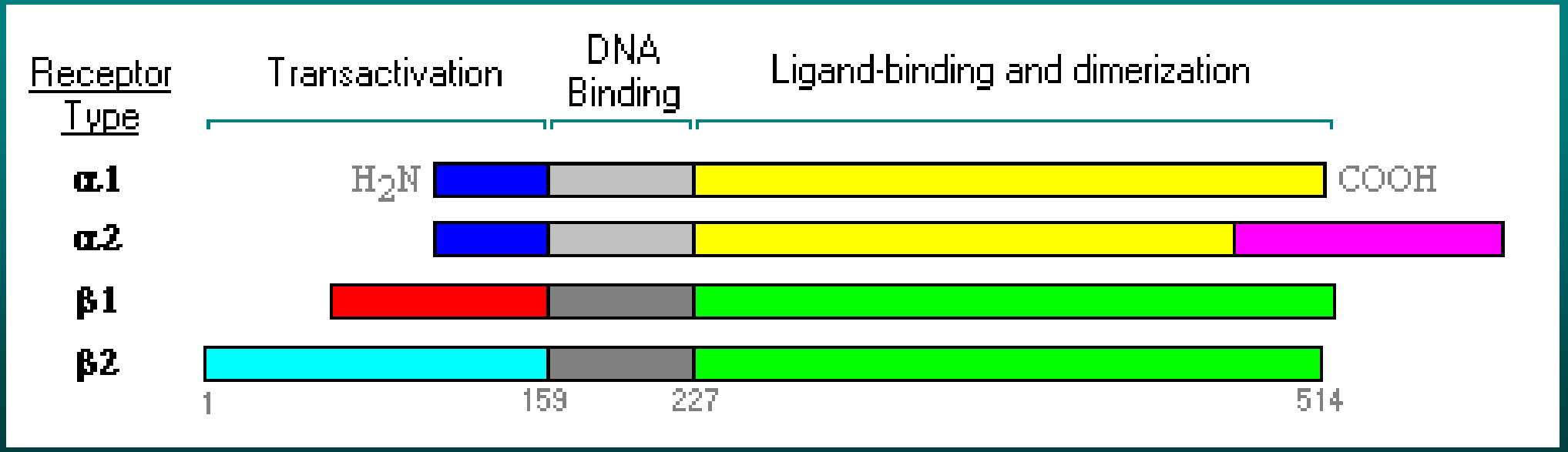
Central nervous system:

- **Both decreased and increased concentrations of thyroid hormones lead to alterations in mental state. Too little thyroid hormone, and the individual tends to feel mentally sluggish, while too much induces anxiety and nervousness.**
- **Of critical importance in mammals is the fact that normal levels of thyroid hormone are essential to the development of the fetal and neonatal brain.**
- **Congenital thyroid deficiency results in cretinism, which includes dwarfism and mental retardation.**



Thyroid hormone receptor (THR)

- Mammalian thyroid hormone receptors are encoded by two genes, designated alpha and beta.
- The primary transcript for each gene can be alternatively spliced, generating different alpha and beta receptor isoforms.
- Currently, four different thyroid hormone receptors are recognized: alpha-1, alpha-2, beta-1 (can bind cyclin D1 and p53) and beta-2.
- Most notably, the alpha-2 isoform has a unique carboxy-terminus and does not bind T3 and may act as inhibitor of other THRs.



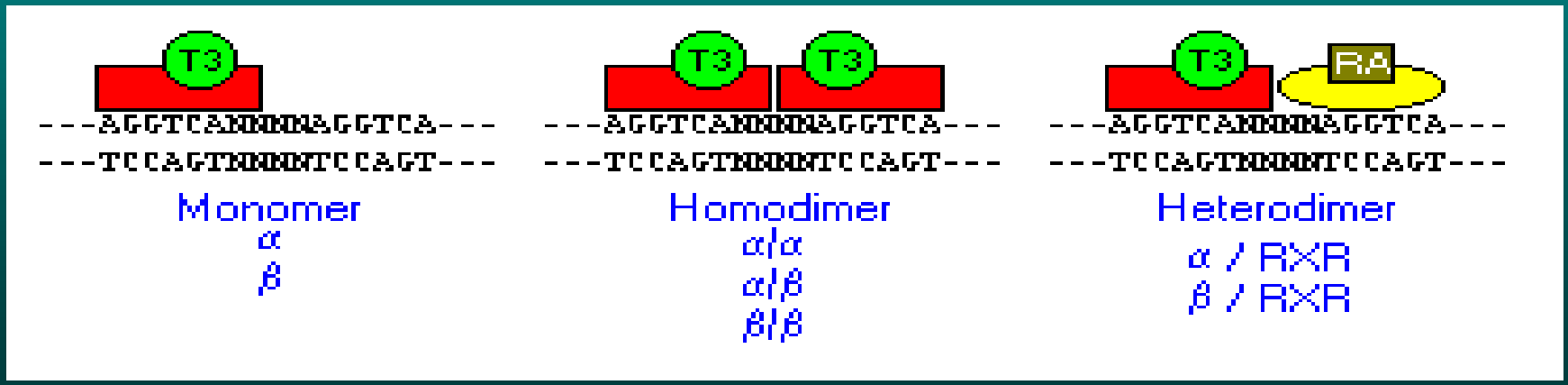
• Thyroid hormone receptors can bind to a TRE as monomers, as homodimers or as heterodimers with the retinoid X receptor (RXR).

• The heterodimer affords the highest affinity binding, and is thought to represent the major functional form of the receptor.

• The most stable binding occurs on the classical DR4 thyroid response element (TRE).

• Thyroid hormone receptors bind to TRE DNA regardless of whether they are occupied by T3. However, the biological effects of TRE binding by the unoccupied versus the occupied receptor are dramatically different.

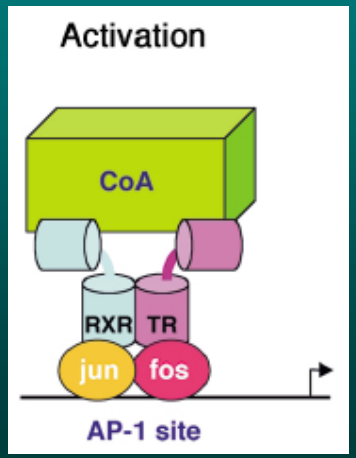
• In general, binding of thyroid hormone receptor alone to DNA leads to repression of transcription, whereas binding of the thyroid hormone-receptor complex leads to activation of transcription.

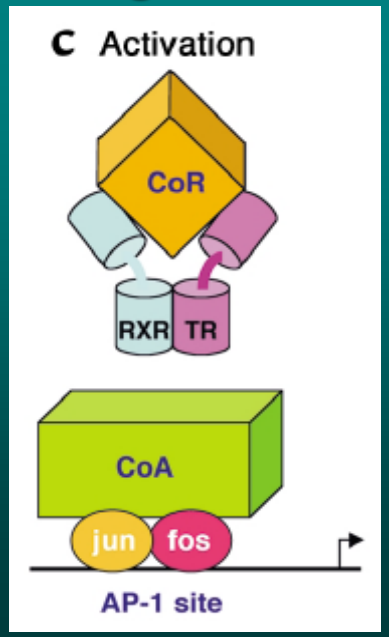


Mode of THR action

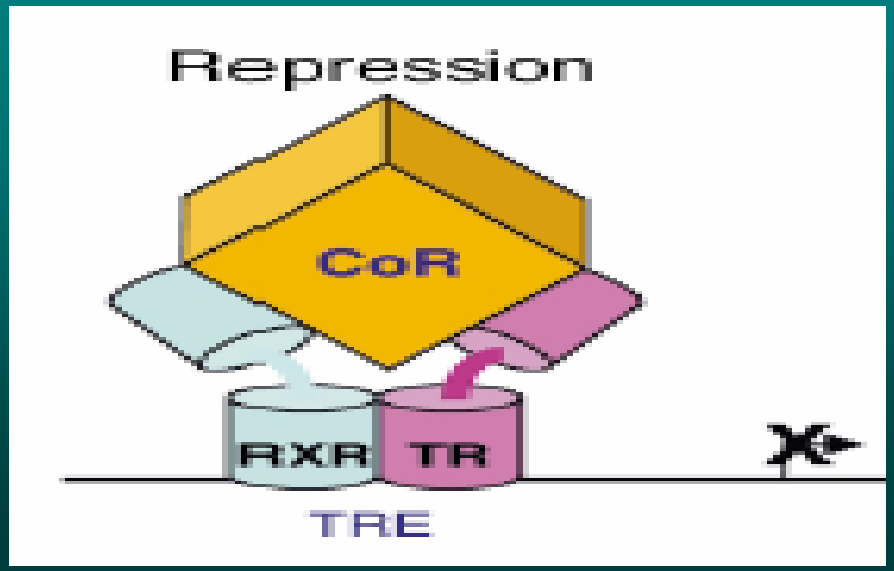
Ligand-free state:

- **The transactivation domain of the T3-free receptor, as a heterodimer with RXR, assumes a conformation that promotes interaction with a group of transcriptional corepressor molecules.**
- **A part of this corepressor complex has histone deacetylase activity (HDAC), which is associated with formation of a compact, "turned-off" conformation of chromatin.**
- **The net effect of recruiting these types of transcription factors is to repress transcription from affected genes.**





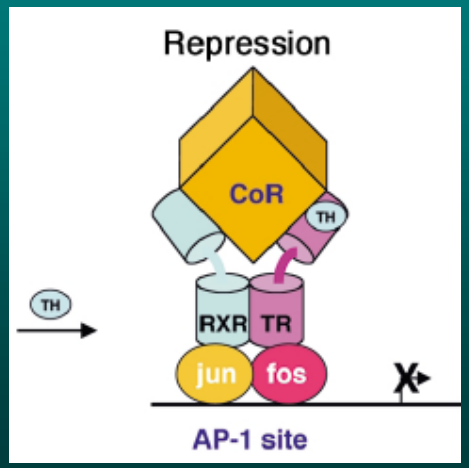
Increased by cycline D1

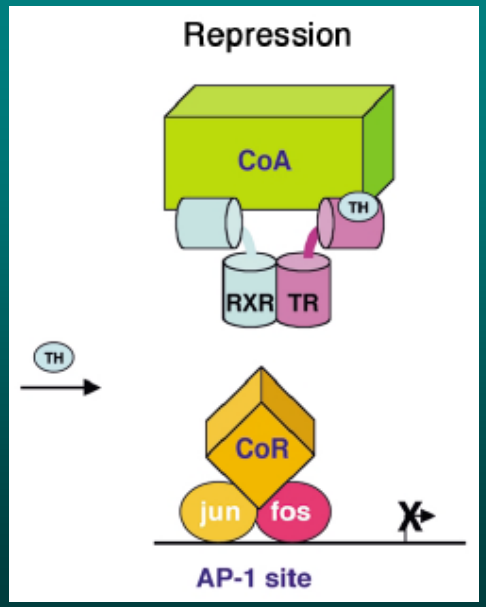


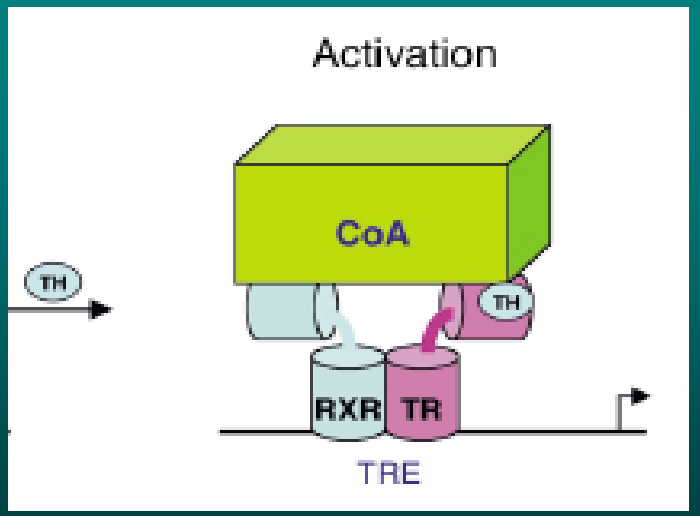
Thyroid hormone receptor

Ligand-bound state:

- **Binding of T3 to its receptor induces a conformational change in the receptor that makes it incompetent to bind the corepressor complex, but competent to bind a group of coactivator proteins.**
- **The coactivator complex contains histone transacetylase (HAT) activity, which imposes an open configuration on adjacent chromatin.**
- **The coactivator complex associated with the T3-bound receptor functions to activate transcription from linked genes.**







Reduced by p53

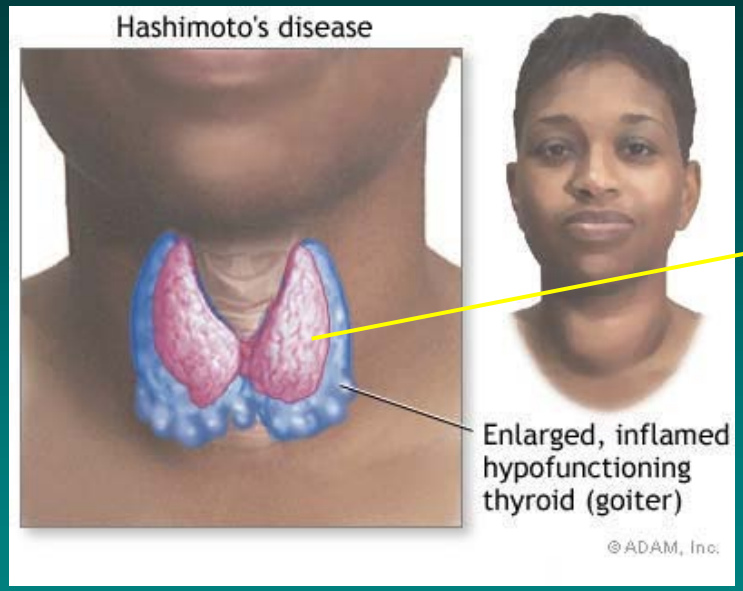
Processes modulated by THR action

Process	Factors That Stimulate or Modulated	T3 Ligand Effects	Thyroid Hormone Target(s) (*downregulates expression)	Interacting Pathways
Basal Metabolic Rate	T3, Metabolic Processes	Stimulates	Na+/K+ ATPase, SERCA-1, UCPs, LPL	Adrenergic
Adaptive Thermogenesis	Cold Exposure, Food Ingestion	Stimulates	UCP1, PEPCK	Adrenergic, Bile Acids, Gluconeogenesis
Regulation of Body Weight	Nutrient Intake	Integrates balance with nutrient intake signals	TRH*, TSH*, spot 14 (*Thrsp*), D2*	TRH, Leptin, Adrenergic, CART, neuropeptide Y, D2
Cholesterol Synthesis and Efflux	Cholesterol Levels	Promotes cholesterol synthesis, efflux	LDL-R, ABCA1	Sterol signaling (SREBP), PPARα, LXR
Fatty Acid Synthesis and Oxidation	Fat Intake, Fat Storage, Long-Chain Fatty Acids	Promotes lipolysis and β-oxidation	CPT1α	Adrenergic, PPARα, LXR
Bile Acid Synthesis	Fat Intake	Decrease (humans)	CYP7A1*(human)	TGR5, D2, FXR, PPARα
Glucose Metabolism	Carbohydrate intake, Serum glucose/insulin	Stimulates gluconeogenesis, Impairs insulin secretion	ACC1, GLUT4, ChREBP	Glucose, Insulin, PPARα, LXR, SREBP, RXR

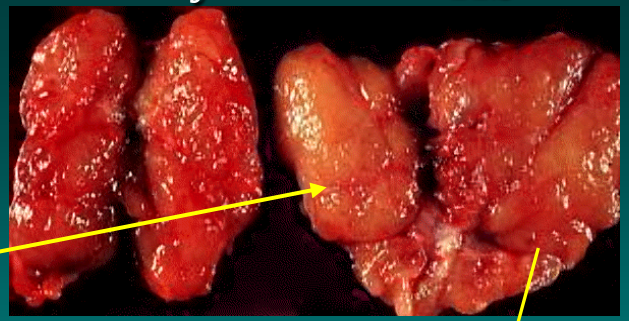
Hypothyroidism

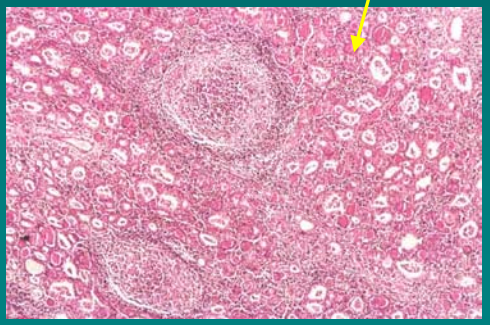
Causes:

- **Iodine deficiency**
- **Primary thyroid disease (e.g. Hashimoto's disease, autoimmune diseases leading to inflammation)**



healthy HS

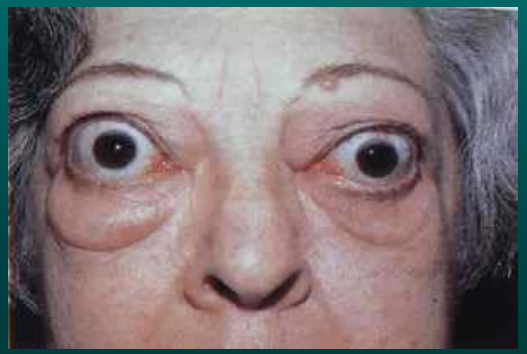




Hyperthyroidism

Causes:

- **Too high secretion of thyroid hormones (less common than hypothyroidism).**
- **Graves disease, an autoimmune disease in which antibodies bind to and activate the thyroid-stimulating hormone receptor, leading to continual stimulation of thyroid hormone synthesis.**
- **Thyroid cancer.**
- **Hamburger thyroxicosis (rare ☺).**



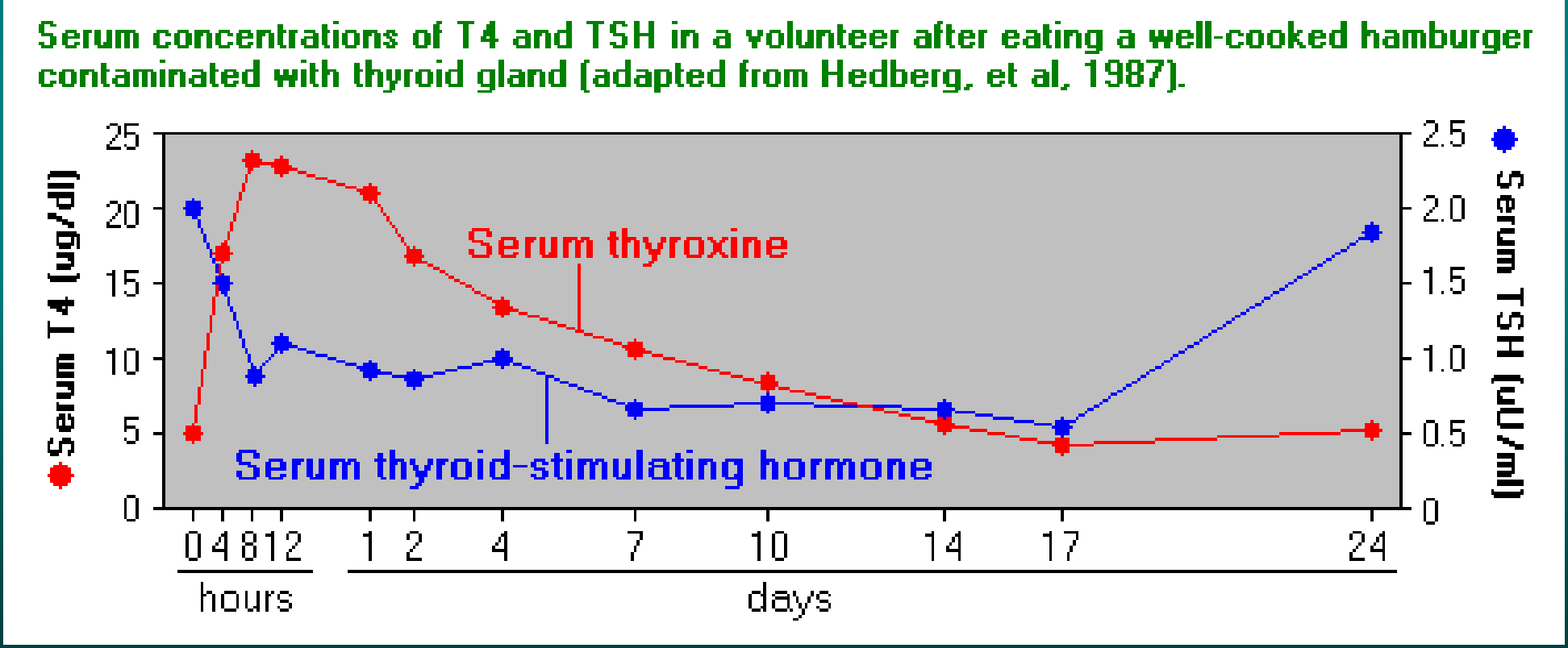
Exophthalmos

Hamburger thyroxicosis

- Thyroid hormones are orally active, which means that consumption of thyroid gland tissue can cause thyrotoxicosis, a type of hyperthyroidism.
- Several outbreaks of thyrotoxicosis have been attributed to a practice (banned), where meat in the neck region of slaughtered animals is ground into hamburger. Because thyroid glands are reddish in color and located in the neck, it's not unusual to get thyroid glands into hamburger or sausage.
- People, and presumably pets, that eat such hamburger can get dose of thyroid hormone sufficient to induce disease.
- It has been described (1987) an outbreak of thyrotoxicosis in Minnesota and South Dakota that was traced to thyroid-contaminated hamburger. A total of 121 cases were identified in USA.
- The patients complained of sleeplessness, nervousness, headache, fatique, excessive sweating and weight loss.

Hamburger thyroxicosis

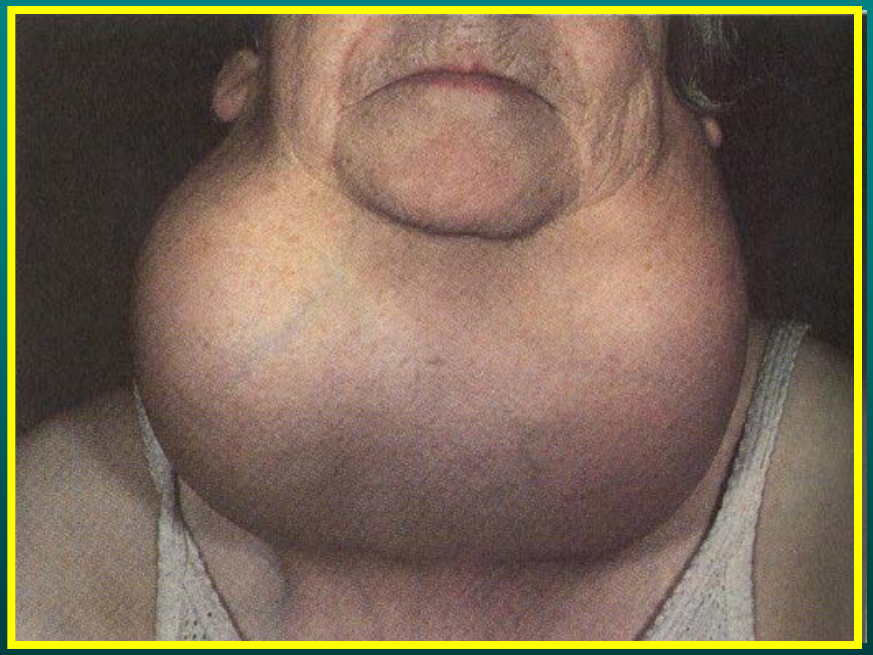
• Serum concentrations of thyroxine and thyroid-stimulating hormone in a volunteer that consumed a *well-cooked*, 227 g hamburger prepared from the contaminated meat. Note how TSH levels were suppressed during the time when thyroxine (T4) concentrations were elevated.



Mutations in THR

- Mutations in the ligand-binding domain of THR can lead to generalized resistance to thyroid hormones.

- Clinically, such individuals show a type of hypothyroidism characterized by goiter, elevated serum concentrations of T3 and thyroxine and normal or elevated serum concentrations of TSH.



Thyroid hormone and fetal development

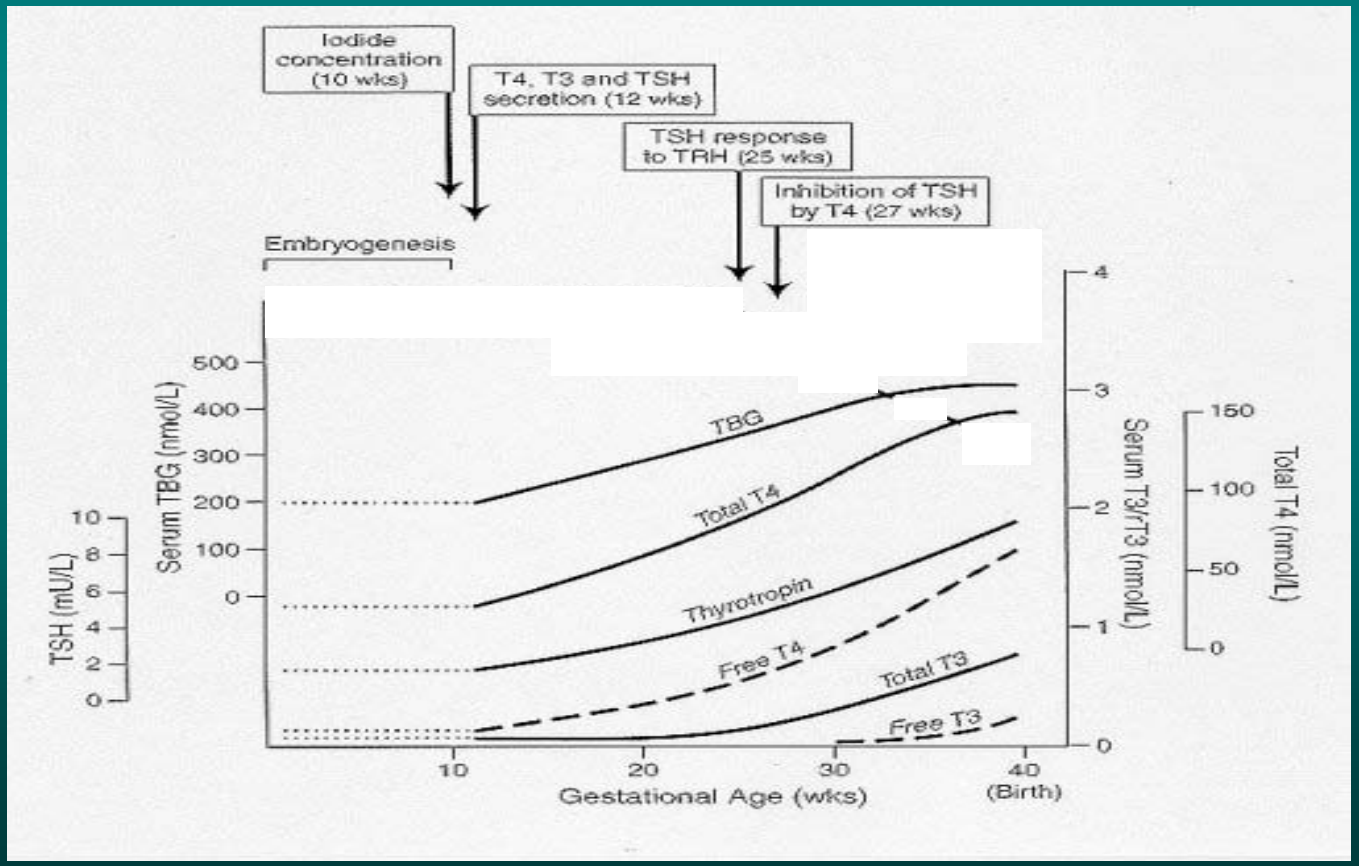
- Thyroid hormones are critical for development of the fetal and neonatal brain, as well as for many other aspects of fetal growth. Hypothyroidism in either the mother or fetus frequently results in fetal disease; in humans, this includes a high incidence of mental retardation.

- The fetus has two potential sources of thyroid hormones - it's own thyroid and the thyroid of it's mother.

- Human fetuses acquire the ability to synthesize thyroid hormones at 10 to 12 weeks of gestation.

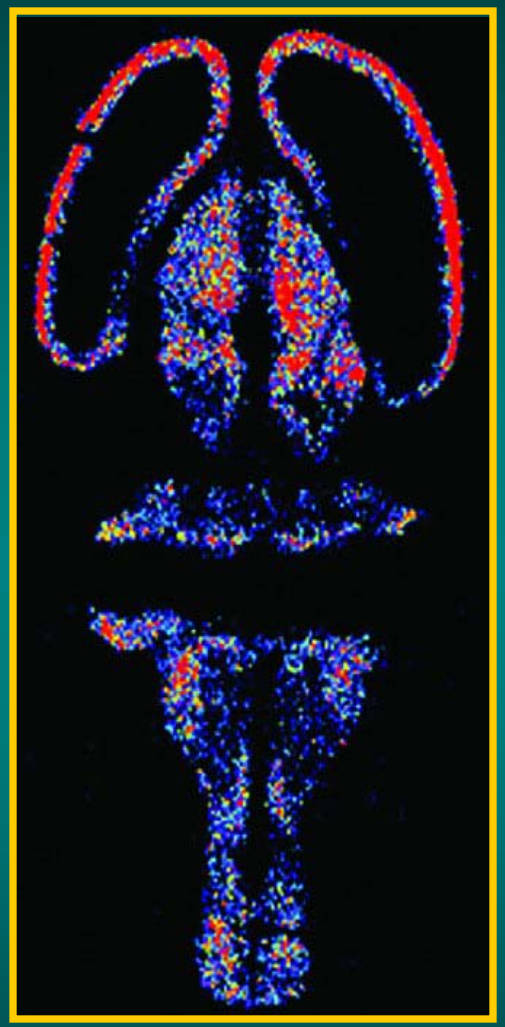
- There is substantial transfer of maternal thyroid hormones across the placenta.

- Additionally, the placenta contains deiodinases that can convert T4 to T3.

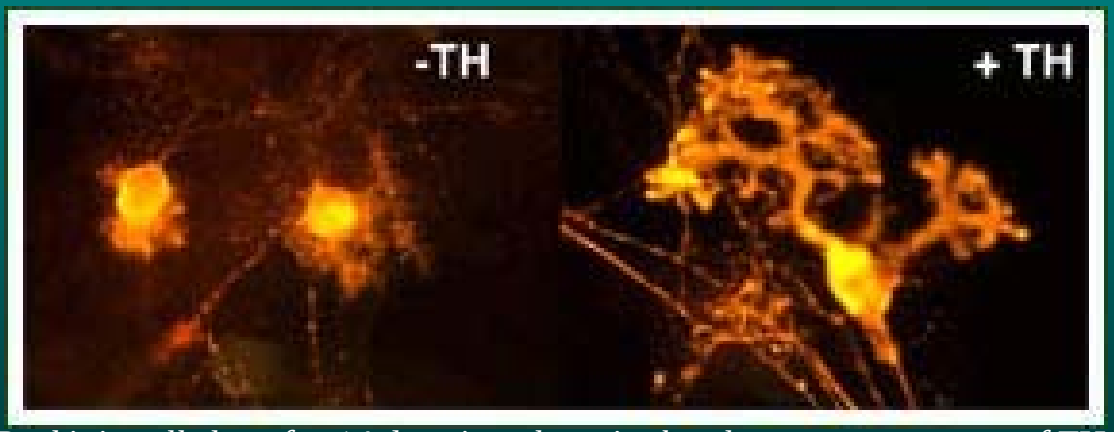


Thyroid hormone and fetal brain development

- In 1888 the Clinical Society of London issued a report underlining the importance of normal thyroid function on development of the brain.
- Thyroid hormones appear to have their most profound effects on the terminal stages of brain differentiation, including synaptogenesis, growth of dendrites and axons, myelination and neuronal migration.
- The promoter of the myelin basic protein gene is directly responsive to thyroid hormones and contains thyroid hormone response element.



A fetal rat brain produced by in situ hybridization with a probe for the rat thyroid hormone receptor.



Purkinje cells kept for 14 days in culture in the absence or presence of TH . TH induced dramatic increase in Purkinje cell dendritic branching.

Thyroid hormone and fetal development

Thyroid deficiency is known to affect fetal development:

* Isolated maternal hypothyroidism: Maternal hypothyroidism typically is not a significant cause of fetal disease because it usually is associated with infertility. When pregnancy does occur, there is increased risk of intrauterine fetal death and gestational hypertension.

* Subclinical hypothyroidism: mild maternal hypothyroidism, diagnosed only retrospectively from banked serum, may adversely affect the fetus, leading in children to such effects as slightly lower performance on IQ tests and difficulties with schoolwork. The most common cause of subclinical hypothyroidism is autoimmune disease, and it is known that anti-thyroid antibodies cross the human placenta.

* Isolated fetal hypothyroidism: failure of the fetal thyroid gland to produce adequate amounts of thyroid hormone. Most children are normal at birth, because maternal thyroid hormones are transported across the placenta during gestation. What is absolutely critical is to identify and treat this condition very shortly after birth. If not, the child will become permanently mentally and growth retarded (cretinism - a marked impairment of the capacity for abstract thought, with preserved vegetative, personal, social functions and memory. Very often associated with deafness).

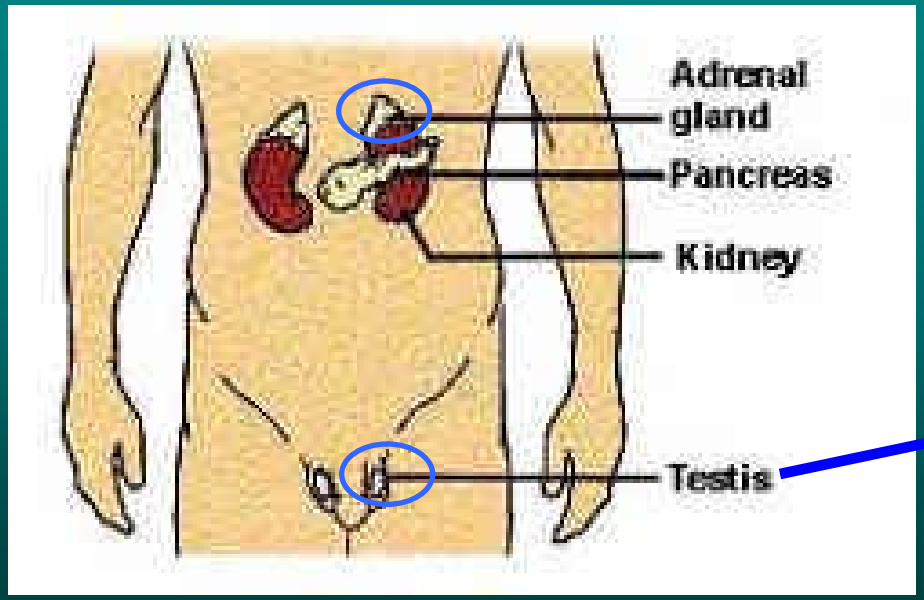
Isolated fetal hypothyroidism:

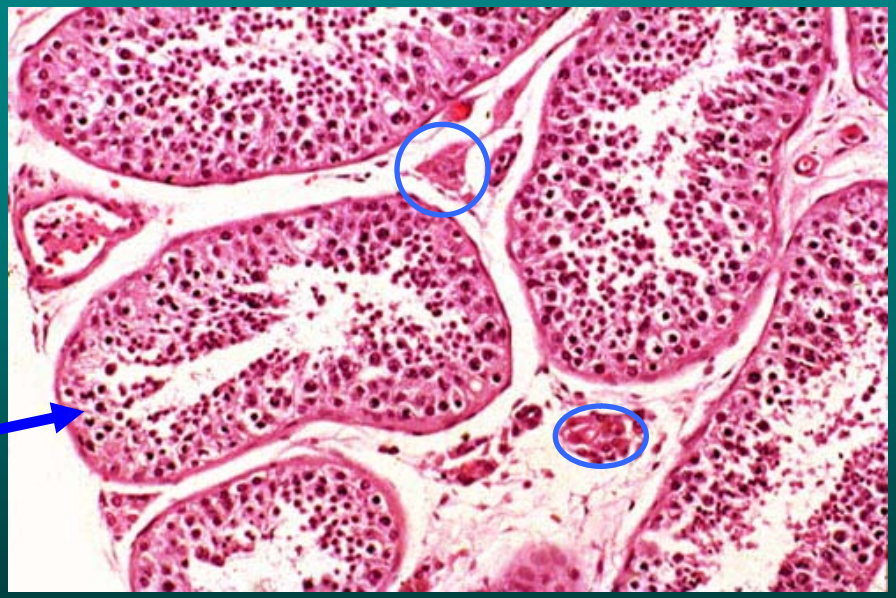
few months

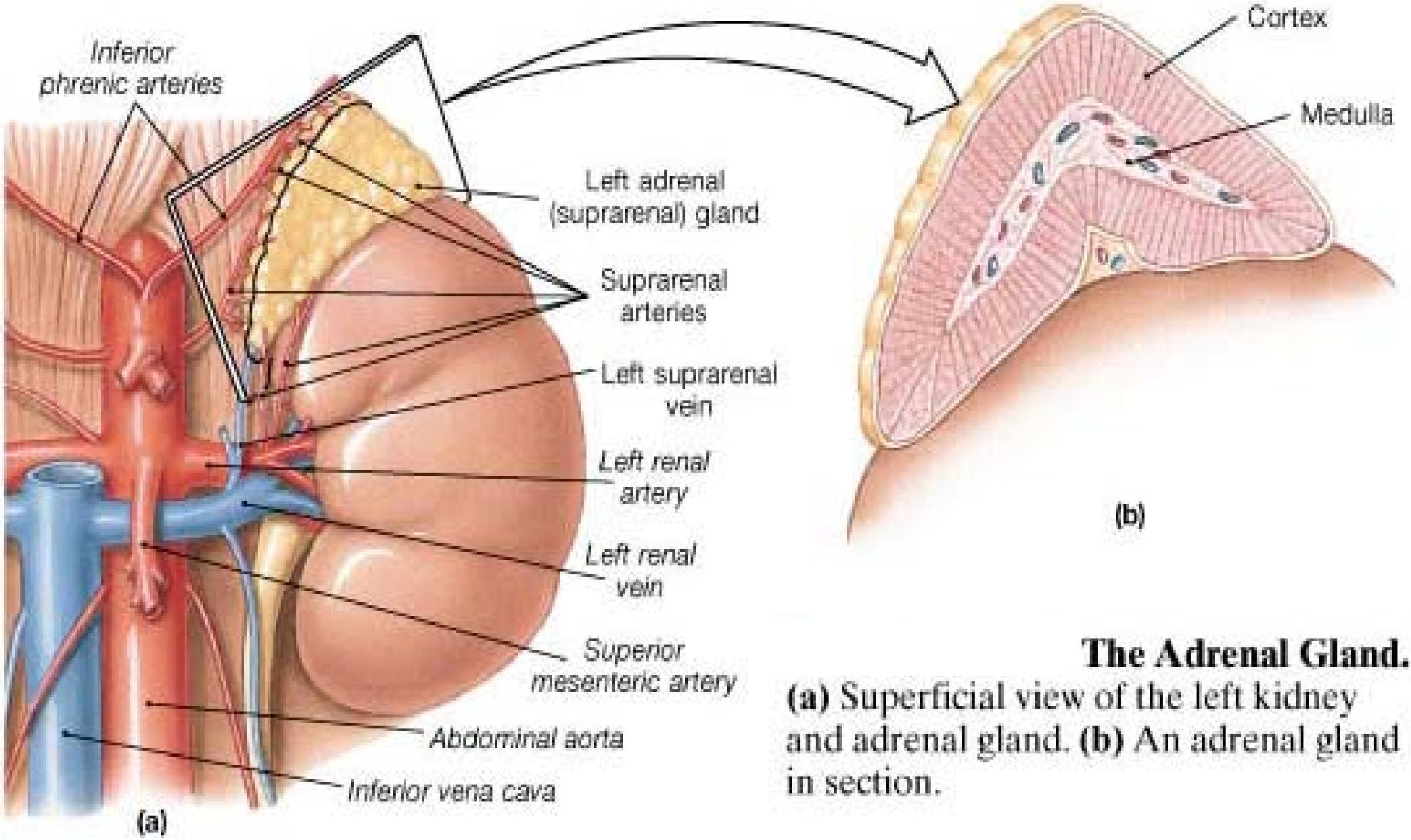
thyroid hormone replacement

Androgens – general characteristics

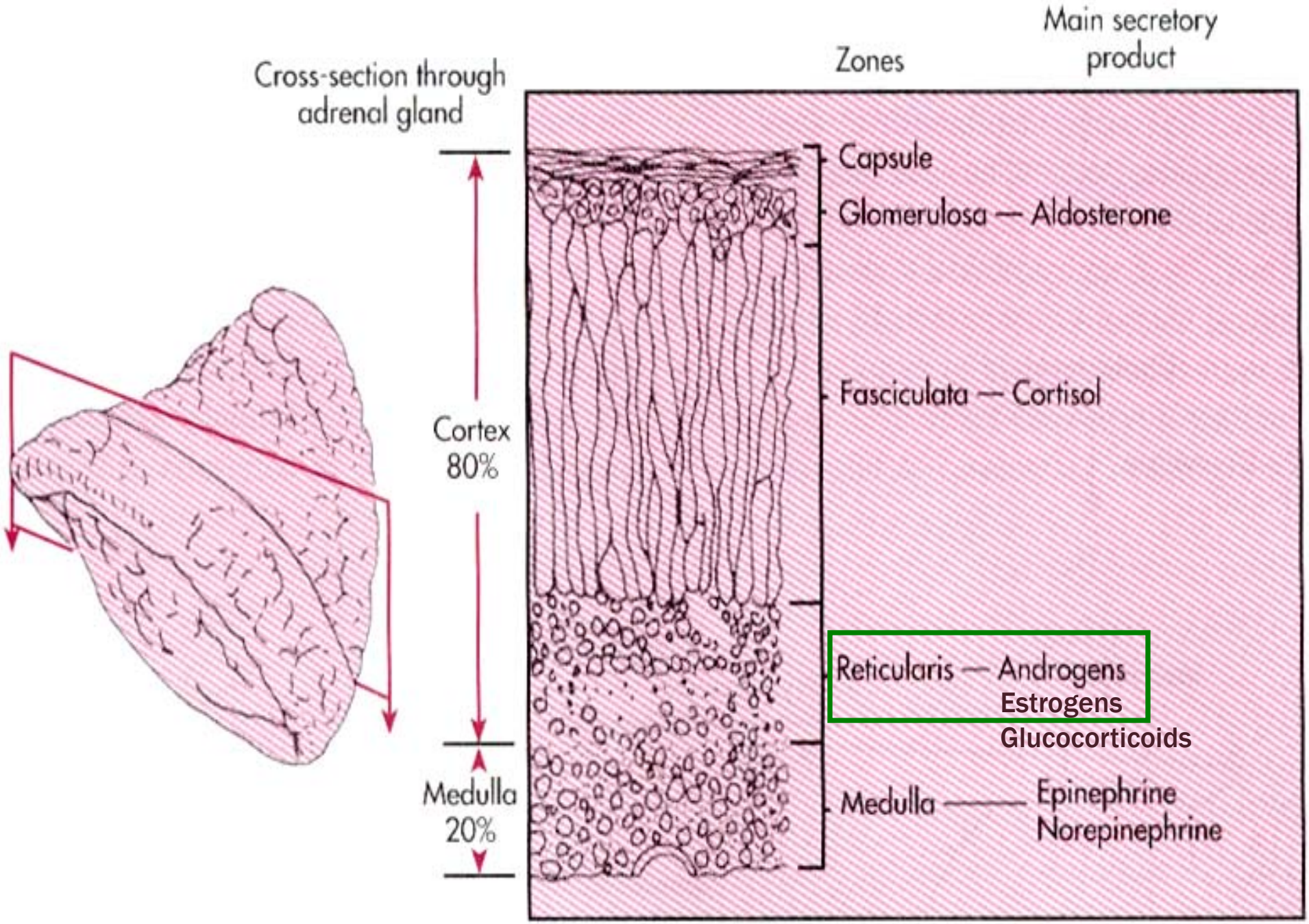
- The most abundantly synthetized ligand of androgen receptors (7 mg/day) is testosterone. It is produced by the **Leydig cells** in response to luteinizing hormone produced in the pineal gland.





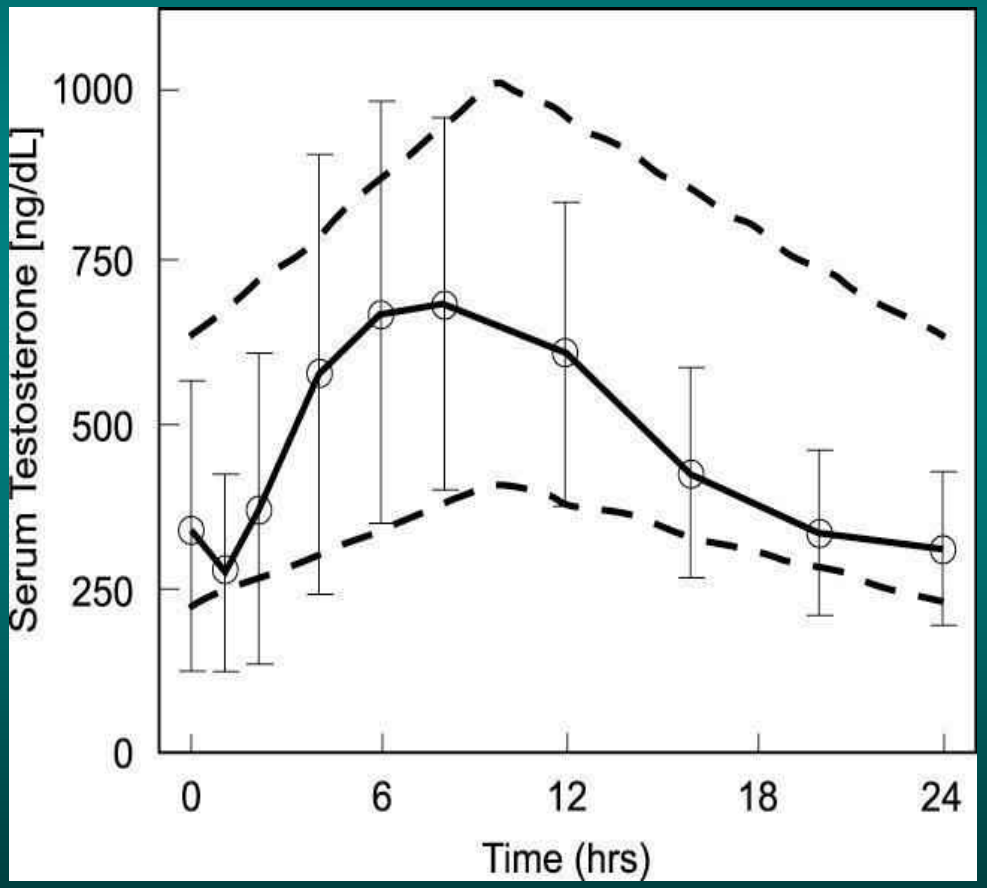


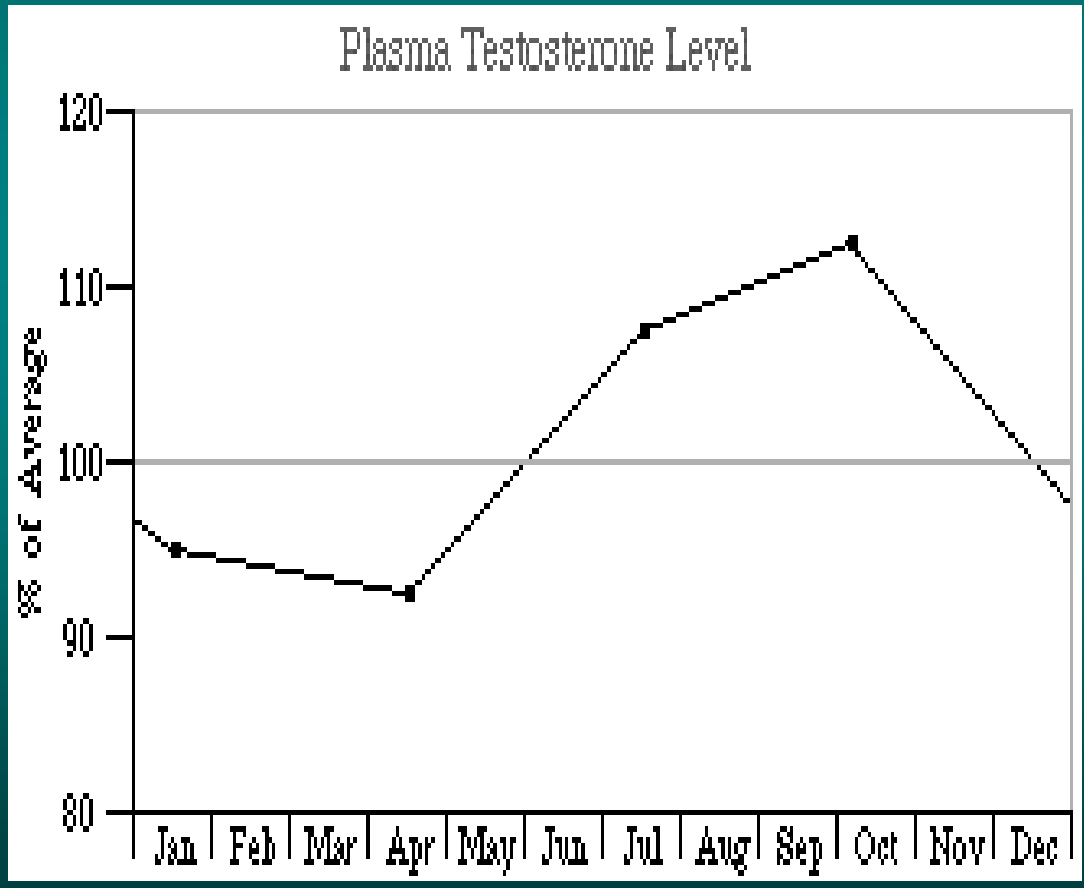
The Adrenal Gland.
(a) Superficial view of the left kidney and adrenal gland. **(b)** An adrenal gland in section.


Cross-section through adrenal gland
Zones
Main secretory product
Capsule
Glomerulosa — Aldosterone
Fasciculata — Cortisol
Reticularis — Androgens
Estrogens
Glucocorticoids
Medulla — Epinephrine
Norepinephrine
Cortex 80%
Medulla 20%

Androgens – general characteristics

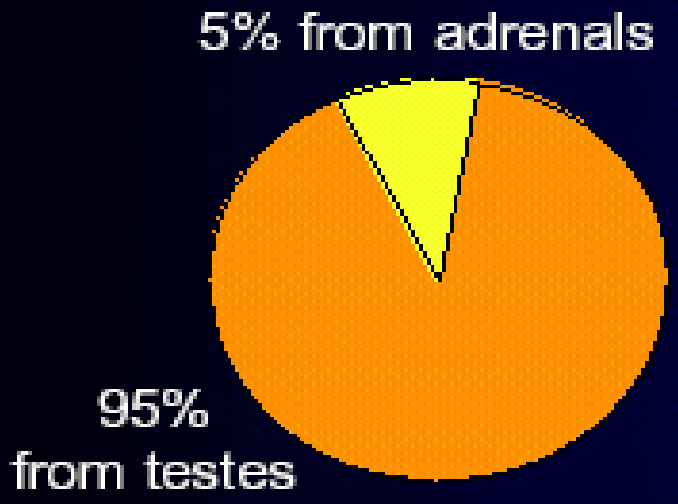
- Production of testosterone changes periodically with circadian and seasonal peaks.



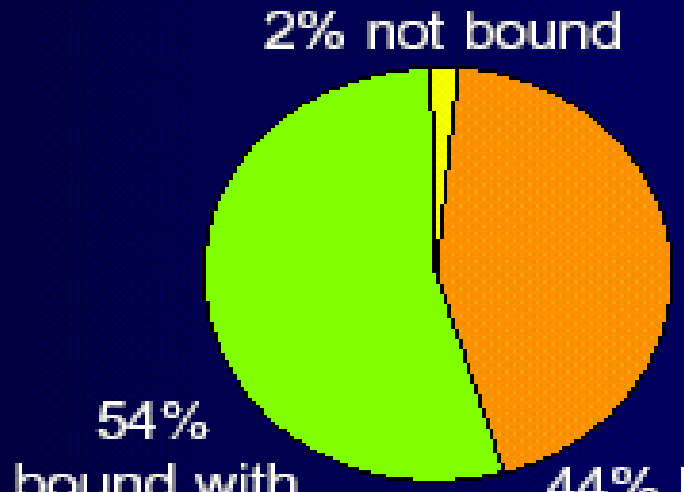


Testosterone

Origin



Distribution

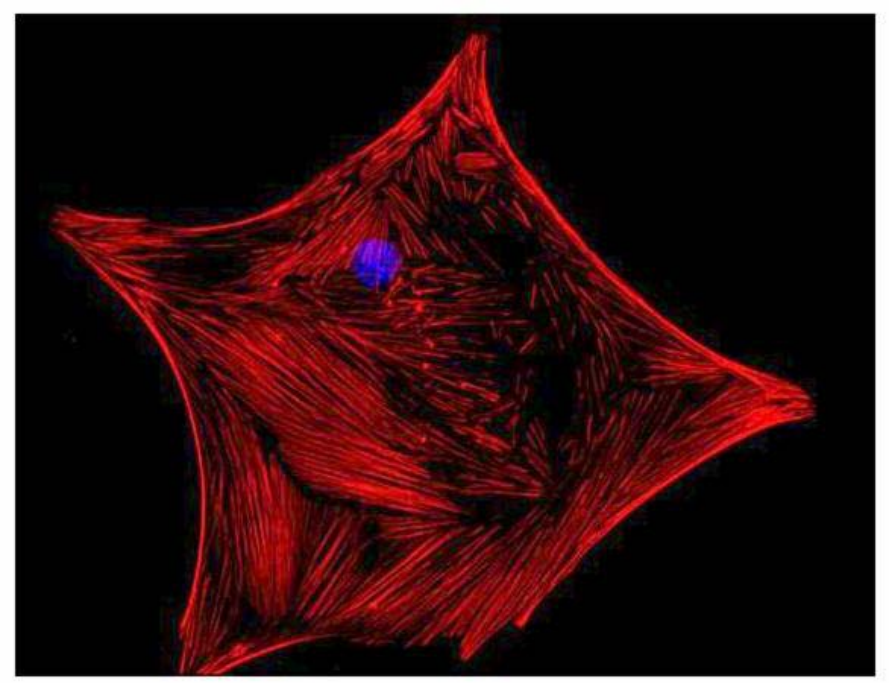


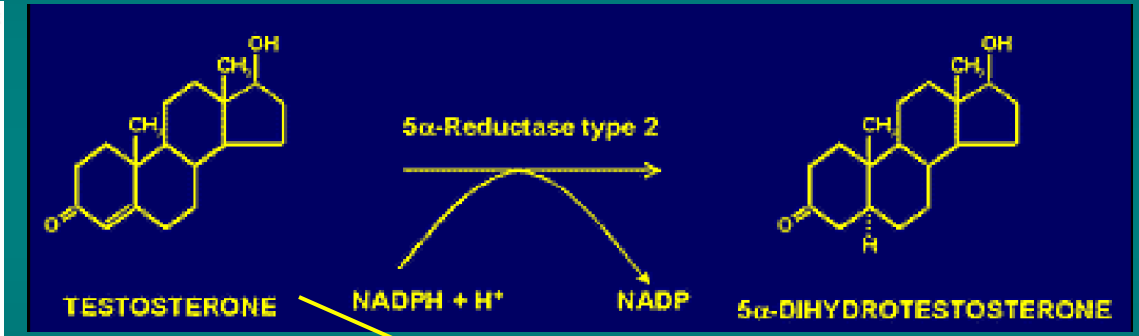
Source: Adapted from Coffey DS. In: Walsh PC, et al, eds. *Campbell's Urology*. 6th ed. 1992:221-266.

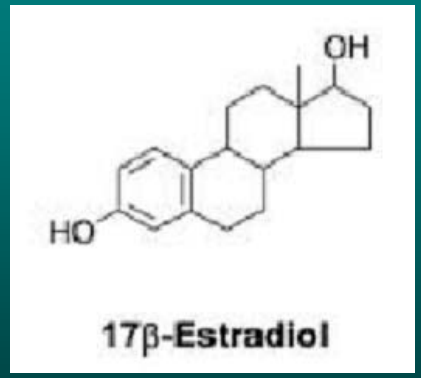
Androgens – general characteristics

- In the target cells testosterone is changed into 2 active metabolites:

  * dihydrotestosterone (DHT) (enzyme: 5α-reductase, expressed in 2 isoforms, I i II)
  * estradiol (enzyme: aromatase)

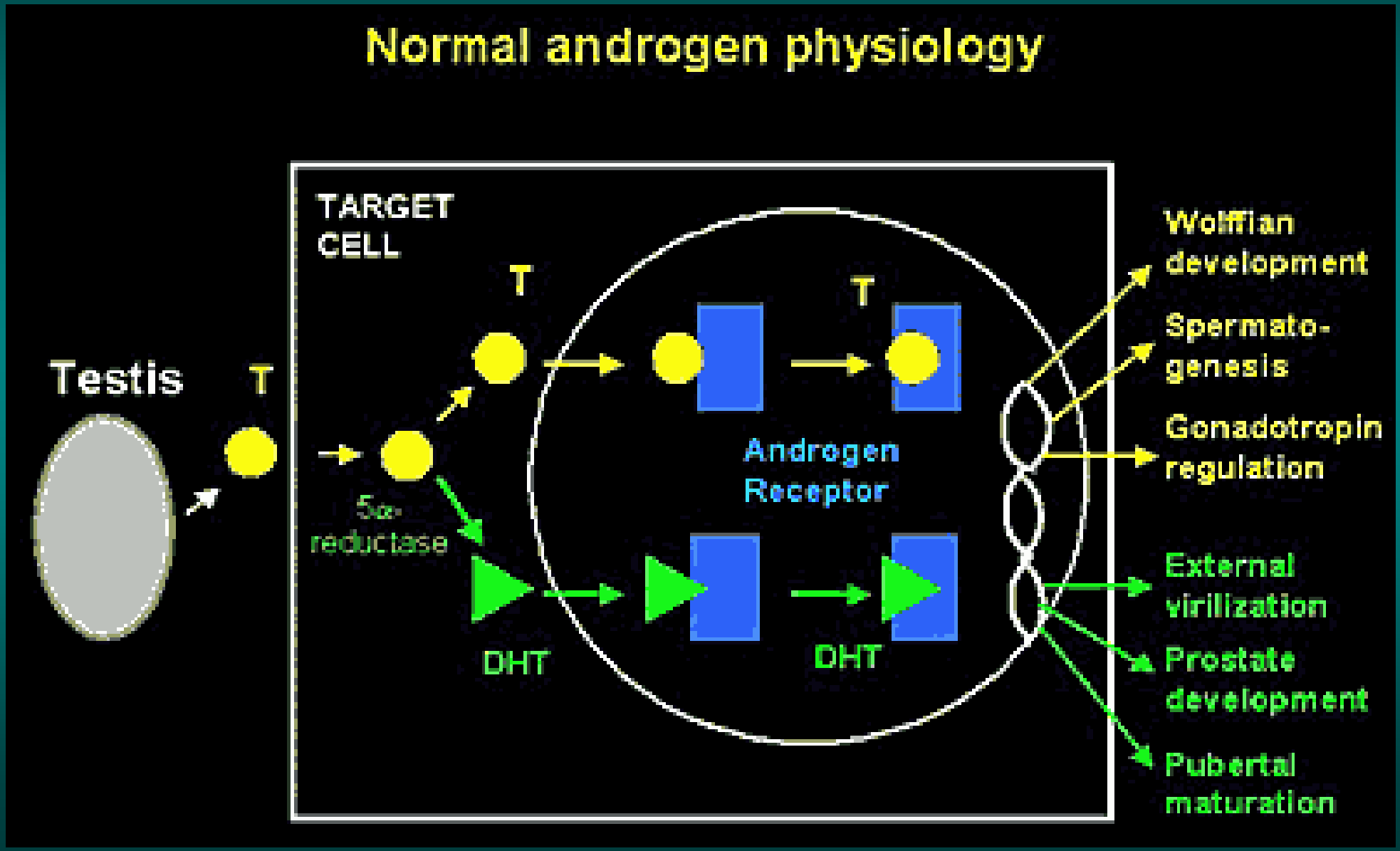






Mouse Leydig cell in primary culture.
Actin fibers stained with labelled-phalloidin (red), DNA (blue).

Respective roles of testosterone (T) and dihydrotestosterone (DHT) in sex differentiation



5α-reductase deficiency:

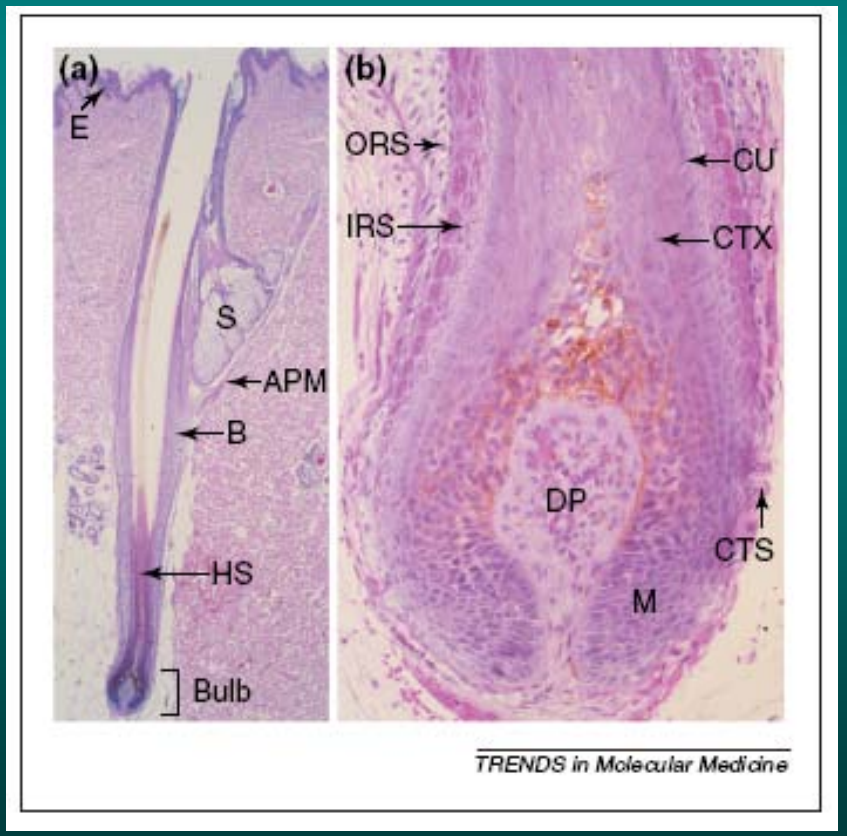
* It may lead to male pseudohermaphroditism, because there is impaired production of DHT from testosterone (testosterone production is normal).

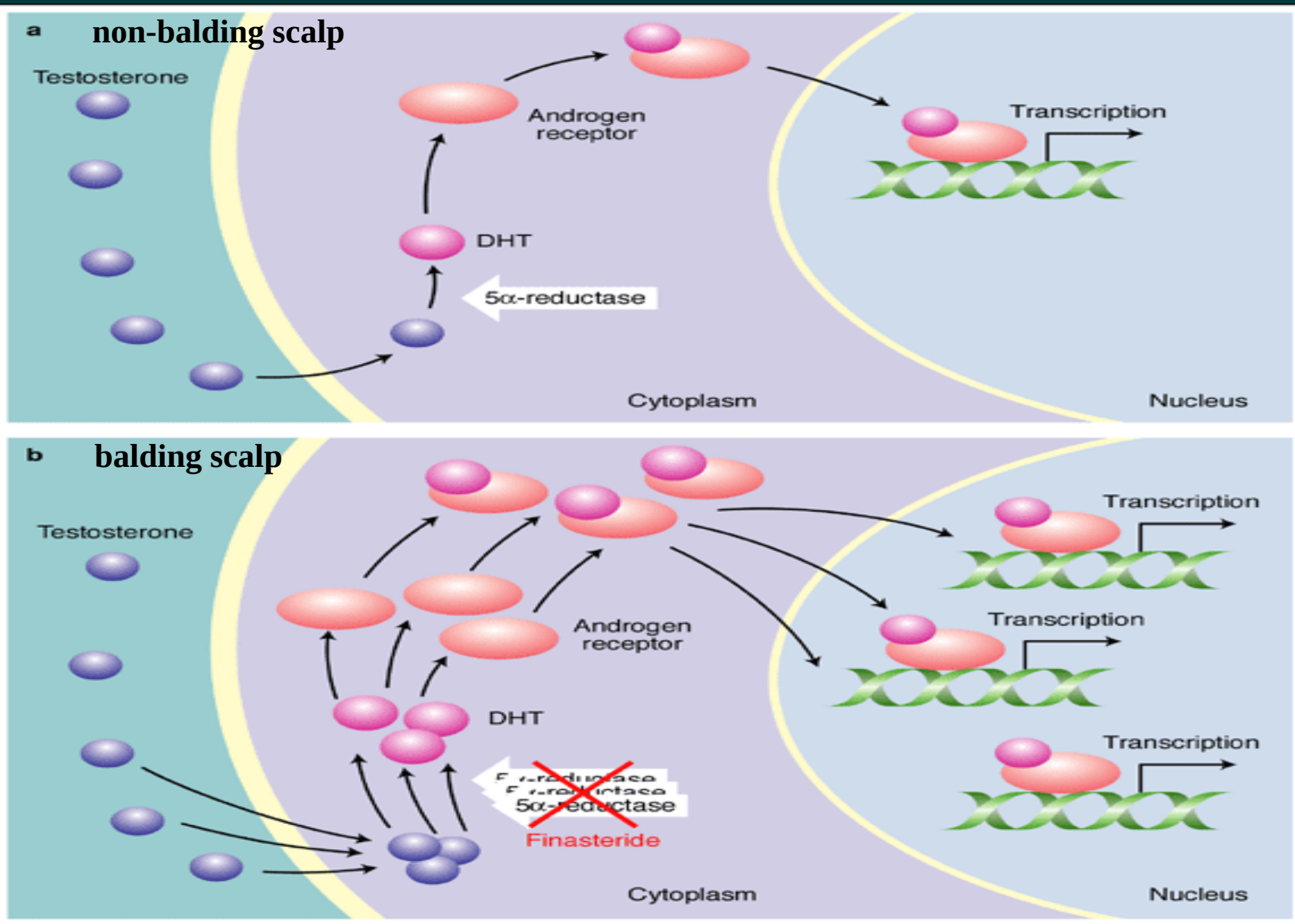
* Type of development (appearence, behavior) is typical for men.

* As the androgen receptors function normally, testosterone is able to bind to them and provide normal sexual function with adequate libido, erectile function, and spermatogenesis, but dihydrotestosterone production is severely limited in prostate and scalp, with low circulating levels.

* The affected individuals have no facial or body hair, do not show temporal hairline recession or vertex balding, have normal scalp hair, and their prostate gland remains small (thus, they are infertile).

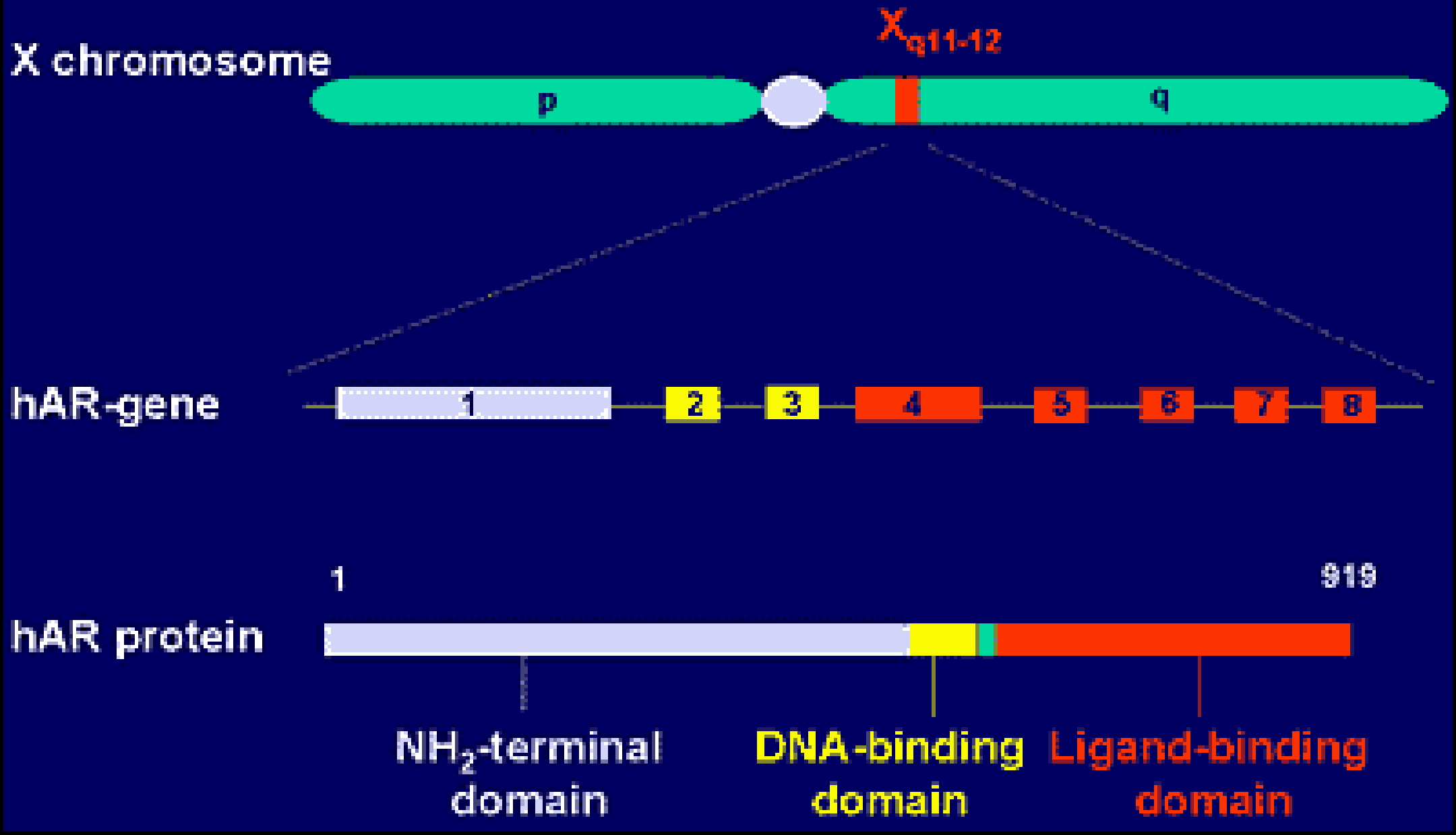
High expression of 5a reductase



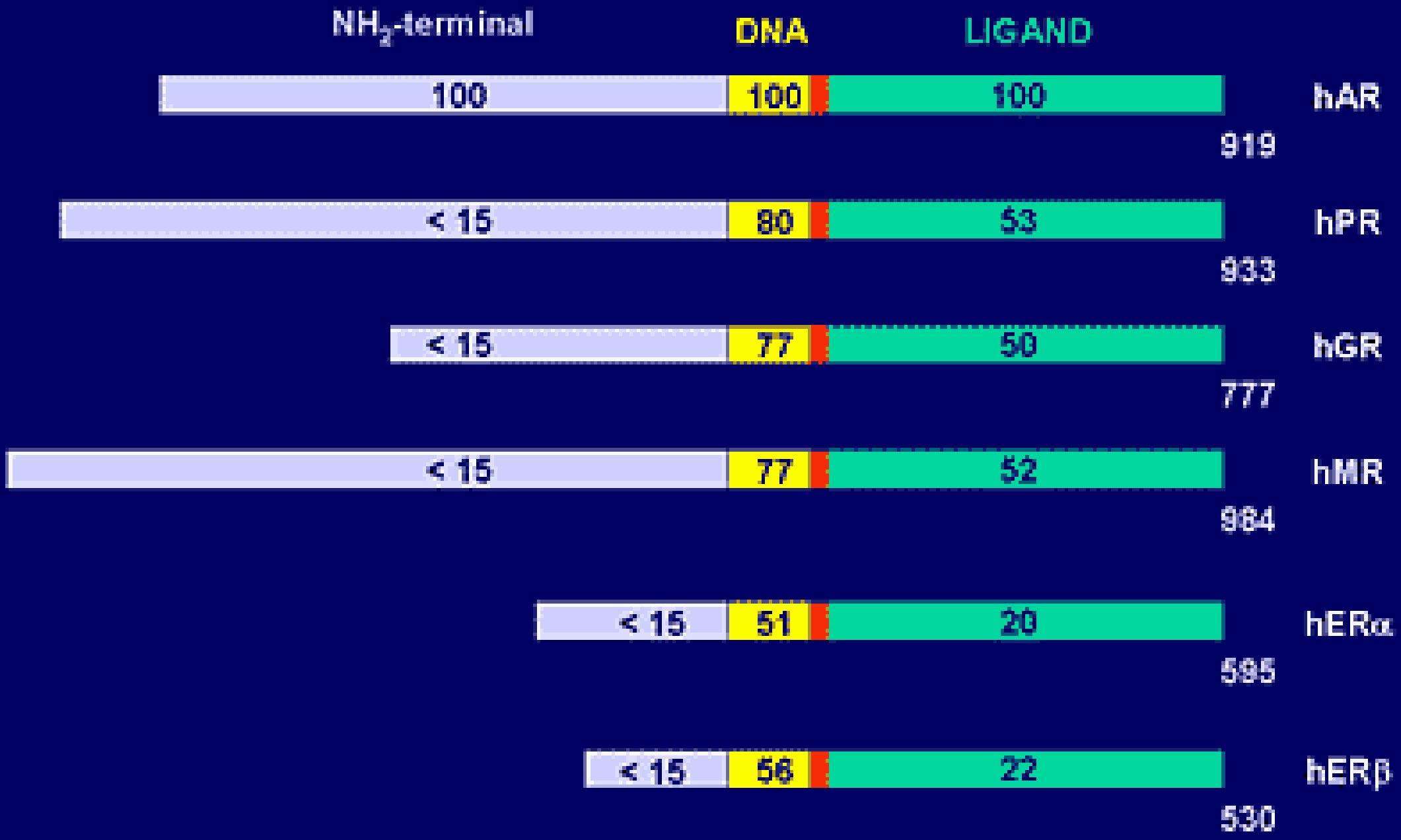


Involvement of androgens and the androgen receptor in male-pattern baldness

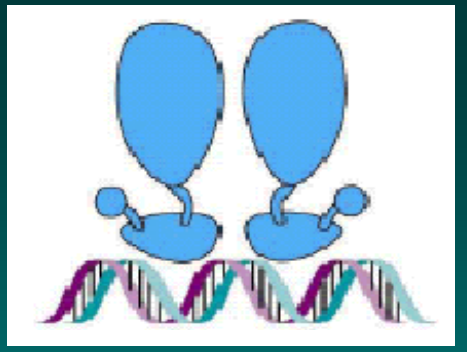
Human Androgen Receptor Gene: structural organization and protein



Sequence homologies between Steroid Hormone Receptors



AR – androgen receptors



- AR was cloned in 1988. There are isoforms of AR (98.4-100 kDa).

- Different sizes of AR proteins result from the polymorphism of glycine-reach sequence (GGC) or glutamine-reach sequence (GAC) at the N-terminus.

- Function of these repetition is not fully recognized, but **elongated GAC fragment decreases transcriptional activity of AR protein.**

- N-terminal repeats of GAC are shorter in the primates phylogenetically more distant from human.

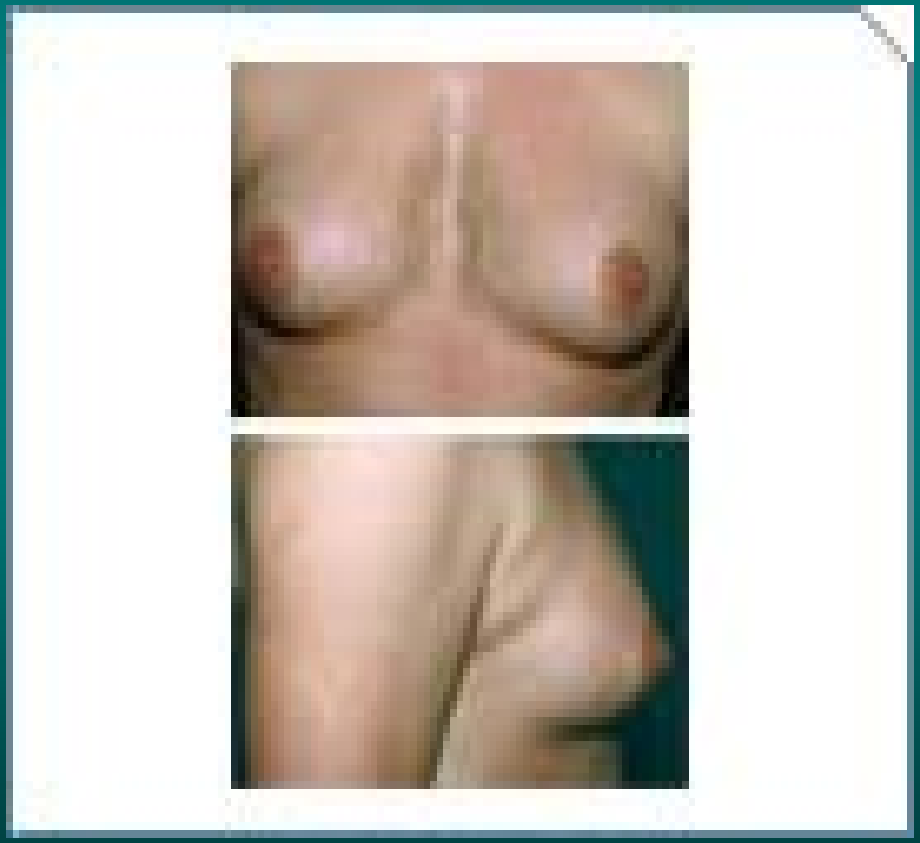
AR – androgen receptors

- Additionally, shorter AR isoform (87 kDa) can be produced as a result of start of translation from an internal metionine, but the role of this protein, whose activity in vitro is low, is not characterized.

- Point mutation in AR may result in acquiring the sensitivity of AR protein to the other ligands (including anti-androgens) or to decreased sensitivity to androgens. They can lead to **Reifenstein's syndrome**

- Symptoms of insensitivity to androgens are:

* gynecomastia,
* atrophy of testes,
* oligosperm or azoosperm,
* increased level of gonadotropin
* absence of sense of smell



Gynecomastia in a man with Reifenstein's syndrome

Kennedy's Syndrome

- Neurogenerative disease (described in 1911 by Dr. Foster Kennedy) manifested with:

  * decreasing sensitivity to androgens in adult men
  * contineous weakness and atrophy of muscle (e.g. facial).

- Symptoms result from lost of motoric neurons. The most pronounced weakness is observed in muscles of face and tongue. Disease starts from proximal muscle in the third to fifth decade and begins from:

  * weakness of facial and arm muscles,
  * tremor of hands,
  * increased level of kreatinin kinase.

- Perhaps the longer polyglutamine CAG fragment at N-terminal AR is associated with earlier onset of the disease.

- Women with long CAG fragment in AR do not show any clinical symtoms, but they have some subtle neurological changes which can be detected during detailed examination.

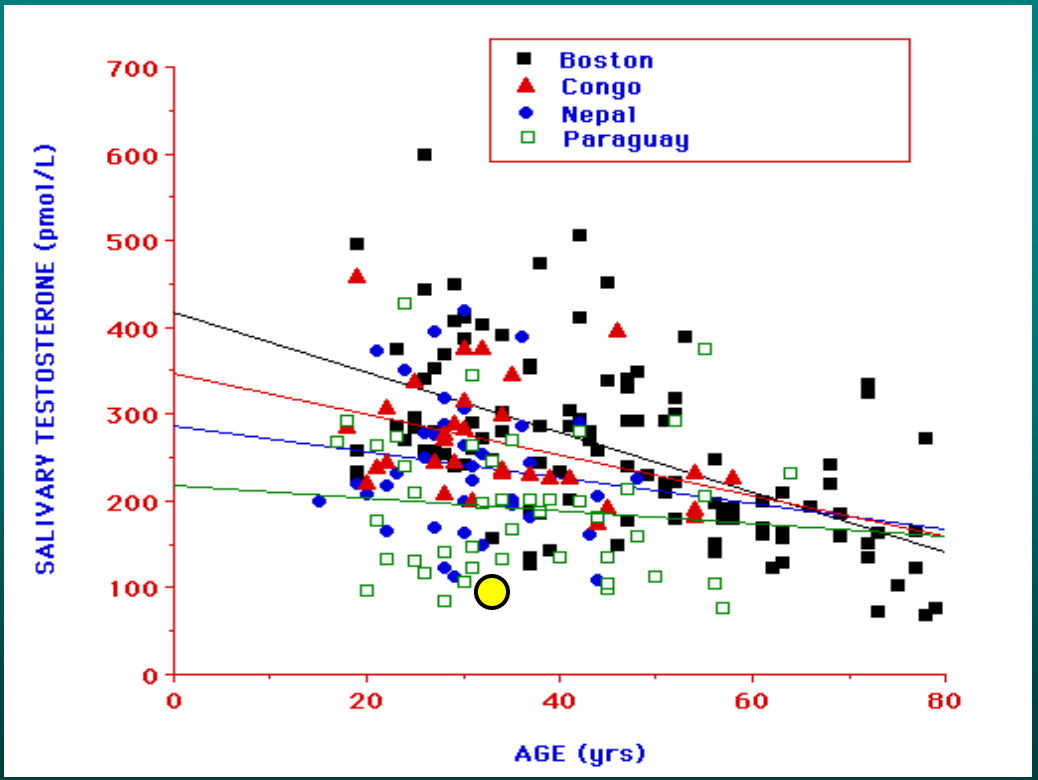
Testosterone – changes with age

- Level of testosterone gradually decreases with age, but the clinical significance of this decrease is not clear.

- No data indicates the correlation between the level of testosterone and sexual behavior, unless the changes are within the physiological range.

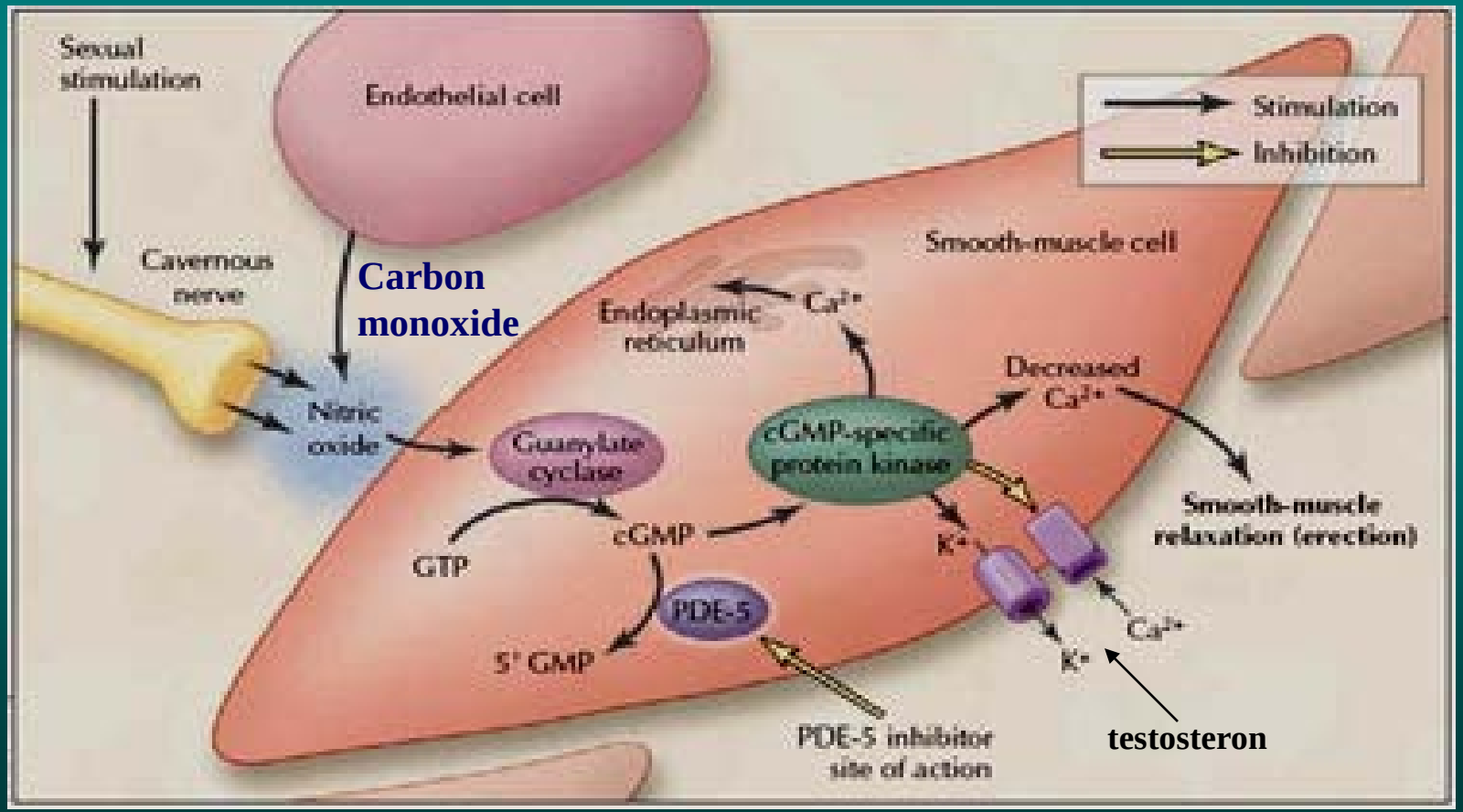
- In men with healthy gonads, but with erectile dysfuctions, supplementation with testosterone does not give any benefits. In hypogonadal men it can give the increase in ejaculation frequency, but does not improves erection itself.

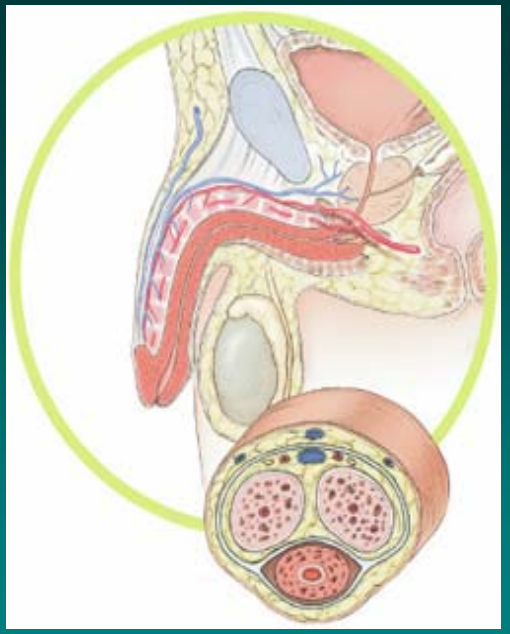
- AR expression starts to decrease from the age 20-30.

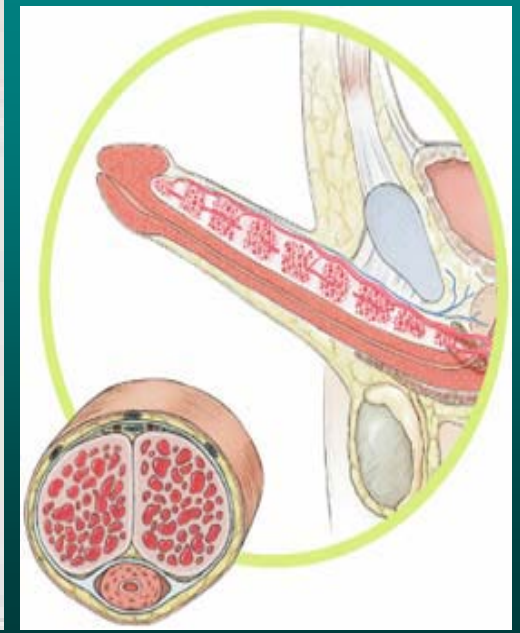


• Nitric oxide is released from nerve endings or from endothelial cells, and stimulates cGMP production. This induces smooth-muscle relaxation by reducing the calcium ion concentration, thus producing an erection.

• The enzyme PDE-5 reverses this cascade of events by rapidly converting cGMP to GMP. All of the PDE-5 inhibitors (e.g. sildenafil), work to inhibit this enzyme, thereby continuing smooth-muscle relaxation and prolonging an erection.





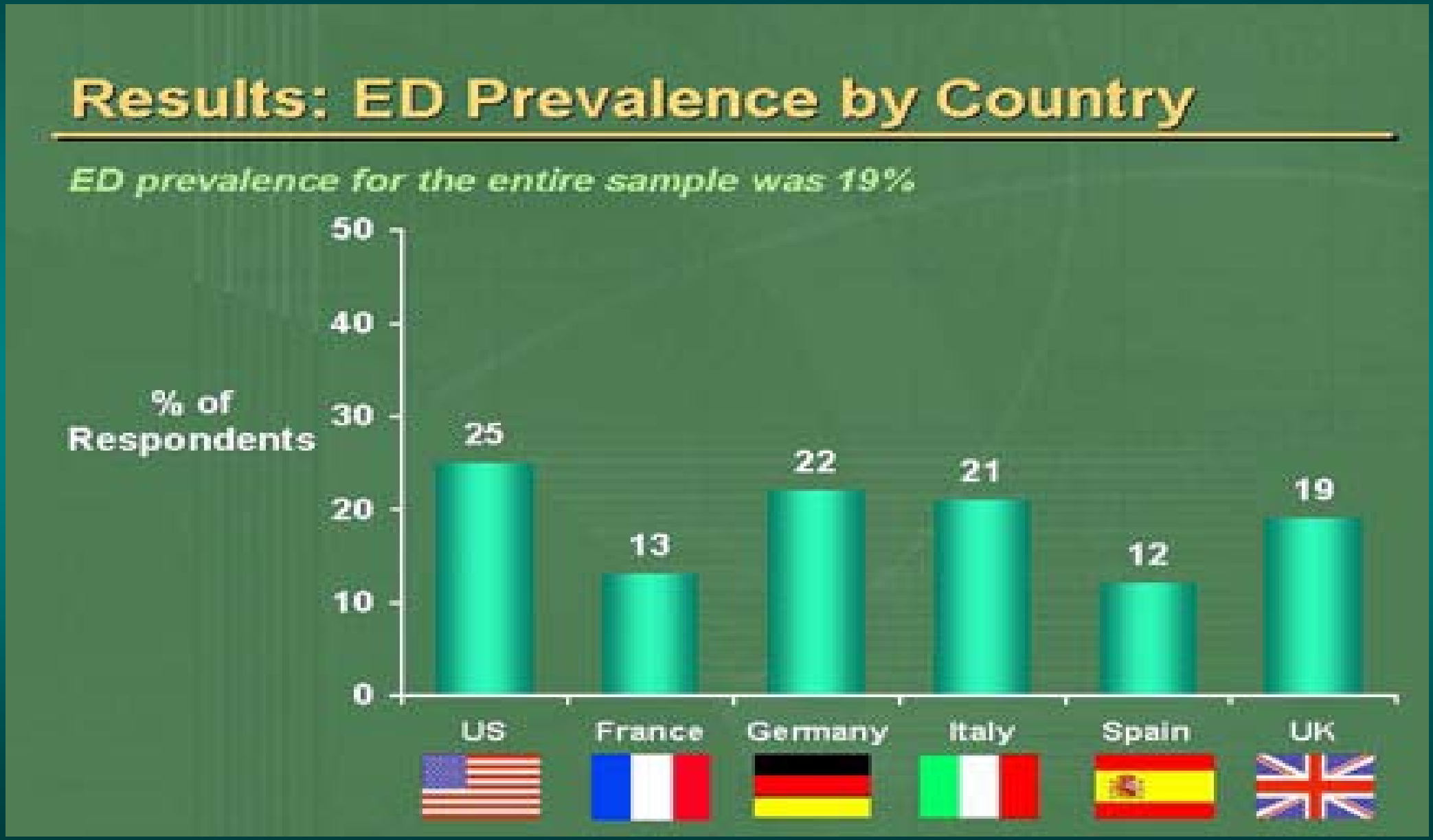


Epidemiology

- Decline in sexual function with age
- 1290 subjects (40-70 yrs)
  - 9.6% complete ED (5.1% at 40 yrs to 15% at age 70)
  - 25.2% moderate ED
  - 17.2% minimal ED

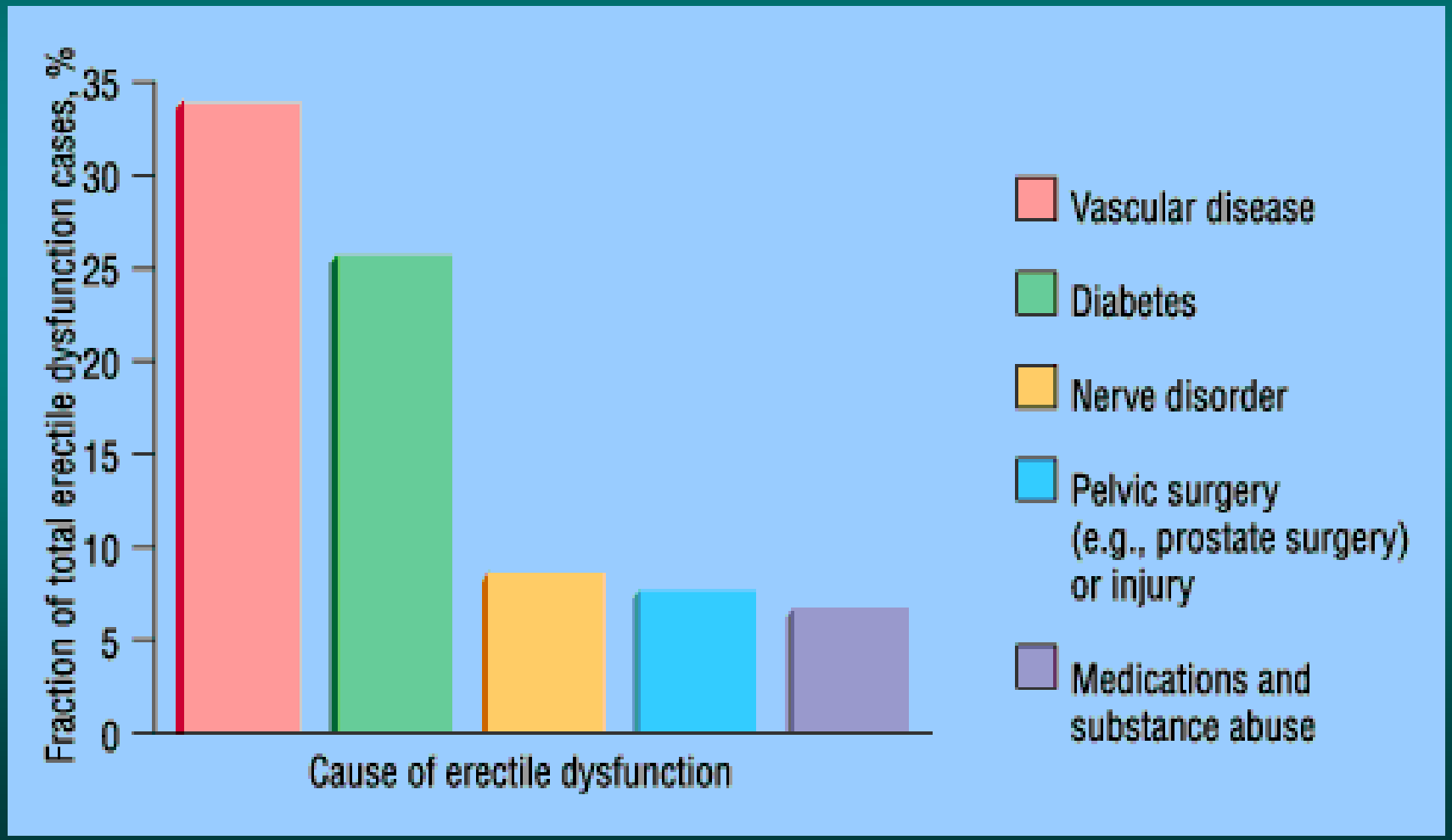
52%

Erectile Dysfunction (ED)

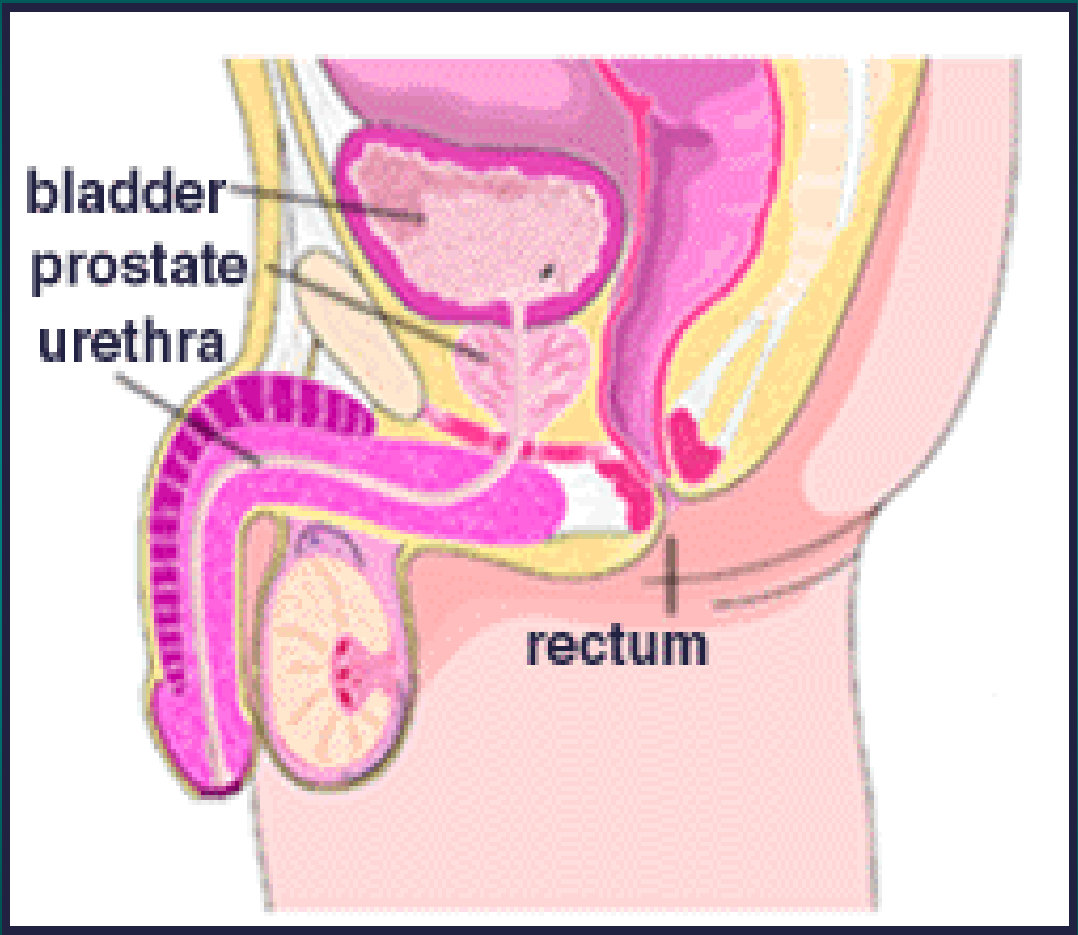


Erectile Dysfunction (ED)

- ED, once thought to be psychogenic
- Later, considered androgenic
- Now, found to be predominately vasculogenic



Prostate gland

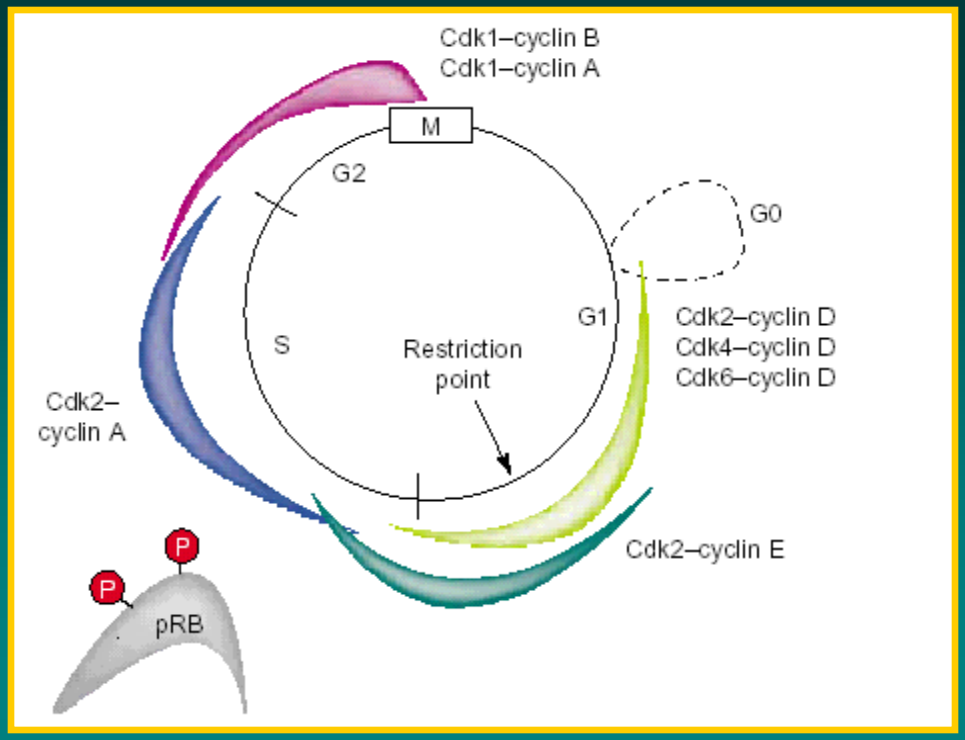


- a sex gland in men about the size of a walnut, surrounds the neck of the bladder and urethra.

- partly muscular and partly glandular, with ducts opening into the prostatic portion of the urethra.

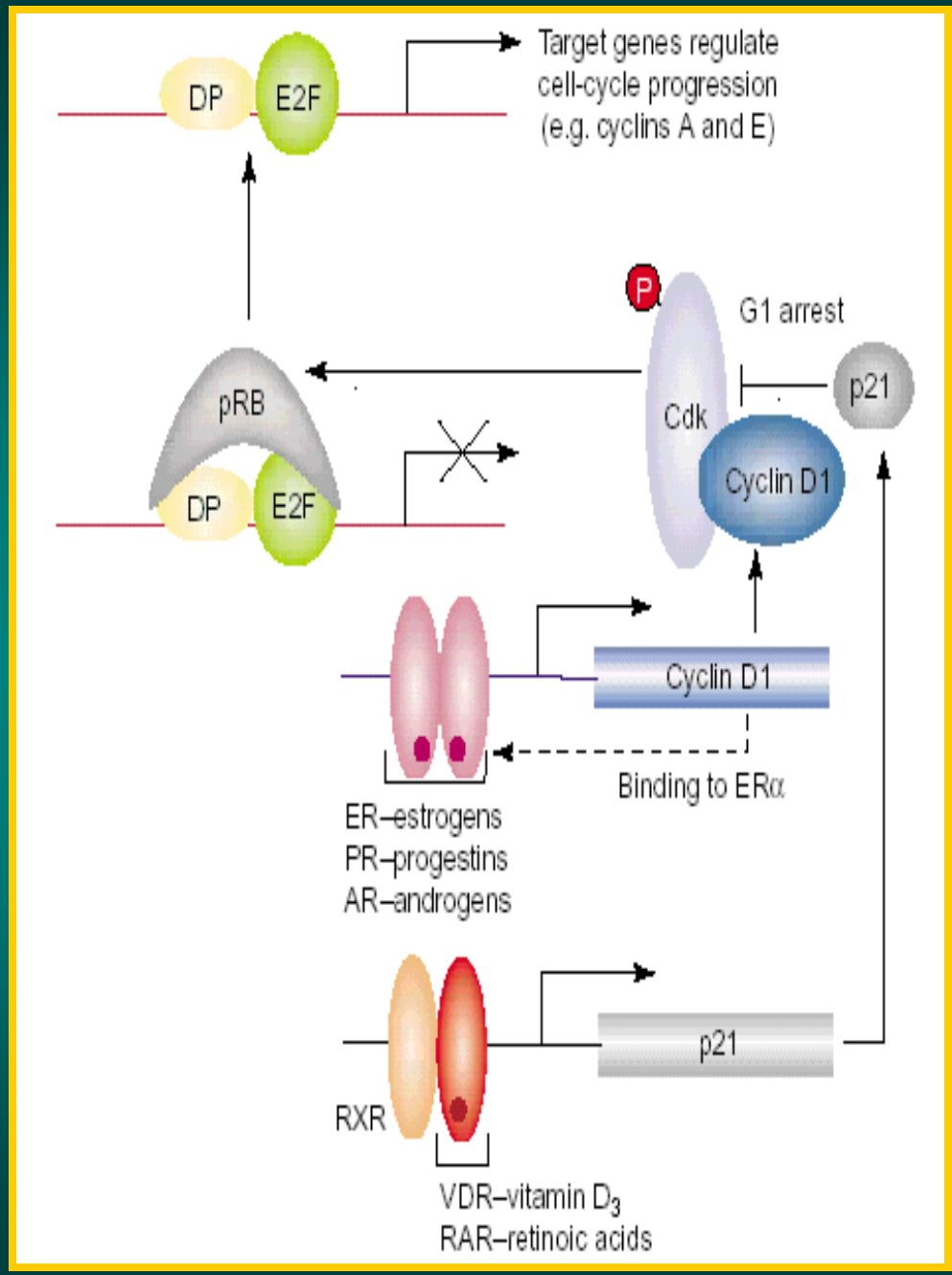
- made up of three lobes: a center lobe with one lobe on each side.

- secretes a slightly alkaline fluid that forms part of the seminal fluid.

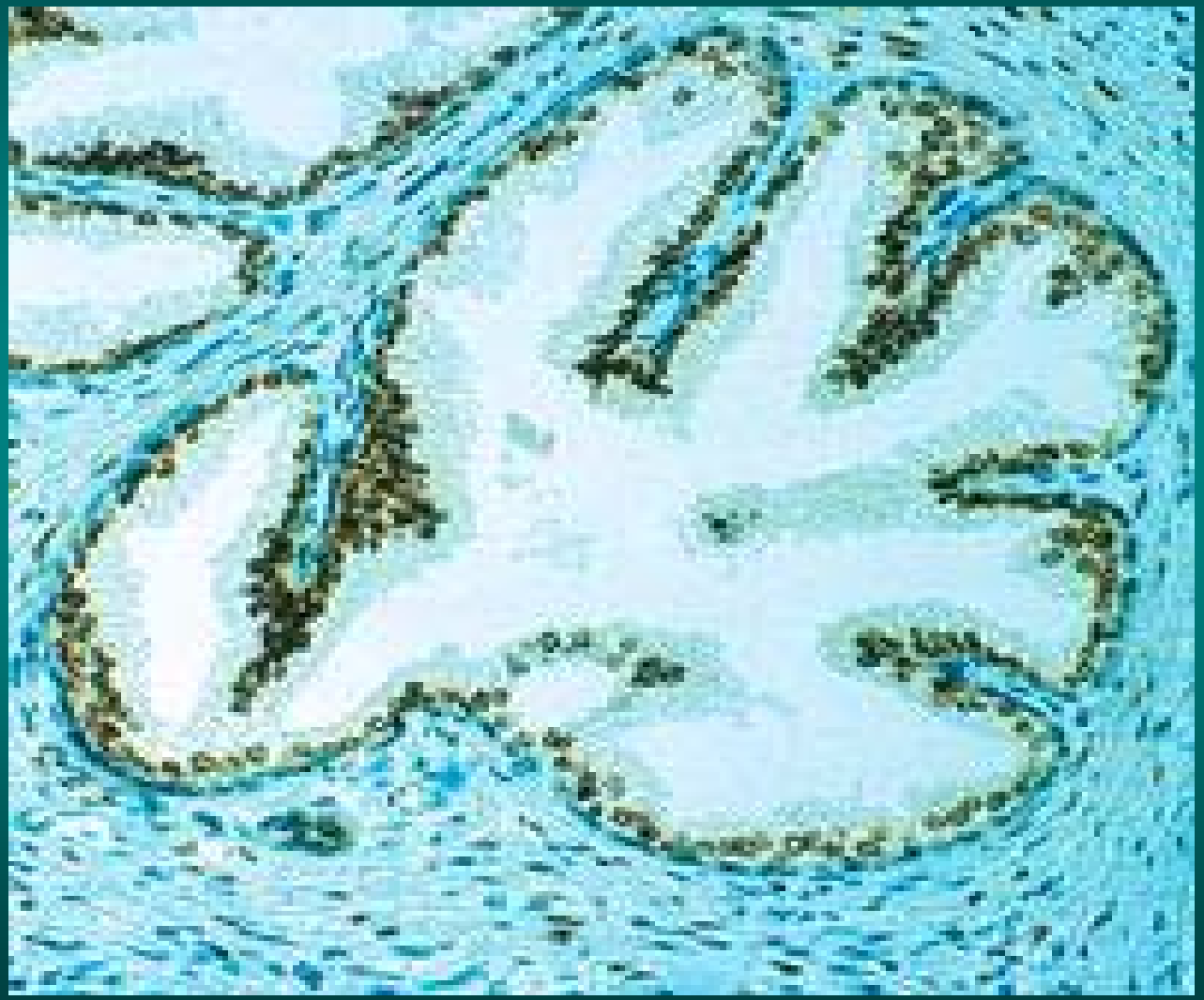


Some nuclear receptors (ER, AR, PR) stimulate expression of cyclin D, which activates Cdk4. It leads to phosphorylation of pRB, and increases transcription of genes increasing proliferation.

Others receptors (VDR, RAR) increase p21 expression, thus block Cdk activity, which keeps cells at G1 phase.



Expression of androgen receptor in prostate



Human prostate tissue stained with androgen receptor antibody.

Androgens are strong mitogens for prostate cells

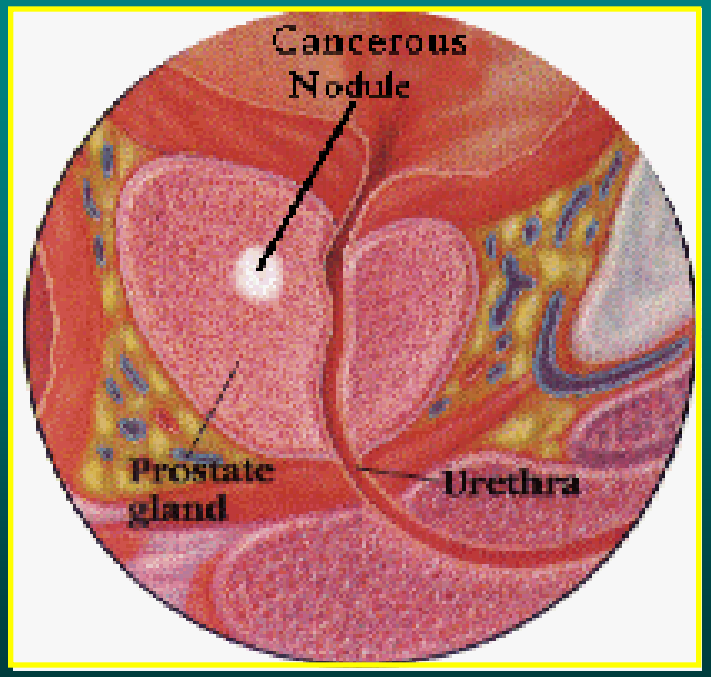
Prostate Cancer Statistics (2003)

- Newly diagnosed cases in the US
  - 220,900
- Deaths due to prostate cancer
  - 28,900
- Second leading cause of death in men
  - Accounts for 10% of male cancer-related deaths
- Incidence is increasing due to earlier detection and screening
  - Of the patients diagnosed, 97% survive at least 5 years

American Cancer Society. Key statistics about prostate cancer 2003.
Jemal A, et al. *CA Cancer J Clin*. 2002;52:23-47.

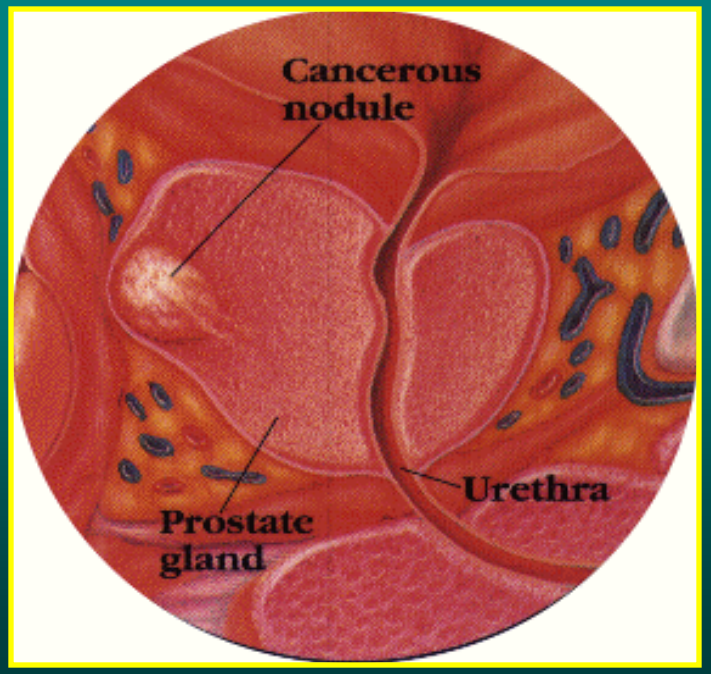
Stage A

- cancer that is only found by elevated PSA and biopsy
- not palpable
- localized to the prostate.
- usually curable,



Stage B

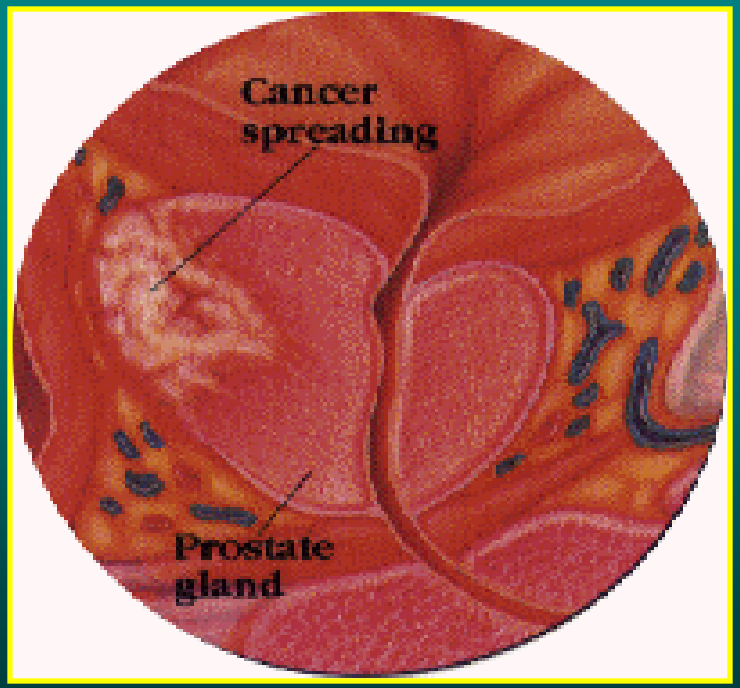
- cancer that can be felt on rectal examination and is limited to the prostate.
- many Stage B prostate cancers are curable.



Stage C

- cancer has already spread beyond the capsule of the prostate into local organs or tissues, but has not yet metastasized or jumped to other sites.

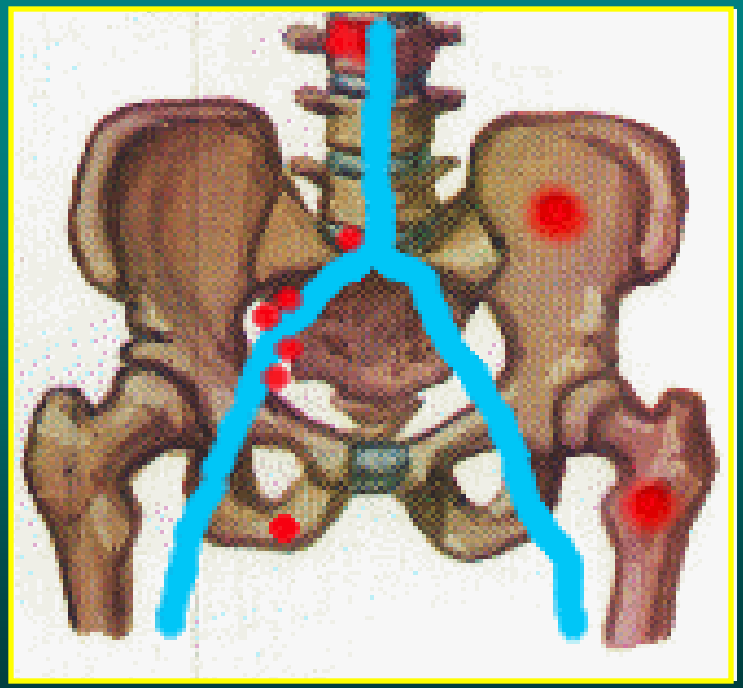
- some Stage C cancers are curable.



Stage D

- cancer has already spread, usually to distant lymph nodes, bones or other sites.

- stage D cancer is not curable but is treatable



Symptoms which may inducate for prostate cancer:

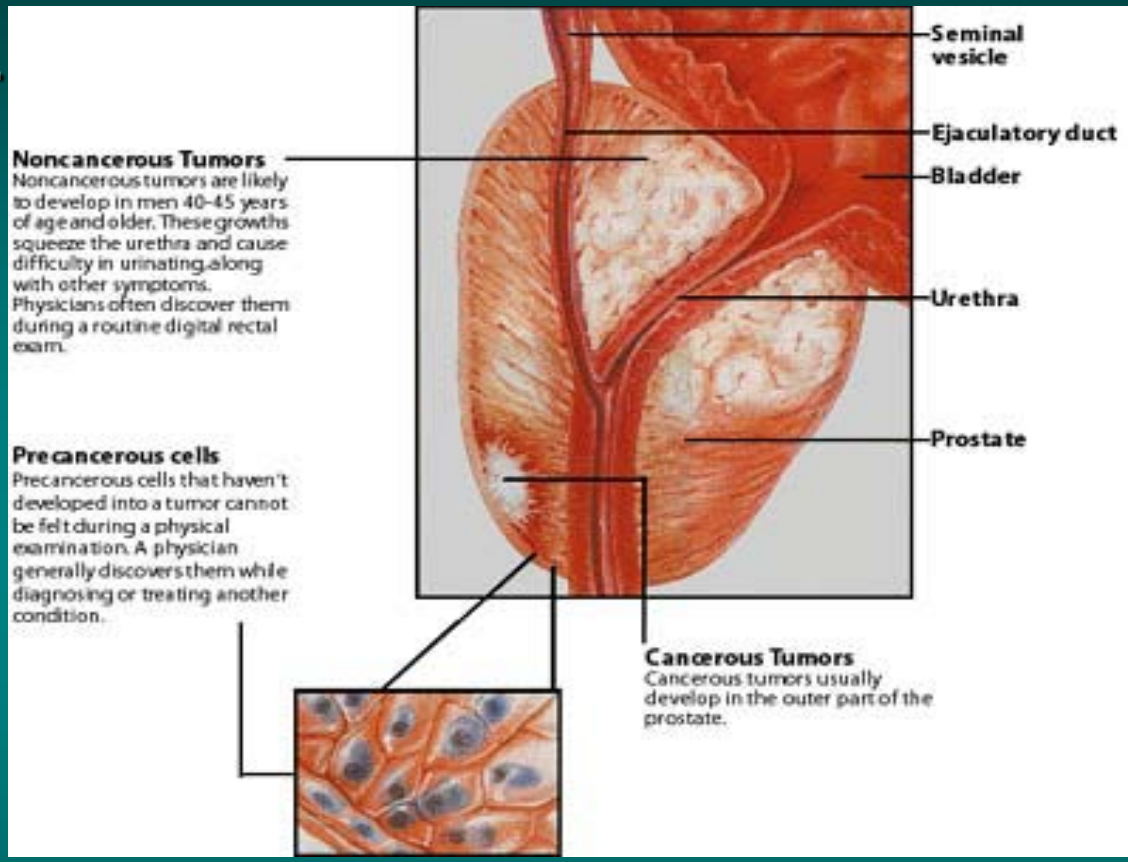
* Inability to completely empty the bladder

* Extremaly slow urination

* Recurrent bleeding from prostate

* Any changes detected by physician during per rectum examination

* Increase in PSA



But

Often prostate cancers growth slowly and many men do well without any treatment

For older men with other serious medical problems the risk involved with surgery may outweigh the potential benefits (thus pharmacological ”castration” is a method of choice).

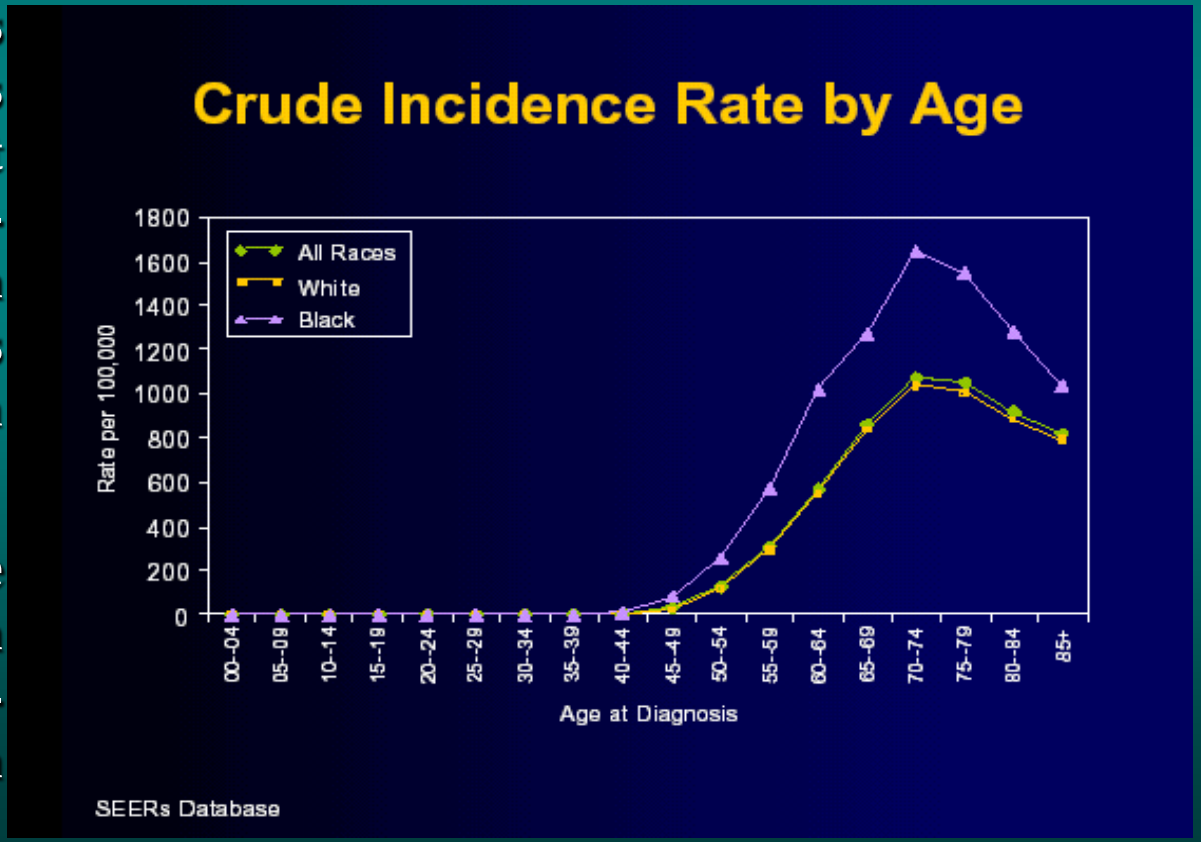
Prostate cancer

- In American population mean number of CAG (glutamine) repetition was in such order: Africans<Europeans<Asians. It correlates with risk of prostate cancer.

- In single described case in the healthy tissues AR had CAG=24, while in tumor CAG=18. However, both lengths were within the normal values.

- In american population Asians are less risked for prostate cancer than Africans (the highest risk) or Europeans. Apart from AR polymorphism, these differences can also be associated with higher level of testosterone in Africans and/or lower activity of 5α reductase in Asians.

- In Japan less clinical cases of prostate cancer is noticed than in USA but in post-mortem investigations the numbers of pre-clinical or latent tumors in both countries are similar.



Androgens and prostate cancer

- Androgens augment the growth of prostate cancers and removal of androgens (castration) strongly decreases tumor growth. Till now, castration or pharmacological inhibition of androgen pathways remains the major method of prostate cancer treatment, despite the high rate of failure, caused by hormone-independent growth of tumors.

- At early phase prostate cancer responds to decreased level of testosterone, but later on it can grow without hormone. It can result from:

  * growth-factor dependent phosphorylation of AR and testostosterone-independent AR activation,
  * AR mutations leading to ligand-independent activation.
  * AR mutation may change the ligand-specificity, thus AR activation may occur in response to non-specific ligands, e.g. estrogens (Also anti-androgens may used in therapy can stimulate the mutated AR).
  * Tumor cells growing independenty of AR stimulation are selected.

Bilateral Orchiectomy

- In 1941, Huggins and Hodges made original discovery of hormonal effect on prostate cancer
- Same studies also showed that bilateral orchiectomy improved pain or neurological symptoms in 71% of patients with metastatic disease
- Advantages:
  - Immediate castration without testosterone surge
  - Outpatient procedure, general anesthesia not required
- Disadvantages:
  - Irreversible

Huggins C, Hodges CV. *Cancer Res*. 1941;1:293-7.
Huggins C, et al. *Arch Surgery*. 1941;43:209.
Schroder FH. *Campbell's Urology*, 8th ed. Philadelphia, Pa. WB Saunders;2002:3190-91.

Hormonal therapy

1. LHRH analogs therapy

* chronic administration of luteinizing hormone-releasing hormone (LHRH) analogs to block endogenous production of luteinizing hormone.
* usually taken orally by the patients but they can be also long-acting implants
* prevents the testes and adrenals from producing male hormones

2. Androgen blockers

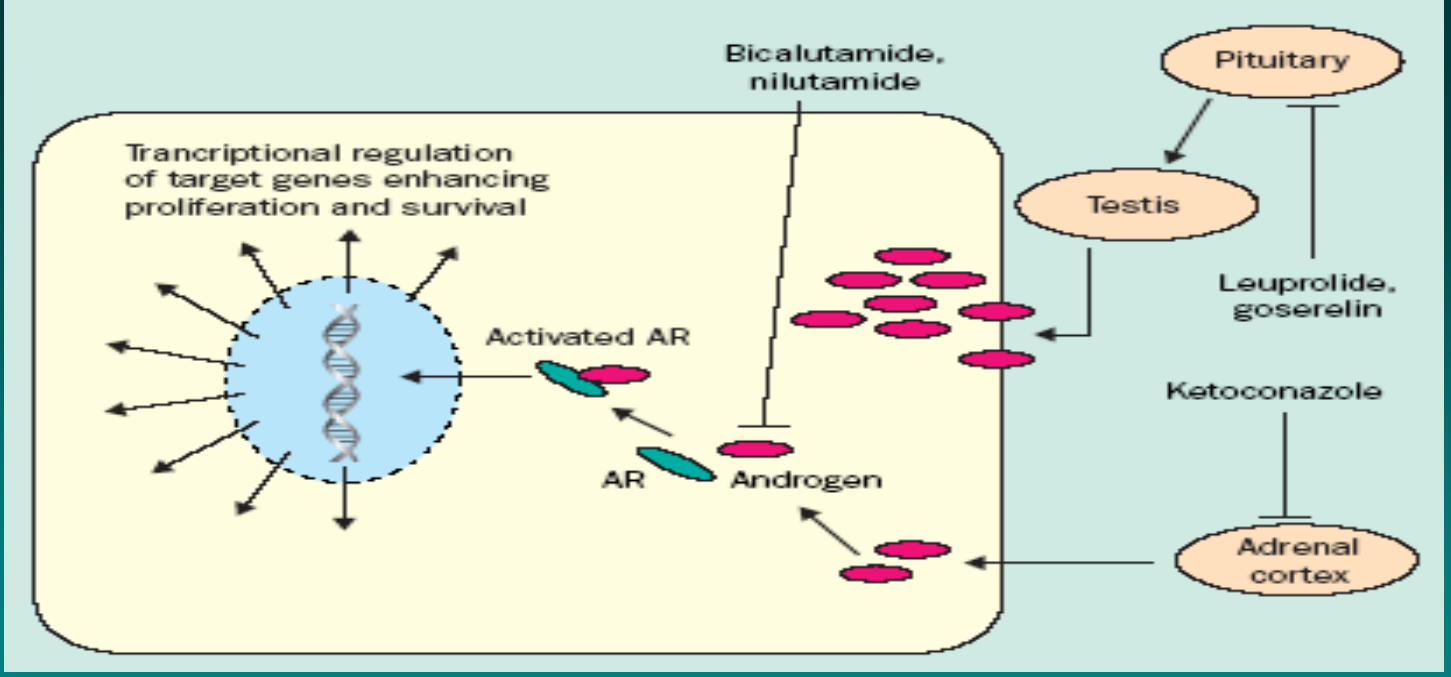
* usually taken orally by the patients but they can be also long-acting implants
* inhibitors of androgen-AR interaction

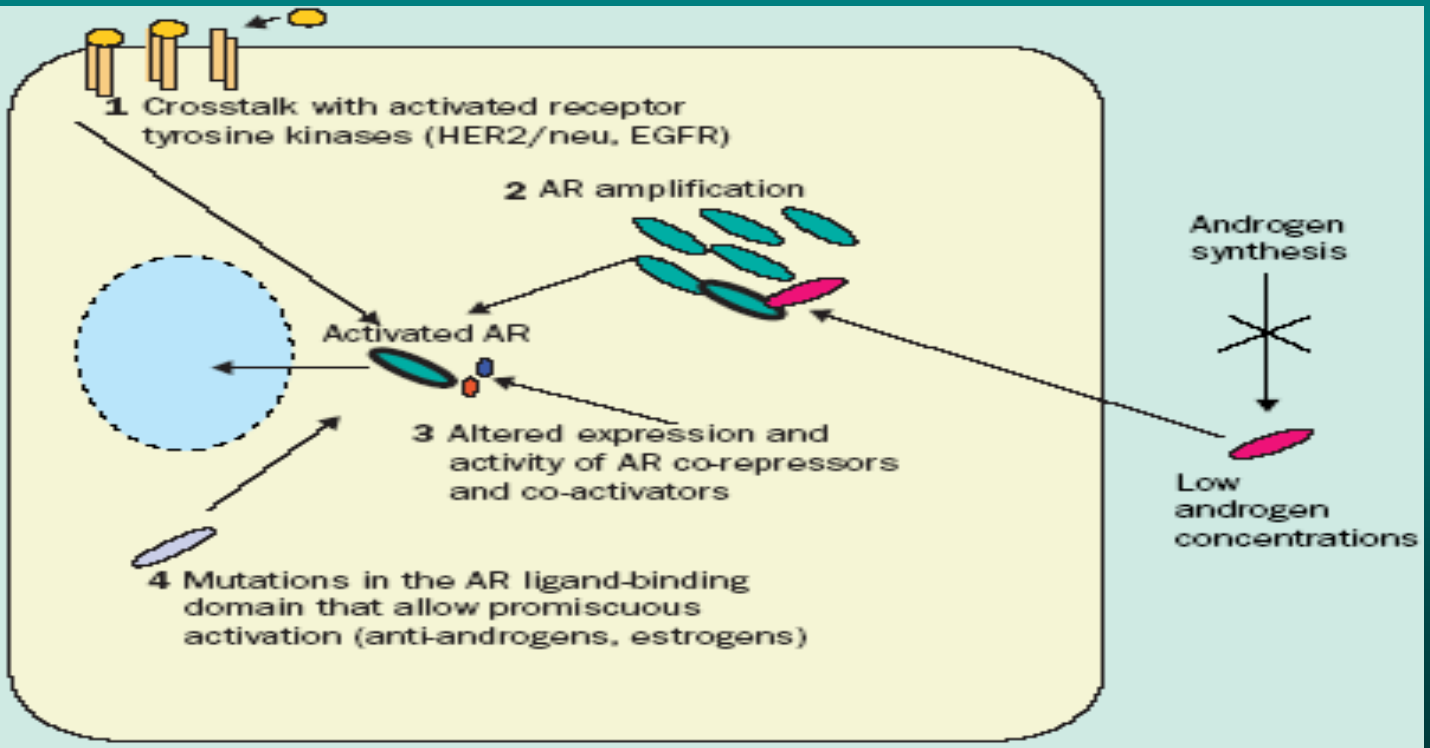
3. Inhibitors of 5α-reductase

* in combination with other drugs (e.g. androgen blockers)

Usually such treatmens improves clinical outcome even for several years

Therapies to prevent activation of androgen receptor





Mechanism by which advanced prostate tumors maintain androgen receptor signaling in a castrate environment

Effects of antiandrogenic hormonal therapy

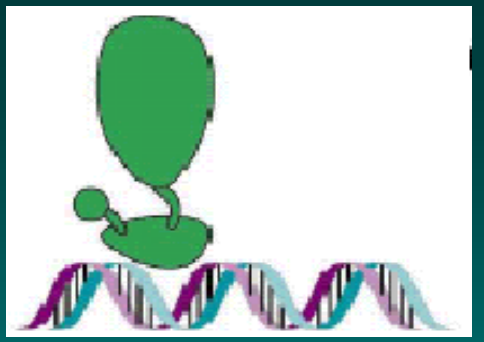
Advantages

- Equivalent in efficacy to bilateral orchiectomy in achieving castration testosterone levels and overall survival
- Number of long acting injectable depot formulations
- Potentially reversible medical castration (vs orchiectomy)
- Injection/implant vs surgery
- Psychological effect

Disadvantages

- Hot flashes
- Decreased libido
- Erectile dysfunction
- Osteopenia→osteoporosis
- Muscle wasting
- Fatigue
- Anemia
- Altered lipid levels
- Decrease in cognitive function

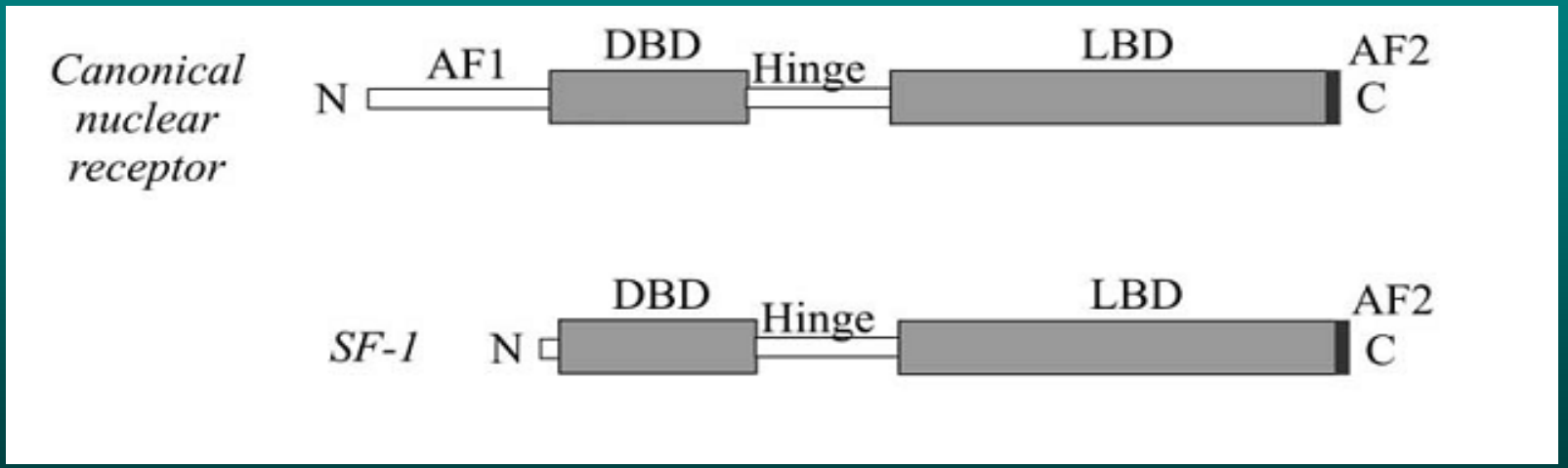
SF-1 (splicing factor-1)



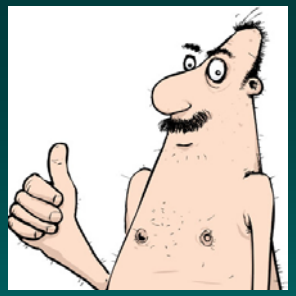
- The human SF-1 gene encodes a 461-aminoacid orphan nuclear receptor.

- SF-1 binds to DNA as a monomer and recognizes variations of the DNA sequence motif, T/CCA AGGTCA. In most cases, SF-1 functions cooperatively with other transcription factors to modulate the timing and level of gene expression.

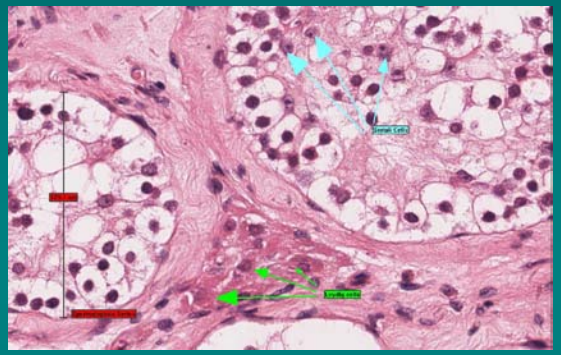
- It is possible that SF-1 is regulated independently of a specific ligand; its pattern and level of expression, interaction with other transcription factors, or posttranslational modifications represent plausible means to control its action.



SF-1



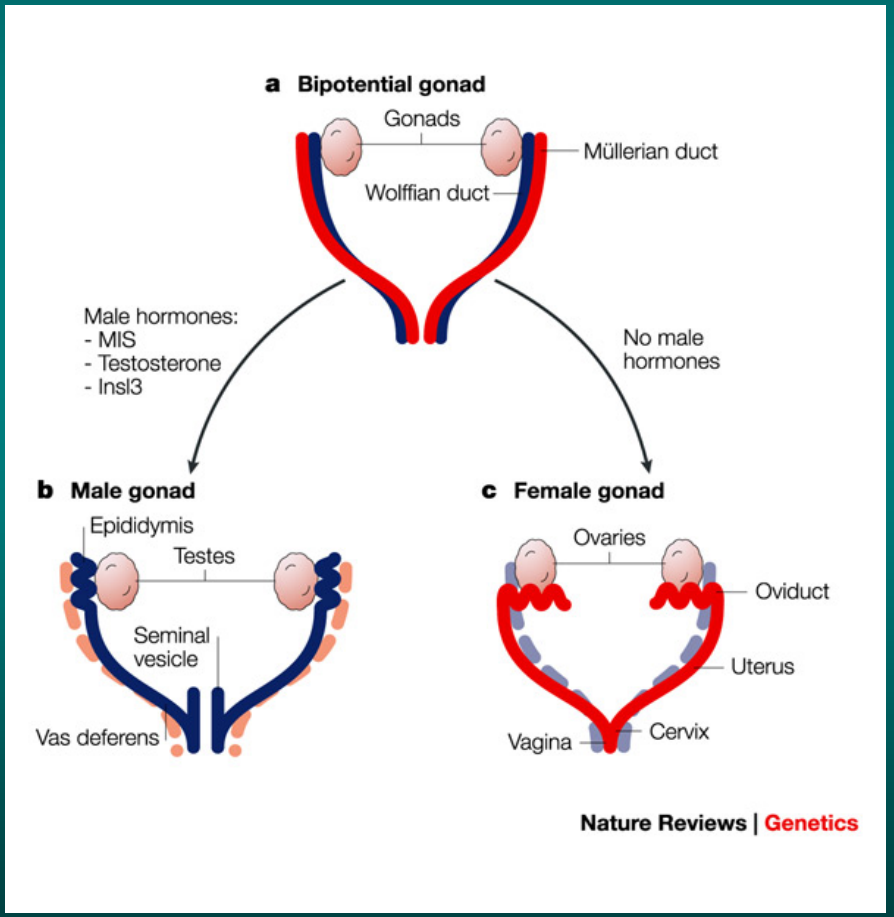
- In the mouse, SF-1 is first expressed in the urogenital ridge at embryonic d9. After gonadal determination (e13), SF-1 is expressed in a population of rapidly proliferating cells in the developing testis.
- In Sertoli cells, SF-1 regulates Mullerian inhibiting substance (MIS) expression, leading to regression of Mullerian structures in males.



- In Leydig cells, SF-1 regulates the steroidogenic enzyme genes that control testosterone biosynthesis.

- SF-1 also plays an important role in the normal development and function of the hypothalamic-pituitary-gonadal axis. It is expressed in the hypothalamus and in pituitary.

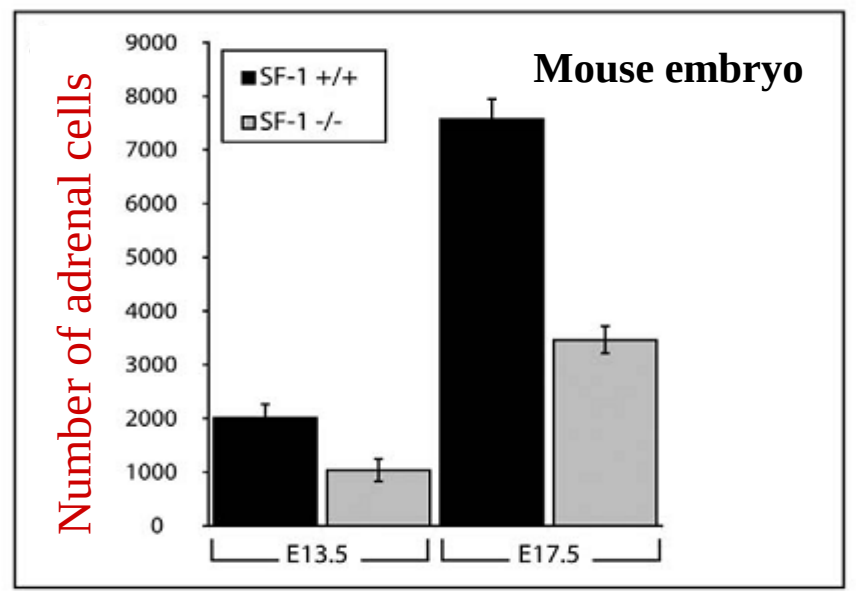
- Thus, SF-1 regulates an many genes involved in sex determination and differentiation, reproduction, and steroidogenesis.



SF-1

- SF-1 is a master regulator of reproduction, because its targets include genes at every level of the hypothalamic-pituitary-gonadal axis, as well as most genes involved in gonadal and adrenal steroidogenesis.

- SF-1 knockout mice have adrenal and gonadal agenesis. The XY mice exhibit male-to-female sex reversal, including persistent Mullerian structures, reflecting the absence of fetal androgens and Mullerian inhibiting substance.



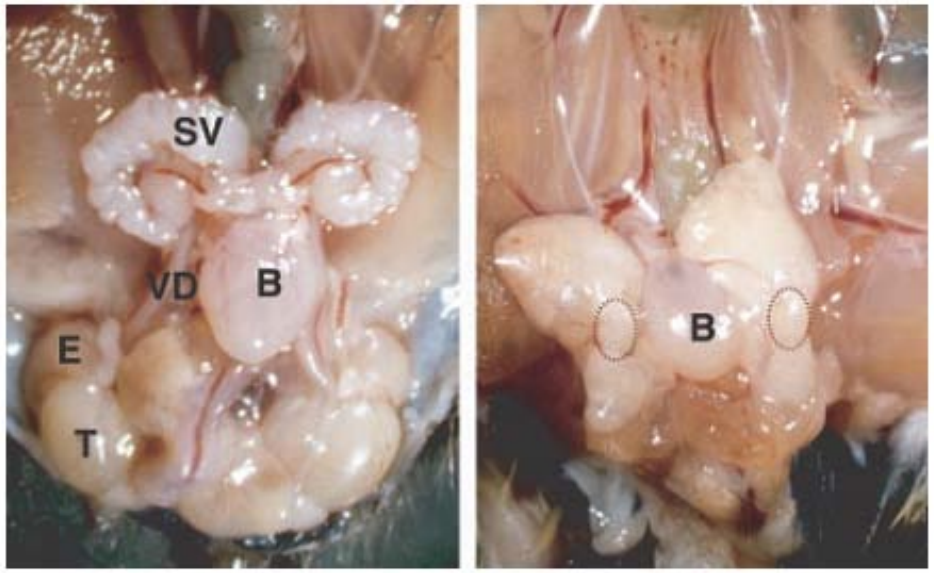
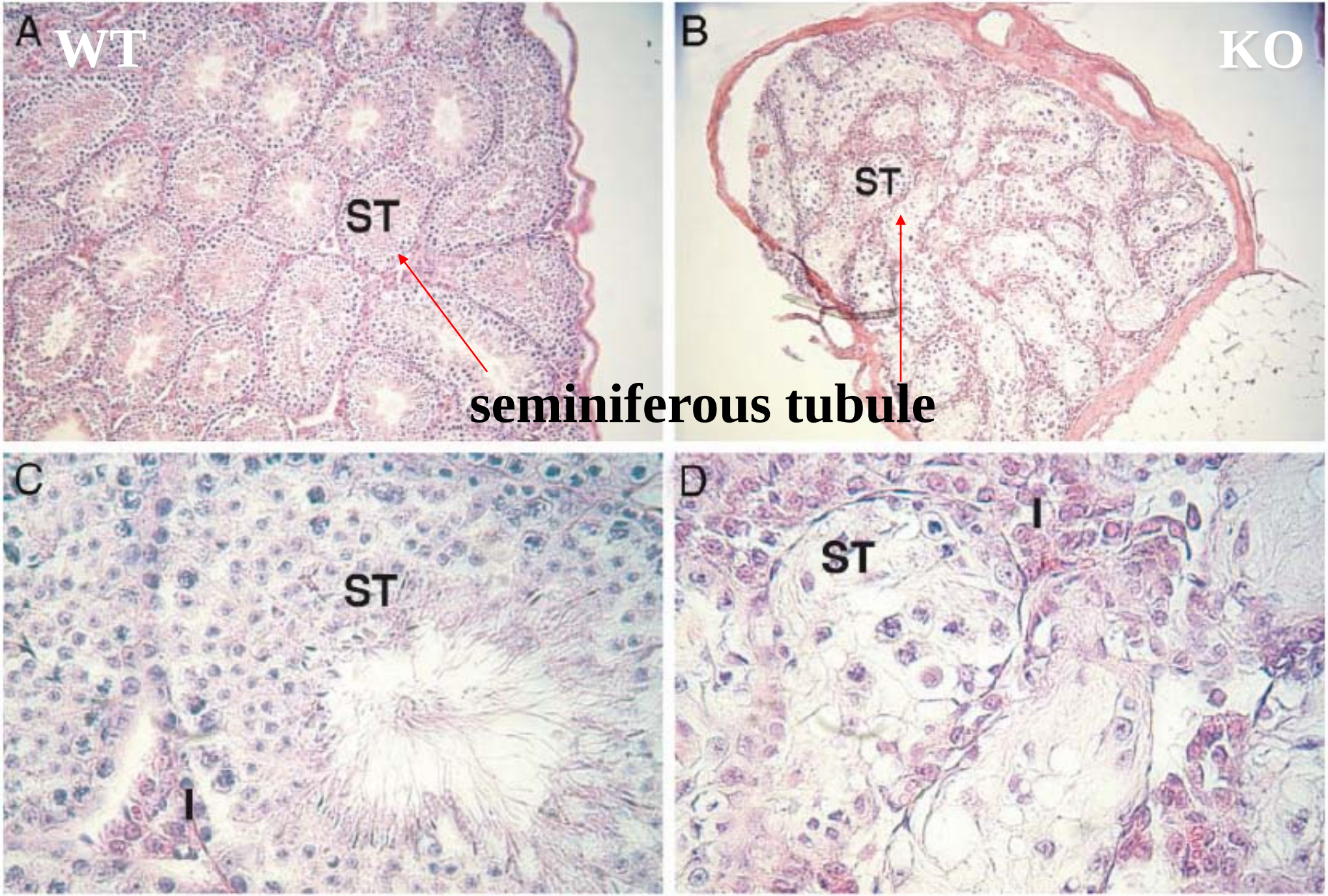


Fig. 2. Structures of the Testes and Internal Genitalia of Gonad-Specific SF-1 KO Mice

Adult WT and gonad-specific SF-1 KO males were killed and their internal structures were displayed. *Left*, WT male. *Right*, SF-1 KO male. Testes in the gonad-specific SF-1 KO male are indicated by the *dotted ovals*. T, Testis; SV, seminal vesicle; E, epididymis; B, bladder; U, ureter; VD, vas deferens.

Jeuyasuria et al. 2004, Mol Endocrinol; Gut et al., Development2005


A WT
ST
B
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seminiferous tubule
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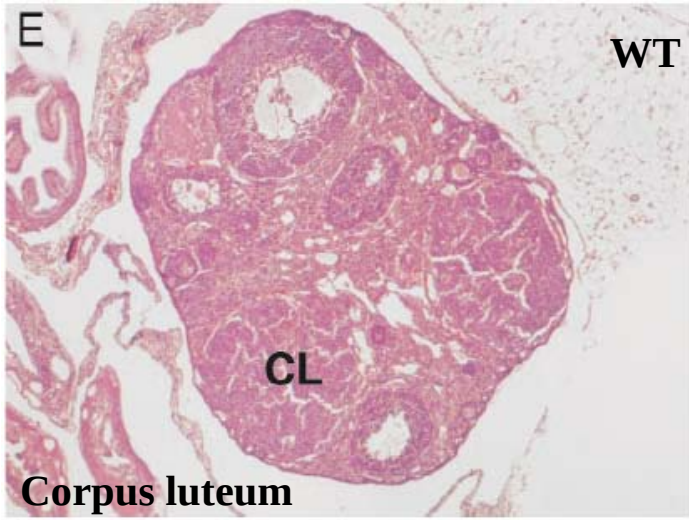
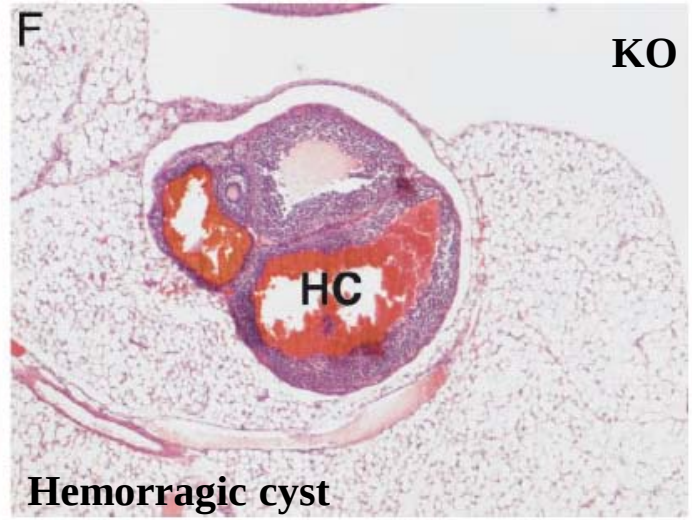
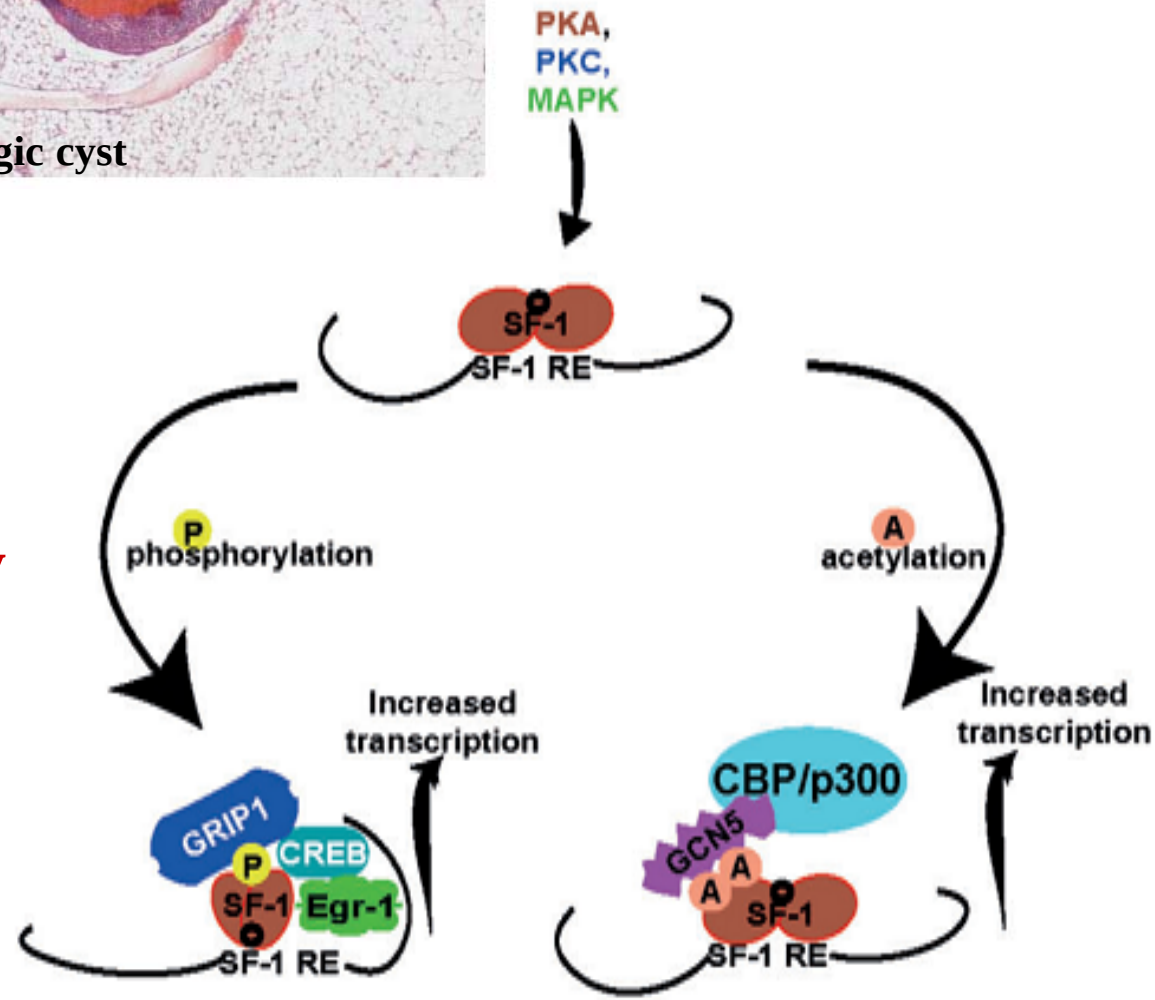




Regulation of SF-1 activity



Fowkes and Burrin, J Endocrin 2003

DAX1 (dosage-sensitive sex reversal-adrenal hypoplasia congenita critical region on the X chromosome, gene 1)

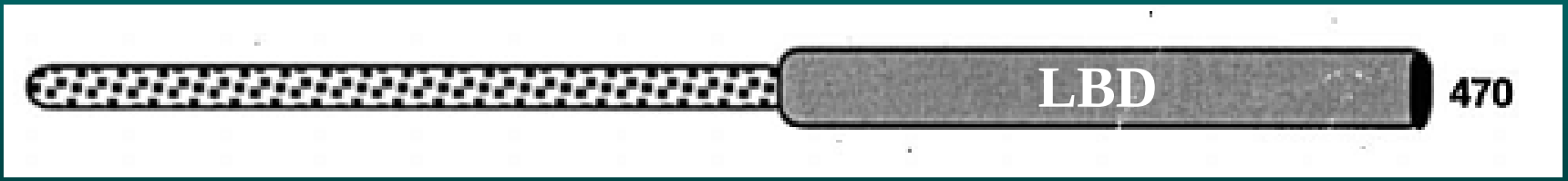
-DAX-1 encodes an atypical nuclear hormone receptor that contains the ligand-binding domain but lacks DNA-binding motif.

- Alternative splicing may generate a second DAX-1 isoform.

- DAX-1 can inhibit the function SF-1 and other nuclear receptors.

-Like SF-1, DAX-1 is expressed not only in the adrenal primordium from its earliest stages of development but also in developing gonads, and pituitary.

- Expression of DAX is positively regulated by SF-1.



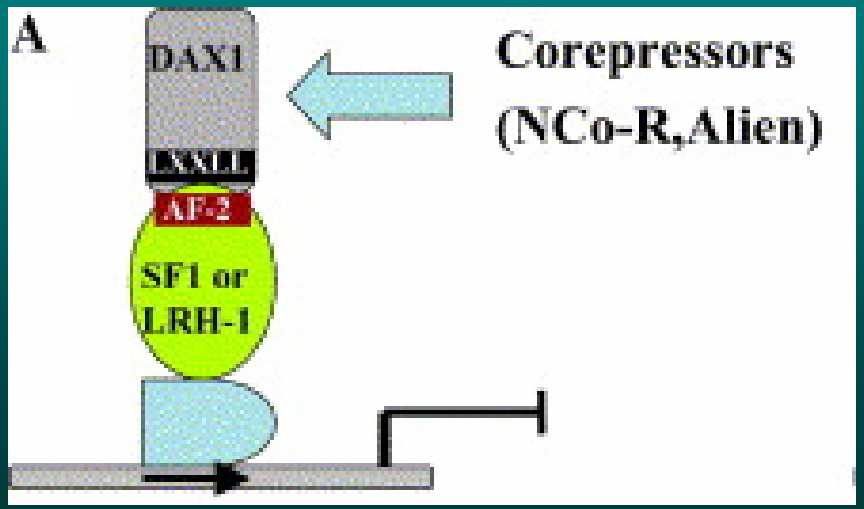
SF-1 and DAX

- The coexpression of DAX-1 with SF-1 in the gonadal and adrenal axes and the adrenal failure seen in patients with mutations in these genes, suggest that DAX1 and SF-1 interact in a common genetic pathway.

- An SF-1 response element has been identified in the DAX1 promoter, and SF-1 activates Dax1 expression.

- In vitro studies show that DAX-1 represses SF-1–mediated transactivation. DAX-1 inhibits transcription of SF-1 target genes.

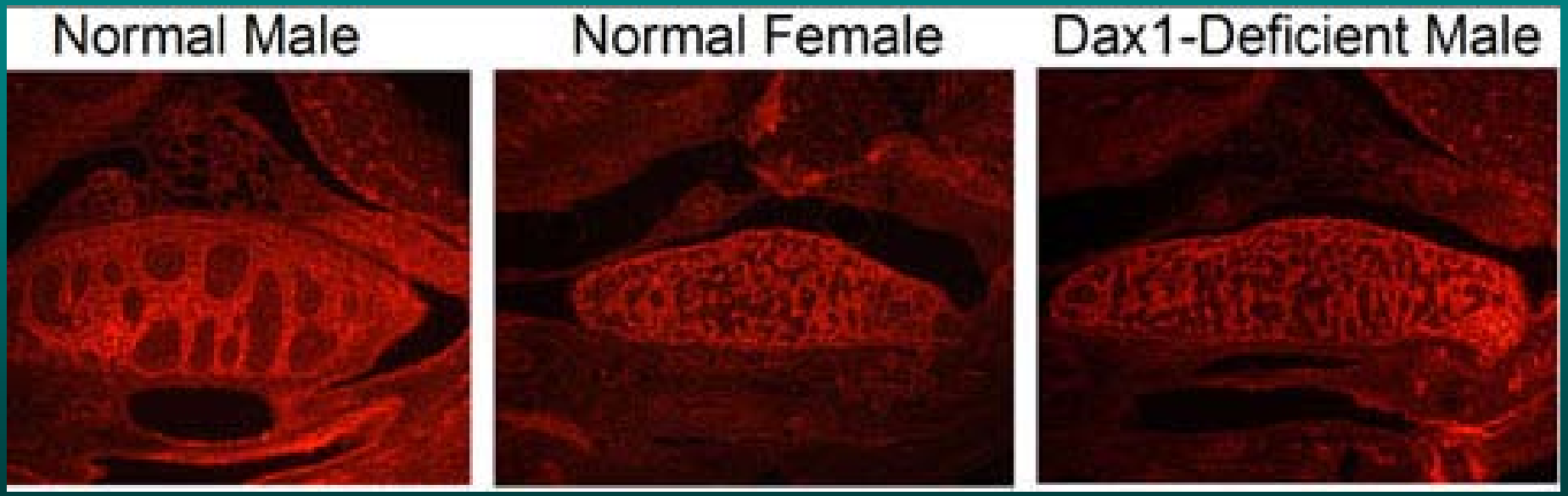
- These complex, reciprocal interactions may represent feedback loops between SF-1 and DAX1 that maintain the appropriate expression level of target genes in the adrenal cortex.



DAX1 (dosage-sensitive sex reversal-adrenal hypoplasia congenita critical region on the X chromosome, gene 1)

- Mutations in the DAX1 gene in humans cause the X-linked form of adrenal hypoplasia congenita, a rare disorder characterized by impaired development of the adrenal cortex and hypogonadism. Affected boys develop adrenal failure shortly after birth or during early childhood, whereas hypogonadism is visible during puberty.

- In Dax-1 KO mice, spermatogenesis was impaired, suggesting a distinct role for DAX1 in sperm development.



http://www.jamesonlab.northwestern.edu/

Thank you and see you next week...

What would be profitable to remember in June:

- Causes and symptoms of thyroid hormone deficiency

- Splicing forms and mode of action of TR.

- Effect of AR polymorphism on risk of diseases

- Strategies of hormonal therapy in prostate cancer

AR-positive

Slides can be found in the library and at the Heme Oxygenase Fan Club page:

https://biotka.mol.uj.edu.pl/~hemeoxygenase